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Constructing a Conceptual Framework of Patient-Reported Outcomes for Metastatic Hormone-Refractory Prostate Cancer

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ABSTRACT

Objective: A conceptual framework for patient-reported outcomes (PROs) is a structured representation of outcome concepts and issues. Our aim was to develop a conceptual framework of PROs for hormone-refractory prostate cancer (HRPC) to support measurement clarity.
Methods: Relevant outcome issues were identified from review of recent clinical trials. This provided content for an interview with 15 metastatic HRPC patients and a survey of 10 practitioners. All participants were asked about the relevance and importance of 26 outcomes and were allowed to nominate new outcomes. Practitioners were also asked to determine which outcomes endorsed by patients were attributable to the disease (symptoms) versus treatment (side effects). Analyses of archived clinical trial data were used to verify and augment the interview and survey results.
Results: Patients endorsed 11 concerns as relevant and important to HRPC including general pain, bone pain, urinary problems, fatigue, appetite loss, constipation, erectile dysfunction, peripheral neuropathy, diarrhea, PSA anxiety, and changes in self image. Practitioner judgments helped classify each concern into one of four categories, disease symptom, treatment side effect, both symptom and side effect, or psychological concern. Additionally, patients endorsed (and practitioners confirmed) the relevance and importance of several general domains of quality of life. Analyses of archived data confirmed the importance of these issues and suggested two additional concerns.
Conclusion: Findings were used to propose a conceptual framework of PROs for metastatic HRPC. Such frameworks can be used to help specify targets for assessment in clinical studies such as treatment trials.
Keywords: conceptual framework, hormone-refractory, patient-reported outcomes, prostate cancer, quality of life.

Introduction

In oncology treatment trials of new medical products, traditional clinical outcomes such as survival, time to disease progression, and objective responses to treatment are usually considered the "gold standards" for determining treatment effectiveness. However, these are not the only outcomes of relevance to patients. Disease symptoms, treatment side effects, functional status, and health-related quality of life (HRQL) are also critical issues to assess when determining the overall impact of therapy on patient well-being. Today, clinical researchers are incorporating patient self-report outcomes into clinical trials with increasing regularity in order to determine not only the objective physiological benefits of treatment, but also how patients subjectively feel and function after therapy [1]. These "patient-reported outcomes" include subjective assessments made by the patient regarding various elements of their health including: symptoms, function, well-being, HRQL, and perceptions about treatment [2].

Patient-reported outcomes (PROs) are typically assessed using questionnaires or surveys administered directly to patients. Although PROs have been used as end points in clinical trials for decades, recent regulatory concern over the validity of existing questionnaires has received attention. Specifically, the U.S. Food & Drug Administration (FDA) published a draft guidance document to inform industry sponsors, clinicians, and researchers on how to develop and use PRO measures to support benefit claims that could potentially be used in product labeling [3]. The guidance summarizes a four-step process by which PROs should be developed, validated, and modified to receive a product label claim. All of these steps must be carefully considered and fully documented by the sponsor intending to use a PRO instrument in a clinical trial, regardless of whether the sponsor intends to develop a new instrument, use an existing instrument (or battery of instruments), or modify an existing instrument [1]. The first step in this process involves the articulation of a conceptual framework of subjective patient-relevant outcomes [3].

A conceptual framework is a diagram of the expected relationships between specific outcome issues (e.g., items in a PRO instrument) and the overall concepts measured by the instrument and represented as scores [2,3]. Some have referred to the conceptual framework as a content map or measurement model [4]. Practically speaking, the framework should answer two key questions. First, what are the principal outcome issues for a given health context, and second, how can these outcome issues be grouped or classified into concepts (i.e., domains)? A well-defined conceptual framework of relevant outcomes is critical because it can justify the use of an existing PRO instrument or the development of a new or modified PRO instrument to support a desired label claim [1]. An inappropriately articulated framework can hinder instrument development as well as the scoring, analysis, and interpretation of PRO data, thus jeopardizing the ability of the PRO findings to be supportive of the target claim [2]. In short, the conceptual framework provides the foundation on which any PRO benefit claim will ultimately rest.

Although there is no standard methodology for constructing a conceptual framework, most researchers rely on an approach

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that combines multiple sources of data. Literature review is often used to summarize relevant outcome issues germane to the health condition under study [4,5]. This can include identification of disease symptoms, side effects of current treatments, and impacts on general HRQL. Reviews of the clinical treatment literature can also help identify existing PRO instruments that may further elucidate important outcomes as well as specify measures that might be used to assess those outcomes in a trial. Patient input is considered vital to the construction of a conceptual framework. Typically, focus groups or qualitative interviews are used to solicit feedback on patients' subjective experience of a given health condition [4–6]. Input from key opinion leaders such as practitioners and other field experts can modify and elaborate the input of patients [4,6]. Ideally, the conceptual framework is constructed using both qualitative and quantitative methods with reliance on multiple sources of information. The process is iterative and can evolve over time as new information about the patient's experience of the health condition and its treatment become available [1,2,4].

In support of a clinical trials' program in hormone-refractory prostate cancer (HRPC), we set out to build a conceptual framework of relevant outcome issues for men with this disease. Prostate cancer is the most commonly diagnosed non-skin cancer in men and the second leading cause of cancer death [7]. Most men are initially diagnosed with early-stage or clinically localized disease. Treatments for clinically localized prostate cancer usually involve early intervention with surgery, radiotherapy, androgen deprivation, or observation [8]. However, almost 10% of men are initially diagnosed with advanced-stage disease, and many others will develop advanced and metastatic disease despite treatment with surgery or radiotherapy [8]. To stem the spread of disease, patients with advanced prostate cancer are typically treated with primary androgen ablation (via surgical or medical castration with or without anti-androgens). Eventually, most men will become refractory to these hormonal treatments [9]. Treatment options for men with HRPC include chemotherapy, secondary hormonal manipulation, radiotherapy (to bones), and radioisotope therapy [10]. Prior to 2005, the goal of all of these treatments was symptom palliation, especially relief of pain from bone metastases. This changed with the publication of two Phase III clinical trials, demonstrating a survival benefit in HRPC patients treated with docetaxel-based chemotherapy [11,12]. In TAX 327, docetaxel-based chemotherapy also resulted in significant reductions in pain and improvements in overall HRQL compared to standard mitoxantrone-based chemotherapy [11]. Although these clinical findings were supportive of regulatory approval of docetaxel-based chemotherapy, the increased survival benefit observed in both studies was modest (<2.5 months). Hence, today's clinical trialists are investigating agents that could improve upon the survival and symptom palliation benefits of docetaxel while maintaining an acceptable toxicity profile. Developing a conceptual framework of PROs will be an important adjunct to these trials because it can help clarify the most critical patient-relevant outcome issues to assess. The objective of this study was to derive a conceptual framework of PROs for HRPC using methods consistent with the FDA Guidance and current expert opinion [3,4].

Overview

We combined information extracted from the published literature with input from patients and experts along with independent verification using analyses of archival data. The flow of work appears in Figure 1. Because each step builds upon the results of a prior step, we will discuss the methods and results of each step separately, leading to the final proposed conceptual framework.

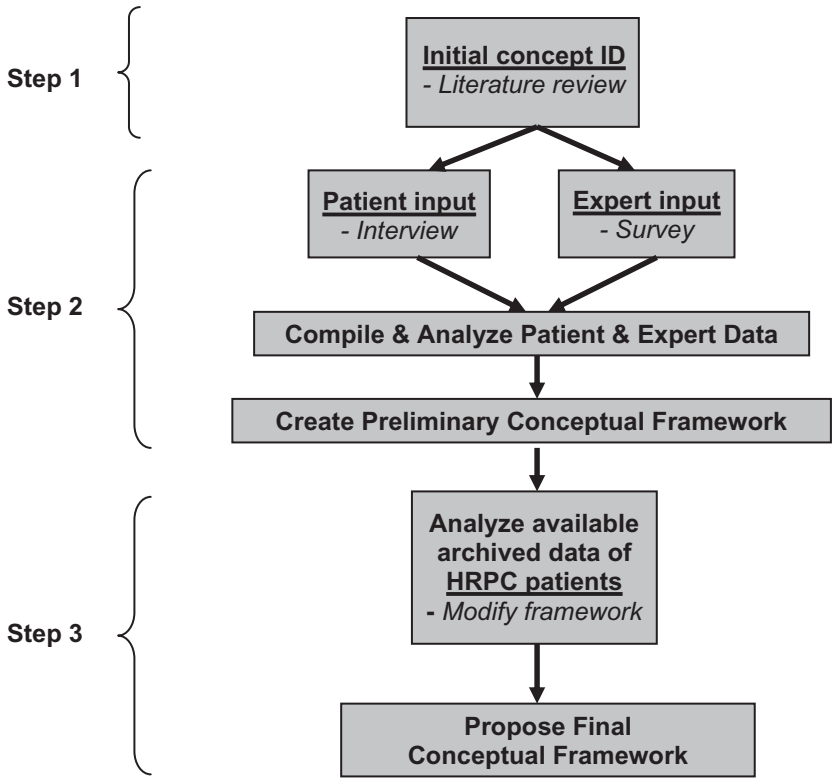

Figure 1 Methods overview and flow of work.

Methods of Step 1—Literature Review

The objective of step 1 was to identify symptoms, complications, toxicities, and HRQL issues associated with advanced HRPC and its treatment. A literature search was conducted to identify the most recently completed randomized clinical trials in HRPC. The search was limited to those trials conducted from 2004, the year in which the two pivotal phase III trials of docetaxel were published (TAX 327 and SWOG 9916) [11,12]. From this literature search, several recently conducted systematic reviews of the treatment literature were also identified. Reviews dating from 2006 were selected to focus on patient outcome issues relevant to the most current standards of treatment.

Search strategy and study eligibility. Two databases were searched, MEDLINE and the Cochrane Register of Controlled Clinical Trials, from 2004 through 2007 (note: the search and review were commenced and completed in January, 2008). The following keywords were used in the search: (prostate cancer OR prostatic neoplasms) AND (hormone-refractory OR androgen-independent OR hormone-resistant) AND (symptom* OR quality of life OR Toxicit*) AND (random* OR clinical OR trial). The MEDLINE search yielded a total of 259 unique citations. Although 32 citations were uncovered from the search of the Cochrane database, all had already been identified in the MEDLINE search. Citation abstracts were reviewed; and the complete article was retrieved if the study was either, 1) a randomized clinical trial (or nonrandomized, but controlled trial) of men treated for HRPC with at least 50 patients per treatment arm; or 2) a prospective, uncontrolled study enrolling at least 200 men with HRPC. Only studies that used PROs as outcomes were eligible for review. For instance, studies using HRQL as a predictor of other clinical outcomes were excluded. Using these criteria we selected 24 studies for review of PROs such as symptoms, treatment side effects/toxicities, and HRQL domains. We also identified five reviews of the recent clinical treatment literature (2006–07) that referenced important data on symptoms, side effects/toxicities, and HRQL. All were structured, systematic literature reviews of randomized trials and/or clinical studies each led by either a formal review group [9,13,14], an outcomes measurement expert [15], or a physician expert [16].

Results of Step 1

Because the objective of this task was to identify outcome issues that could form the basis for interview and survey queries of patients and practitioners, attention was focused exclusively on extracting information about patient-relevant outcomes such as symptoms, side effects/toxicities, and HRQL. Regarding the clinical studies literature (clinical trials and large-scale prospective, observational studies), data were extracted on baseline (pretreatment) symptoms of disease, changes in symptoms and HRQL over time, and treatment side effects/toxicities. Outcome issues were extracted for later query if: 1) they were frequently observed prior to treatment (e.g., notably heightened at baseline or used as stratification criteria); 2) they were found to change over time in multiple studies or study arms; or 3) they represented frequently occurring side effects or toxicities (e.g., any grade toxicity occurring ≥50%) or were severe and noticeable (e.g., a grade 3 or 4 toxicity occurring ≥10%). Findings from reviews of the treatment literature were used mainly to corroborate the findings from clinical studies; however, any salient new outcome issues could also be highlighted for later query.

PROs in clinical studies and reviews. Among the clinical studies pain was the most frequently observed symptom at baseline.

Table 1 Patient-reported outcomes showing change in HRPC clinical studies (no. of times identified per treatment arm)

Concern or domain	Count
Pain	10
Prostate Cancer-specific concerns (PCS)*	9
Global QOL	8
Emotional function	5
General QOL (total scores of measure—ie., FACT-P)**	5
Fatigue	4
Physical function	4
Nausea/vomiting	3
Analgesic use	2
Functional well-being/role function	2
Depression	1
Appetite	1

*Prostate cancer subscale (PCS) of the FACT-P. Consists of 12 items assessing: pain-4, weight loss-1, appetite-1, masculine image-1, bowel function-1, urination problems-3 (frequency, straining, activity limitation), and erectile dysfunction-1. **FACT-P consists of subscales measuring: physical, functional, social, emotional, and prostate cancer-specific concerns.

Pain was heightened at baseline in 7 of 22 studies (note: two studies were HRQL analyses from SWOG 9916) [17,18]. More specifically, bone pain was reportedly heightened at baseline in 3 of 22 studies. In the two pivotal trials of docetaxel, TAX 327 and SWOG 9916, self-reported pain was used to stratify patients prior to randomization [11,12]. Table 1 provides frequency counts of the number of times certain PROs were found to have changed over time (per treatment arm). Clinical reviews of the treatment literature verified the relevance of many of these same PROs (including, prostate cancer-specific concerns, pain, general quality of life, physical, role, and emotional function). Additionally, constipation was reportedly improved in some trials of chemotherapy [13]. Those concerns/domains that appear more than once in clinical studies or were highlighted in clinical reviews were marked for later query with patients and practitioners.

Side effects and toxicities in clinical studies and reviews. Treatment side effects or toxicities were selected from clinical studies if they met at least one of the following criteria: 1) it was observed in any study arm at a rate ≥50% (any grade), OR 2) it was severe (i.e., grade 3 or 4) and was observed in a study arm at a rate ≥10%. The most frequently reported side effect/toxicities included fatigue and nausea/vomiting; however, alopecia, gynecomastia, infection, pain, bone pain, and diarrhea were also reported more than once (see Table 2). Toxicities based on clinical chemistry (i.e., hematologic toxicities) were noted, but not further considered because the objective was to identify outcome issues that rely exclusively on patient self-report.

Clinical reviews of the treatment literature verified the relevance of nausea/vomiting and diarrhea with both being associated with more than one drug treatment for HRPC. A review of the epothilones [16] identified peripheral neuropathy (tingling in the hands and feet) as a frequently occurring toxicity. Hence, this was added to the list of issues for later patient and practitioner query. Overall, a total of 22 outcome issues were marked for later query including the following: fatigue, nausea, vomiting, diarrhea, constipation, other bowel problems, hair loss, breast enlargement, infections, pain (in general), bone pain, peripheral neuropathy, appetite loss, weight loss, urinary obstruction/frequency, erectile dysfunction, masculine self-image, physical function, emotional distress, functional well-being, social function, and global quality of life.

Table 2 Major side effects or nonhematologic toxicities identified in HRPC clinical studies (no. of times identified per treatment arm)

Side effect/toxicity	Count
Fatigue	15
Nausea or vomiting	7
Alopecia	3
Gynecomastia	2
Infection	2
Pain	2
Bone pain	2
Diarrhea	2
Musculoskeletal tox. (unspecified)	1
Cardiovascular event	1
Dyspnea	1
Edema	1
Anorexia	1
Hand-foot syndrome	1
Injection site reaction	1
"Body as a whole"	1
Flushing	1

Methods of Step 2—Patient Interviews and Practitioner Surveys

Patient interviews. A patient was considered eligible for this study if he met all of the following inclusion criteria: 1) a rising PSA while on hormonal therapy; 2) a castrate level of testosterone; and 3) experience of an anti-androgen withdrawal response (i.e., regression of tumor associated with the suspension of anti-androgen therapy). Additionally, the patient had to have at least one of the following to be deemed eligible: a positive image on bone or CT scan (i.e., an image indicative of neoplastic spread to the bones), a rapid PSA doubling time, or a severely elevated PSA (considered by the clinician to be indicative of HRPC). Patients meeting these criteria were identified by their treating oncologist (D.S.) who was caring for 45 HRPC patients during the three month recruitment window. All were receiving treatment at NorthShore University HealthSystem (Evanston, IL, USA). The study was introduced by the oncologist during a regular follow-up visit. Interested patients then met with a research assistant for a more complete description of the study. To maximize the likelihood of thematic content saturation, we targeted a sample size of 15 patients, a number consistent with current recommendations for purposive samples for qualitative interviews [19]. The 15 patients who agreed to participate were subsequently contacted to arrange a time and place for the interview. No data were collected on patients who declined to participate. Interviews were conducted between April and June, 2008 by the first author (D.E.) who has prior experience conducting one-on-one research interviews with prostate cancer patients [20]. All patients were compensated $60 for their time. The study was reviewed and approved by the Institutional Review Board of NorthShore University HealthSystem (IRB No. EH-08-209). All patients provided written informed consent prior to the interview.

The patient interview was divided into an open and closed-ended section. In the open-ended section, patients were first asked to reflect on their experience with advanced HRPC and to identify the most important symptoms, complications, or concerns to monitor when assessing the value of treatment for the disease. Upon identifying each issue, patients were then asked to rate the importance of the issue on a 0–10 scale (0 = not important to 10 = extremely important). Following completion of the open-ended section, patients were asked about the relevance and importance of 26 additional issues. These included the following: fatigue, nausea, vomiting, diarrhea, constipation, other bowel problems (respondent specified), hair loss, breast enlargement, infections, general pain, bone pain, peripheral neuropathy (tingling in hands/feet), appetite loss, weight loss, urinary obstruction/frequency, other urinary problems (respondent specified), erectile dysfunction, other sexual problems (respondent specified), masculine self-image, PSA anxiety, physical function, emotional distress, functional well-being, social function, social support, and global quality of life (QOL). These issues were drawn from the step 1 literature review with some being further specified or expanded. For instance, although not explicitly mentioned in the literature reviewed, PSA anxiety was included in the interview protocol as a disease-specific marker of emotional distress. Furthermore, both social function (ability to participate in social activities) and social support (existence of social relationships and the assistance provided from these relationships) were included in the protocol because they are domains often rolled into scale and total scores from commonly used PRO measures (e.g., the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and the Functional Assessment of Cancer Therapy-Prostate [FACT-P]). Finally, to account for the possibility of other urinary complications besides frequency or obstruction and other sexual complications besides erectile dysfunction, we included items tapping "other urinary problems" and "other sexual problems" and asked patients to specify. Brief definitions of the more general domains of function (i.e., physical function, emotional distress, functional well-being, social function, social support, and global quality of life) were provided to patients prior to their judgment of relevance and importance. These definitions were informed by standard descriptions of these domains (see http://www.nihpromis.org). They are provided in the appendix found at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i5_Eton.asp. For any concern endorsed as relevant, patients were subsequently asked to rate it on the 0–10 importance scale. Demographic (i.e., age, race, education) and clinical information (i.e., treatment, metastasis, PSA) were also collected by patient query and medical chart review.

Practitioner surveys. A list of potential practitioner participants was generated by the first and last author (D.E. and D.C.). The list represented all of the major medical specialties who treat or care for advanced, HRPC patients (i.e., medical oncology, surgical oncology, radiation oncology, and nursing). Practitioners were eligible if they reported having at least 3 years experience treating or caring for at least 100 advanced HRPC patients. Most of these practitioners were known to the authors from prior collaborations. Others were suggested by contacted practitioners who lacked sufficient time to participate themselves. In total, 18 practitioners were invited. Four failed to respond to multiple queries and another four declined citing lack of time. Self-report surveys were electronically distributed to 10 practitioners. The sample was purposively selected to provide diversity in discipline (i.e., medicine, nursing), specialty (i.e., medical oncology, radiation oncology, urology), and geographic region. We preferred the survey format over interviews to facilitate timely data capture from an experienced group of practitioners from different geographic regions. Completed surveys were returned to the first author (D.E.) and practitioners were compensated $60 for their time.

The practitioner survey protocol was also divided into open and closed-ended sections. Practitioners completed the open-ended section first, returned it, and were then sent the closed-ended section to complete. In the open-ended section, practitioners were first asked to reflect upon their experience

Table 3 Patient clinical characteristics

Most recent PSA	Median = 23.12 ng/mL Range: 1.78 to 335.00 ng/mL (note: Data missing from 2 patients)	
PSA rising at time of interview?	Yes	9 (60%)
	No	6 (40%)
Metastasis?	Yes	15 (100%)
	No	0 (0%)
Patient-reported performance status (Eastern Cooperative Oncology Group: ECOG)	ECOG 1 (some symptoms, no bed rest during day)	9 (60%)
	ECOG 0 (normal activity)	3 (20%)
	ECOG 2 (req. bed rest < 50% of waking day)	3 (20%)
Current or past 6 month chemotherapy?	Yes	10 (67%)
	No	5 (33%)
Current or past 6 month radiotherapy?	Yes	4 (27%)
	No	11 (73%)
Hormone therapy in past month?	Yes	12 (80%)
	No	3 (20%)
Bisphosphonate therapy in past month?	Yes	12 (80%)
	No	3 (20%)

treating HRPC and provide a list of the most important symptoms, complications, or concerns to monitor when assessing the value of treatment for the disease. Like the patients, they also rated the importance of each issue on their list using the 0–10 (not important to extremely important) scale. Finally, practitioners were asked to judge whether each identified issue was more likely a disease-related symptom, a treatment-related side effect, both a symptom and side effect, or neither a symptom nor side effect.

In the closed-ended section of the survey, practitioners were asked to judge the relevance of the 26 issues identified in step 1. For those issues endorsed as relevant to HRPC, two more determinations were made. First, the practitioner was asked to rate the importance of the issue on the 0–10 scale. Second, the practitioner was asked to judge whether the endorsed issue was more likely a disease-related symptom, a treatment-related side effect, both a symptom and side effect, or neither a symptom nor side effect. Practitioners also provided descriptive information about themselves including age, gender, discipline, and specialty and experience treating/caring for HRPC patients.

Results of Step 2

Patient interviews. Patients ranged in age from 50 to 93 years with a median age of 72.8. Most were white/Caucasian (80%) or white/Hispanic (13%). One African American man participated. Most were college graduates (67%); however, a few (20%) had no more than a high school education. Most were also married (87%) and retired (67%). Clinical characteristics appear in Table 3. All patients had metastatic prostate cancer and most had evidence of disease progression (rising PSA) at the time of the interview. Notably, PSA had stabilized for several men by the time of the interview, likely resulting from ongoing treatment for their malignancy. Most patients (80%) rated themselves as being symptomatic according to Eastern Cooperative Oncology Group criteria. Patients were receiving a variety of treatments including chemotherapy, hormonal therapy (e.g., leuprolide, bicalutamide, goserelin), and bisphosphonate therapy.

Patients identified a total of 38 complications in the open-ended portion of the interview. Overall, minimal coding of responses was necessary because, in most instances, the patients' verbatim responses were used. In the few instances where multiple responses seemed to reflect a common underlying concern, two of the authors (D.E. and D.C.) discussed and agreed upon a single name for the concern (e.g., "fatigue" and "tiredness" were named "fatigue"). We checked for thematic content saturation in the following manner. First, responses from the first 12 interviews were summarized. Next, patient responses from the last three interviews were compared with the results of the first 12 interviews to determine whether any new themes (i.e., outcome issues) emerged. An additional four issues emerged in the final three interviews (11% of the total number of issues provided by patients). Two of these four issues were already represented in the closed-ended portion of the interview. Hence, there was sufficient evidence to conclude that saturation had been reached after 15 interviews.

The 38 complications were entered into a table showing the frequency of endorsement of each along with its mean importance rating. Two rules were articulated to select eligible complications for inclusion in a preliminary version of the conceptual framework. A complication was selected if, 1) it was recalled by more than one patient; and 2) it had a mean importance rating of at least 5.0 (i.e., moderately important). Table 4 displays the eight complications that met these inclusion rules (note: data on all 38 complications are available from the first author).

Judgments of the 26 issues reviewed by patients in the closed-ended portion of the interview were also entered into a data table of frequency and mean importance. Two rules were articulated to select eligible complications or QOL concerns for inclusion in the preliminary version of the conceptual framework. A complication was selected if, 1) >50% of patients endorsed it as a concern of HRPC (regardless of the mean importance score); or 2) >25% of patients endorsed it as a concern of HRPC and it had a mean importance rating of at least 5.0 (moderately important). These selection thresholds are slightly more restrictive than those used

Table 4 Complications identified in open-ended section of patient interview and eligible for inclusion in the preliminary framework

Complication	Frequency of endorsement	Mean importance rating
Fatigue	9	7.44
General pain	3	6.00
Leg muscle soreness/weakness	3	5.67
Cognitive decline/memory loss	2	9.00
PSA anxiety	2	8.50
Diarrhea	2	7.50
Bone pain	2	6.50
Disrupted taste sensation	2	6.00

Note. Importance rated from 0 (not important) to 10 (extremely important).

Table 5 Complications/quality of life issues rated in the closed-ended section of the patient interview and eligible for inclusion in the preliminary framework

Complication or QOL concern	Frequency of endorsement (%)	Mean importance rating
PSA anxiety	15 (100%)	8.0
Fatigue	15 (100%)	6.5
Physical function	11 (73%)	7.2
Emotional distress	10 (67%)	6.9
Urinary problems (increased frequency, straining)	9 (60%)	6.7
Global QOL	9 (60%)	6.4
Constipation	9 (60%)	4.8
Functional well-being	8 (53%)	6.1
Erectile dysfunction	8 (53%)	5.6
Bone pain	7 (47%)	6.6
Peripheral neuropathy (tingling in hands or feet)	7 (47%)	5.7
General pain	7 (47%)	5.0
Diarrhea	6 (40%)	6.2
Masculine self-image	5 (33%)	7.4
Social function	5 (33%)	5.6
Appetite loss	4 (27%)	7.8

Note. Importance rated from 0 (not important) to 10 (extremely important).

for the open-ended complications because recognition is less cognitively challenging than recall. Table 5 displays the sixteen complications that met one of the inclusion rules (note: data on all 26 complications are available from the first author).

Combining results from the open- and closed-ended portions of the patient interview yielded a total of 19 unique outcome issues to serve as candidates for inclusion in the preliminary conceptual framework. Note that five of these selected issues appeared in both portions of the interview. Results from the practitioner surveys were next used to fully outline a preliminary version of the conceptual framework.

Practitioner surveys. Eight physicians (all male) and two nurses (both female) submitted completed surveys. The physicians represented the specialties of medical oncology (5), urology (2), and radiation oncology (1); one nurse worked in medical oncology, the other worked in urology. Geographically, six practitioners were based in the United States (three Midwest, two East Coast, one Mid-Atlantic), two were based in Australia, one was based in Canada, and another was based in Europe. Median age of the practitioners was 46.0 years (range 39–56 years). Most (70%) had already treated or cared for at least 500 HRPC patients and almost all (90%) had been treating or caring for HRPC patients for over 5 years.

In developing the PRO conceptual framework, we relied principally upon patient input, with support provided by practitioner input. Data from the practitioners were not used to elucidate any new outcome issues for inclusion in the framework, rather they were used to clinically verify and categorize the outcome issues already identified by HRPC patients as relevant. The 19 patient-endorsed candidate outcome issues were subjected to a clinical verification procedure using the data from the practitioner surveys. An outcome issue was considered "clinically verified" if more than 25% of practitioners endorsed it as relevant in either the open- or closed-ended section of the survey. Table 6 shows that 16 of the 19 patient-endorsed issues were verified by practitioners as being relevant to HRPC. Practitioners were also asked to make a judgment regarding the etiology of any disease-related issue that they endorsed. Response options included: 1) exclusively a disease symptom; 2) exclusively a treatment side effect; 3) both a symptom and side effect; or 4) neither a symptom nor side effect. The etiologic classification was determined by the vote of the majority of practitioners. Results are shown in the rightmost column of Table 6. Note that this judgment was not made for general QOL issues because general domains of QOL can be determined by multiple factors.

Preliminary version of the conceptual framework. Our preliminary version of a conceptual framework of PROs for metastatic HRPC features 16 outcome issues classified into five broad categories. These include the following: 1) specific symptoms of disease (overall pain, bone pain, urinary obstruction/frequency); 2) specific physical side effects of treatment (constipation, erectile dysfunction, peripheral neuropathy, diarrhea); 3) physical symptoms of disease and side effects of treatment (fatigue, appetite loss); 4) specific psychological concerns (PSA anxiety, change in self-image); and 5) general QOL and well-being (physical function, functional well-being, social function, emotional distress, global QOL). In step 3, we used quantitative analyses of archived PRO data to confirm and/or modify the preliminary framework into a final conceptual framework of PROs in metastatic HRPC.

Methods of Step 3—Analyses of Archived Data

We had available to us PRO data from a Phase III clinical trial of HRPC. Conducted in the early 1990s, this two-arm trial compared the palliative effects of mitoxantrone chemotherapy with prednisone to prednisone alone [21]. The dataset was particularly useful as it contained individual item-level responses on two PRO instruments, the Prostate Cancer-Quality of Life Instrument (PROSQOLI) and the Quality of Life Module-Prostate 14 (QOLM-P14) [22]. Collectively, these instruments represented many of the issues identified in our preliminary conceptual framework as well as a few issues not in the current version of the framework. This allowed us to test the fitness of the current

Table 6 Practitioner verification and etiologic classification of patient-endorsed concerns

Specific-disease related concern	Practitioner verified?*	Etiology†
Overall pain	Yes	Exclusively symptom
Bone pain	Yes	Exclusively symptom
Urinary problems (obstruction/frequency)	Yes	Exclusively symptom
Constipation	Yes	Exclusively side effect
Erectile dysfunction	Yes	Exclusively side effect
Peripheral neuropathy	Yes	Exclusively side effect
Diarrhea	Yes	Exclusively side effect
Masculine self-image	Yes	Exclusively side effect
Fatigue	Yes	Both symptom & side effect
Appetite loss	Yes	Both symptom & side effect
PSA Anxiety	Yes	Both symptom & side effect
Leg muscle soreness/weakness	No	N/A
Cognitive decline/memory loss	No	N/A
Disrupted taste sensation	No	N/A
General QOL concern	**Practitioner verified?**	**Etiology**
Physical function	Yes	N/A
Emotional distress	Yes	N/A
Global quality of life	Yes	N/A
Functional well-being	Yes	N/A
Social function	Yes	N/A

*A concern is clinically verified if it is endorsed by more than 25% of practitioners in either the open- or closed-ended section of the survey. †Etiology determined by the majority vote of practitioners. Possible responses included: (1) Exclusively symptom of disease (2) Exclusively side effect of treatment (3) Both a symptom of disease and side effect of treatment (4) Neither a symptom of disease nor side effect of treatment.
N/A, not applicable.

version of the framework (i.e., confirmation) and to potentially augment the framework with issues un-represented in the current version (i.e., modification). Approval to analyze these data was granted by the trial's principal investigator (Ian Tannock, MD).

Patients and procedure. One hundred sixty-one advanced HRPC patients participated in the trial comparing mitoxantrone + prednisone (n = 80) to prednisone alone (n = 81). All had documented metastases, were symptomatic, and had progressing disease despite standard hormonal therapy [21]. Patients randomized to the mitoxantrone arm received it intravenously every 3 weeks. All patients received oral prednisone at a dosage of 10 mg/day. Patients were examined clinically every 3 weeks at which time they completed the PROSQOLI and QOLM-P14 (note: the first or "baseline" assessment occurred at the outset of the first cycle of treatment). The PROSQOLI consists of nine linear analog self-assessment scales that relate to pain, physical activity, fatigue, appetite, constipation, urinary problems, family/marriage relationships, mood, and overall well-being. Each scale consists of a 100-mm line with anchors on the left (0) indicating poorest function/most symptomatic and the right (100) indicating best function/least symptomatic. A score of 50 is indicative of moderate function/symptomatology. The QOLM-P14, a prostate cancer-specific module developed according to guidelines of the EORTC, assesses pain, hair loss, disrupted taste sensation, fatigue, cognitive dysfunction, and urinary problems. Each of the 14 items is rated on a four-point ordinal scale (1-not at all, 2-a little, 3-quite a bit, 4-very much) with a higher score indicative of worse function/more of the symptom.

Baseline endorsement frequencies of the PROSQOLI and QOLM-P14 items were first determined. This allowed identification of problems occurring prior to the administration of any study treatments, ostensibly identifying disease symptoms as opposed to treatment side effects. We paid particular attention to those items endorsed as "moderately" to "severely" problematic by at least a third (33%) of patients. Moderately to severely problematic is defined here as a score of ≤ 50 on any PROSQOLI item and a rating of either "quite a bit" or "very much" on any QOLM-P14 item. We also plotted prospective mean scores for each item by treatment group to help determine whether these problems and concerns change with treatment. Area under the curve (AUC) analysis was used to compare the prospective item-level scores across treatment group. Specifically, the AUC was calculated for the *i*th individual using a trapezoidal approximation:

$$AUC_i = \sum_{j=1}^{n} (t_j - t_{j-1}) \frac{Y_{ij} + Y_{i(j-1)}}{2}, \; j = 1 \ldots n$$

where Y_{ij} indicates the item score and t_j indicates the time (cycle). To minimize bias due to missing data, we plotted scores for the first seven cycles only. By cycle 7, nearly 50% of patients had missing PRO data. For those patients dropping out prior to cycle 7, their worst observed score was assigned for all subsequent assessments in the AUC calculation. For intermittent missing data, linear interpolation was used to impute the missing value. The mean AUC was compared across the two treatment arms using two-sample *t*-tests.

Results of Step 3

Six of the nine PROSQOLI items were scored moderately to severely problematic by at least 33% of all patients at baseline. These included the following items: fatigue (61%), constipation (43%), pain (42%), overall well-being (36%), appetite loss (36%), and physical activity (33%). Furthermore, six of the 14 QOLM-P14 items were rated moderately to severely problematic by at least 33% of patients at baseline. These included the following items: taking medicine for pain (73%), feeling pain during physical activity (54%), pain interfering with social activities (48%), urination interfering with sleep (37%), pain interfering with family activities (37%), and pain while sitting or lying down (34%). Most of the outcome issues being addressed by these items are already a part of the preliminary conceptual framework. Hence, the baseline trial data confirm many aspects of the preliminary framework. One issue, taking medicine for pain, although not explicitly delineated within the framework, is subsumed within the domain of overall pain.

Results of the AUC analyses comparing prospective scores of the PROSQOLI and QOLM-P14 items across treatment group are shown in Table 7. There were no significant differences on any of the PROSQOLI items. However, the treatment groups did significantly differ on five items from the QOLM-P14: pain during physical activity ($P = 0.03$), pain while sitting or lying down ($P = 0.03$), pain remaining after taking medication ($P = 0.003$), upset by hair loss ($P = 0.003$), and bother about changes in taste sensation ($P = 0.004$). The corresponding curves of these items appear in Figure 2a–e. As Figure 2a–c show, pain appears to decline substantially more over the course of treatment with mitoxantrone chemotherapy than with prednisone alone. This further confirms the importance of a pain domain within the conceptual framework. The findings for hair loss and changes in taste sensation (Fig. 2d,e) provide evidence supportive of a modification in the preliminary framework. Patients treated with mitoxantrone chemotherapy became increasingly distressed by these problems over the course of treatment, more so than patients treated with prednisone alone.

Proposing a Final Conceptual Framework of PROs in HRPC

The final version of the conceptual framework of PROs in metastatic HRPC appears in Figure 3. It consists of the 16 outcome issues derived from the patient and practitioner queries, many of which were also confirmed by analyses of an archived dataset, as well as two additional issues determined to be relevant through the analyses of the archived patient data. Given that both hair loss and changes in taste sensation appeared to manifest after treatment with chemotherapy, they are classified as physical side effects of treatment in the final model.

Discussion

We used a combination of qualitative and quantitative methods to derive a conceptual framework of PROs for metastatic HRPC. Our final model included 18 outcome issues categorized into five general content domains, 1) specific physical symptoms of disease; 2) specific physical side effects of treatment; 3) physical symptoms of disease and side effects of treatment; 4) specific psychological concerns; and 5) general aspects of QOL and well-being. Though our study samples were small, they were not unrepresentative. Like most HRPC patients, most of the men in our study were symptomatic, had high and rising PSA levels, and were receiving a variety of treatments to control their disease including hormonal ablation, chemotherapy, and bisphosphonate therapy. Furthermore, the practitioners queried all had considerable experience caring for and treating HRPC patients, and were representative of all of the major medical specialties that treat HRPC. This coupled with the insights provided by analyses of a larger dataset of HRPC patients lends confidence in the robustness of our proposed framework.

Table 7 Area under the curve analyses of PRO data from the mitoxantrone trial in HRPC

	M + P*		P*		
PROSQOLI	N	Mean (SD)	N	Mean (SD)	*P*-value
Pain	79	433 (162)	76	400 (152)	0.190
Physical Activity	79	451 (142)	76	436 (134)	0.498
Fatigue	79	347 (151)	76	339 (156)	0.743
Appetite	79	452 (164)	76	455 (191)	0.909
Constipation	79	403 (160)	76	421 (189)	0.522
Relationships	79	587 (129)	76	587 (120)	0.997
Mood	79	472 (148)	76	471 (146)	0.948
Urination†	50	552 (143)	47	522 (176)	0.359
Well-being	79	435 (144)	76	426 (148)	0.700
QOLM-P14	N	Mean (SD)	N	Mean (SD)	
Pain during physical activity	79	14.8 (4.8)	76	16.5 (5.0)	0.030
Pain while sitting or lying down	79	13.0 (4.1)	76	14.6 (5.6)	0.033
Pain wakes you up at night	79	11.1 (3.8)	76	12.1 (4.7)	0.145
Pain interferes with enjoyment of family	79	11.9 (4.6)	76	12.7 (5.3)	0.327
Pain interferes with social activity	79	13.1 (4.6)	76	14.0 (5.9)	0.301
Upset by hair loss	79	8.5 (3.0)	74	7.4 (1.2)	0.003
Bothered by changes in taste	79	11.7 (4.3)	76	9.8 (3.5)	0.004
Felt drowsy	79	13.4 (4.5)	76	14.1 (5.1)	0.375
Felt confused	79	9.9 (3.6)	76	10.0 (3.7)	0.846
Taking medication for pain	79	18.0 (4.6)	76	18.8 (5.5)	0.358
Pain remained after taking medication	78	11.2 (3.0)	75	12.9 (4.1)	0.003
Dissatisfied with pain relief	79	10.0 (3.1)	75	10.5 (4.2)	0.398
Getting up at night to pass urine†	52	8.8 (2.7)	48	9.6 (4.0)	0.263
Nightly urination interfered with sleep†	52	14.1 (4.2)	48	14.6 (5.4)	0.572

*M + P = mitoxantrone + prednisone. P = prednisone alone. †Items reflecting urinary problems were added midway through the trial. PROSQOLI: Prostate Cancer Quality of Life Instrument. QOLM-P14: Quality of Life Module-Prostate 14.

A conceptual framework helps to specify the most important outcomes of interest in a given disease population. Pragmatically, it can be used to guide the development of an assessment strategy. In instances where existing outcome measures are lacking, the framework provides the supportive rationale for creating a new outcome measure. However, in contexts where suitable outcome measures already exist, the framework is no less useful as it can be used to select from among available instruments. In HRPC, standardized assessments of many of the outcomes featured in the final framework already exist. For example, the EORTC and FACT measurement systems offer general core instruments and prostate-cancer-specific modules that address most of the issues outlined in the framework. Furthermore, side effects of treatment can be efficiently captured using standard adverse event criteria, which can be either clinician- or patient-reported [23,24]. The decision to either use existing measures or create a new measure will depend upon the outcomes that are most salient to a given study as well as the relevance and quality of any existing measures. When relevant and high-quality measures are already available, as they would seem to be in this disease context, then creation of a new measure may be unnecessary.

Two other useful models are informed by the conceptual framework. A conceptual model of outcomes can provide a broader theoretical understanding of the disease and treatment process. Whereas the conceptual framework specifies a broad taxonomy of patient-focused outcomes relevant to a given disease or health condition, a conceptual model goes one step further by proposing causal linkages and relationships among these outcomes. Generic as well as disease-specific conceptual models have been proposed by others [5,6,25,26]. Such models are valuable as they can help clarify the expected impacts of a disease and its treatment on patient well-being. This can facilitate hypothesis generation and may even pinpoint targets for intervention. Although it is possible to hypothesize a conceptual model from our data, it is best considered preliminary, given the limits imposed by the small sample size and the collection of data at a single time point.

A second model potentially informed by this conceptual framework is an end point model one might conceive for a new clinical trial. Such a model shows the relationships across clinical, patient-reported, and other end points, and has relevance to investigators working in a regulatory approval context [4]. A sample end point model for a hypothetical treatment for HRPC is shown in Figure 4. Such models are the theoretical basis for the intervention and therefore provide the foundation on which a desired labeling claim rests.

Our study is not without limitations. First, as noted, we conducted semistructured qualitative interviews on a relatively small sample of patients. Interviewing more patients might have resulted in a different framework, though recent evidence suggests that as few as 12 interviews are enough to achieve saturation in thematic content [19]. Notably, we found that 89% of the outcome issues identified in the open-ended portion of the interview were reflected in the first 12 patient interviews. In the last three patient interviews, only four new outcome issues arose two of which were also queried in the closed-ended portion of the interview. Second, it is possible that the use of a different qualitative method such as focus groups would have produced different results. We chose the interview format for pragmatic reasons. One-on-one interviews were easier to schedule either before or after a routine clinic visit or in some cases between visits in the patient's home. Furthermore, we felt that some of the more symptomatic men would have greater difficulty traveling to a separate group session and therefore might be less inclined to participate. Third, diversity in the patient sample was limited by recruitment at a single clinical site in the midwestern United States with less representation of patients from racial and ethnic minority groups. Finally, although the confirmatory statistical analyses were a strength of our study, we had access to only one

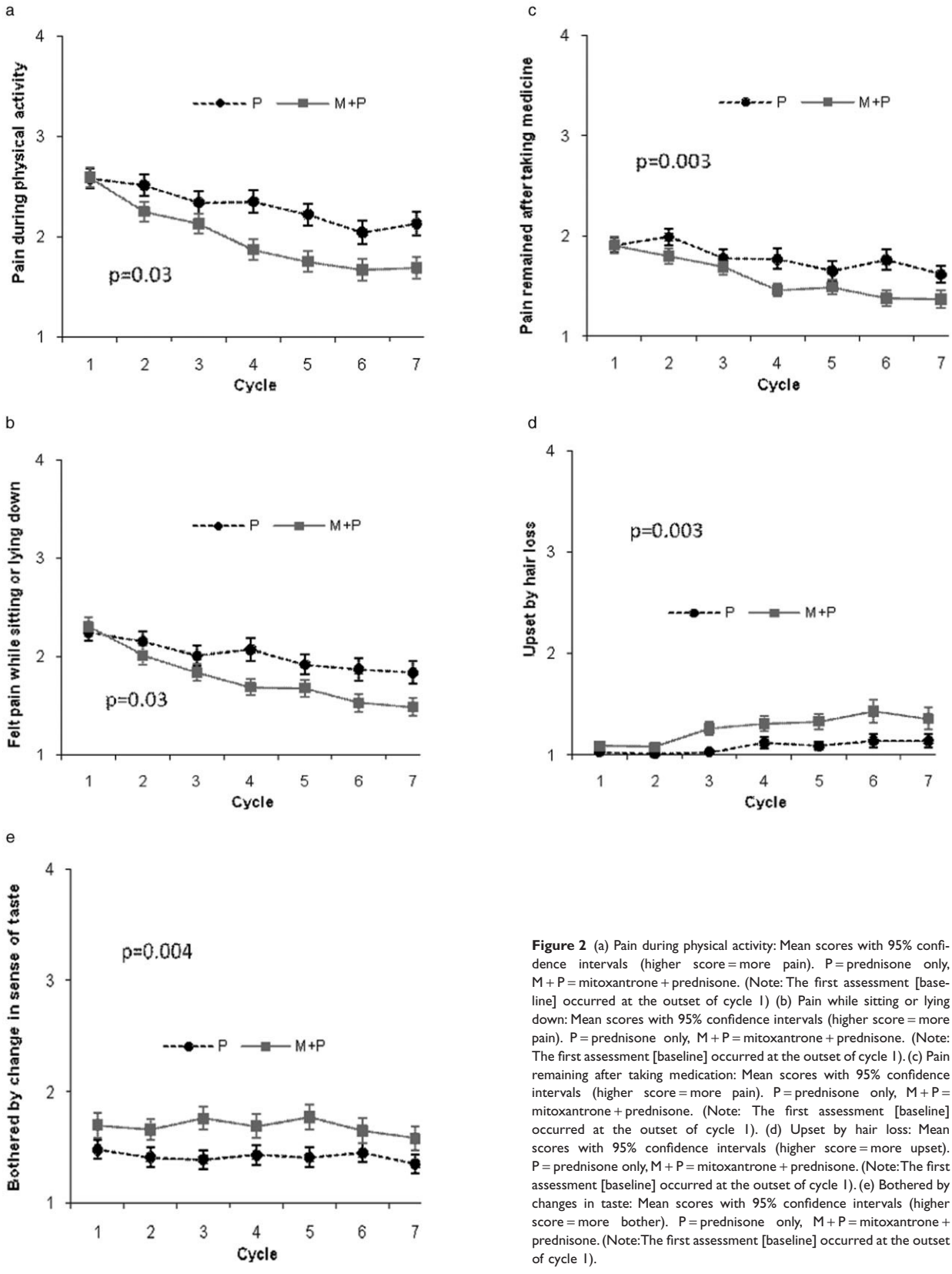

Figure 2 (a) Pain during physical activity: Mean scores with 95% confidence intervals (higher score = more pain). P = prednisone only, M + P = mitoxantrone + prednisone. (Note: The first assessment [baseline] occurred at the outset of cycle 1) (b) Pain while sitting or lying down: Mean scores with 95% confidence intervals (higher score = more pain). P = prednisone only, M + P = mitoxantrone + prednisone. (Note: The first assessment [baseline] occurred at the outset of cycle 1). (c) Pain remaining after taking medication: Mean scores with 95% confidence intervals (higher score = more pain). P = prednisone only, M + P = mitoxantrone + prednisone. (Note: The first assessment [baseline] occurred at the outset of cycle 1). (d) Upset by hair loss: Mean scores with 95% confidence intervals (higher score = more upset). P = prednisone only, M + P = mitoxantrone + prednisone. (Note: The first assessment [baseline] occurred at the outset of cycle 1). (e) Bothered by changes in taste: Mean scores with 95% confidence intervals (higher score = more bother). P = prednisone only, M + P = mitoxantrone + prednisone. (Note: The first assessment [baseline] occurred at the outset of cycle 1).

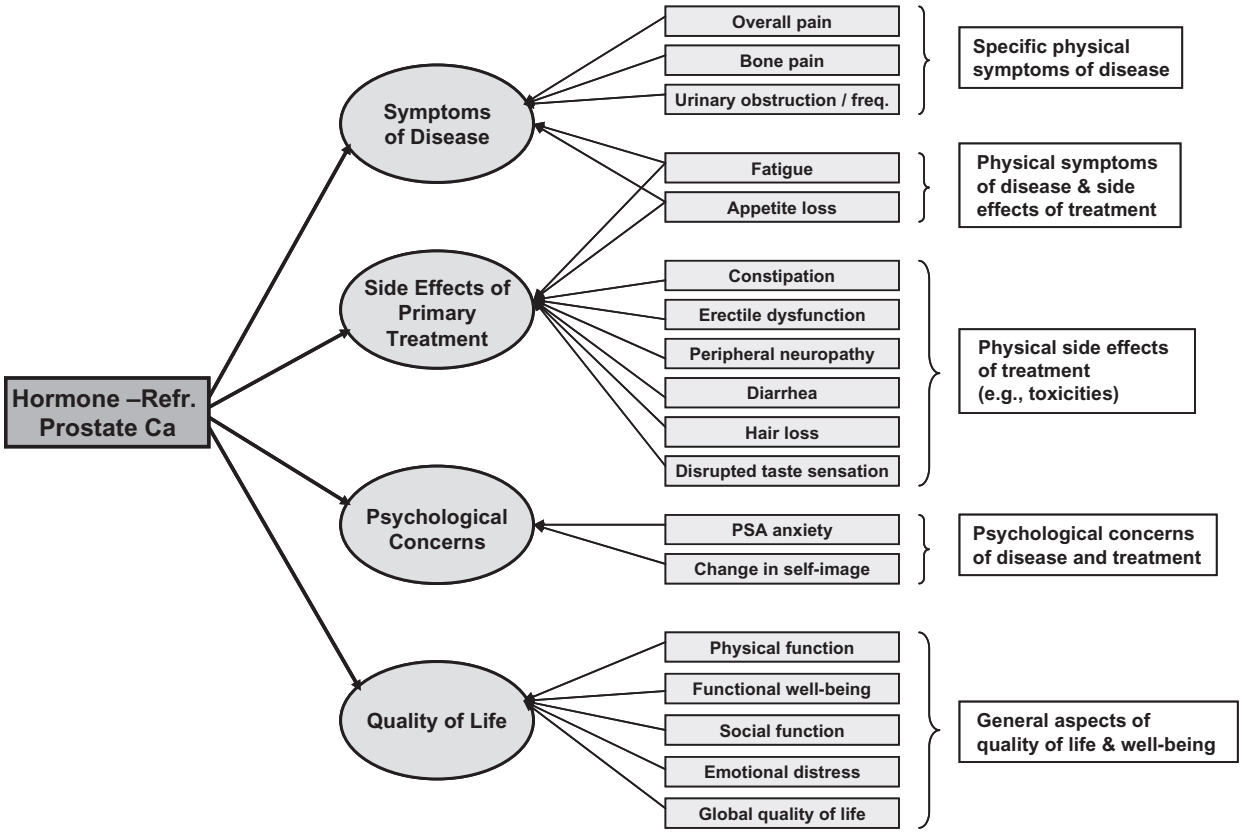

Figure 3 Final conceptual framework.

archived dataset of HRPC patients treated with a limited number of therapies. Availability of more item-level PRO data from a greater number of instruments and representing a wider range of treatments could have led to slightly different conclusions about the framework.

Conclusion

We have developed a conceptual framework of salient, patient-relevant outcome issues for metastatic HRPC. It identifies several critical target areas for assessment including, disease symptoms, treatment side effects, psychological concerns, and general aspects of QOL. The framework can help guide investigators in the selection of outcomes and may even help pinpoint areas suitable for intervention. Although it may be revised as new data are made available and new therapeutics are discovered, this initial version can serve as the basis from which future conceptual frameworks and models can be derived.

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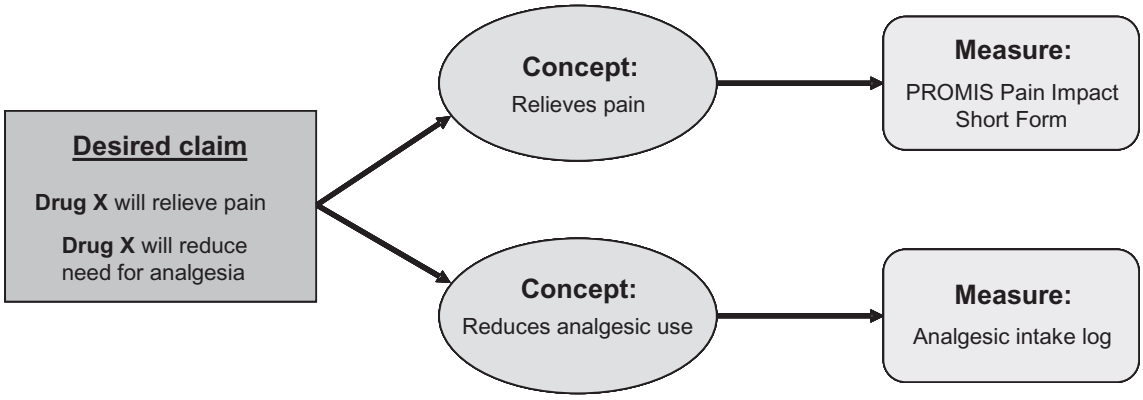

Figure 4 Hypothesized end point model for a hypothetical treatment of hormone-refractory prostate cancer.

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