*Special Article*

# Measuring Outcomes in Randomized Prospective Trials in Palliative Care

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***Abstract***

*Palliative care aims to improve the quality of life of patients and their families and reduce suffering from life-threatening illness. In assessing palliative care efficacy, researchers must consider a broad range of potential outcomes, including those experienced by the patient's family/caregivers, clinicians, and the health care system. The purpose of this article is to summarize the discussions and recommendations of an Outcomes Working Group convened to advance the palliative care research agenda, particularly in the context of randomized controlled trials. These recommendations address the conceptualization of palliative care outcomes, sources of outcomes data, application of outcome measures in clinical trials, and the methodological challenges to outcome measurement in palliative care populations. As other fields have developed and refined methodological approaches that address their particular research needs, palliative care researchers must do the same to answer important clinical questions in rigorous and credible ways.* J Pain Symptom Manage 2007;34:S7–S19. 

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*Death, quality of dying, outcome assessment, quality of health care, quality indicators, health care, end-of-life care, family, proxy, terminal care, attitude to death*

## *Background*

The World Health Organization (WHO) defines palliative care as " … an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1] The goal of clinicians, researchers, and policy makers should be developing and implementing high quality, cost-effective approaches to providing palliative care to patients who are suffering from chronic disease or are near the end of life.[2–4] The definition of palliative care suggests that research in patients with advanced illness needs to consider a broad range of patient outcomes. Qualitative and observational research has created a greater understanding of the important aspects of palliative care and identified relevant targets for intervention studies to improve clinical practice at the end of life. Clinical research can guide care improvement and policy innovation in palliative medicine by determining best practices through the conduct of intervention trials using the most robust designs. For discrete clinical questions, the prospective randomized controlled trial (RCT) design best controls bias and chance in evaluating efficacy and thus maximizes the rigor and utility of the evidence.

Given the importance of the RCT design to improving palliative care delivery and outcomes, it is notable how few RCTs have been conducted in the field.[5,6] Moreover, outcomes assessment in patients who are near the end of life presents unique methodological challenges.[7–16] As part of an effort to advance the palliative care research agenda, an international, interdisciplinary panel of palliative care experts met in Pasadena, California in November 2004 to address methodology in RCTs in palliative care. The general goal of the meeting was to address core conceptual and operational issues facing clinical research in palliative care by developing an exemplary randomized trial for the treatment of malignant bowel obstruction (MBO). As part of the larger meeting, an Outcomes Working Group discussed conceptual and methodological issues surrounding clinical trial evaluation strategies. This article summarizes the Working Group's discussions and provides recommendations that are meant to aid researchers in developing RCTs in palliative care.

## *Conceptualizing Outcomes in Palliative Care Research*

As evaluations of palliative care interventions evolve to use RCT methodology, clinically relevant and valid outcomes assessment is required. The conceptual basis of outcomes assessment recognizes that clinical care innovations should be evaluated by measurable improvements in aspects of value to patients.[17,18] In palliative care, the patient's and his or her family's subjective experience and perspective are widely regarded as the appropriate vantage point from which to identify the relevant research endpoints and evaluate the outcomes of palliative care.[1,4]

### *Recommendation: Outcomes Measurement Should Assess Multidimensional Aspects Shown to Be Important to Patients with Advanced Disease*

Patients with advanced disease face a wide range of physical, emotional, social, and spiritual challenges. Studies have elucidated relevant domains of value to patients with advanced disease and their families,[18–25] and most recently, the National Consensus Project has organized guidelines around particular aspects of care in their *Clinical Practice Guidelines for Palliative Care*.[4,26] We identified nine research-relevant, patient-reported, or family member/caregiver-reported outcome domains (see Table 1) for evaluation of palliative and

*Table 1*
**Domains and Selected Examples of Measures for Research in Palliative and End-of-Life Care**[a]

| Domain | Measurement Tools |
|---|---|
| Symptom management | McGill Pain Questionnaire, Wisconsin Brief Pain Questionnaire, Brief Pain Inventory, Memorial Pain Assessment Card, Edmonton Symptom Assessment System, Memorial Symptom Assessment Scale, Profile of Mood States, Center for Epidemiologic Studies Depression Scale, and RAND Mental Health Inventory |
| Whole person and maintaining QOL | QUAL-E, McGill QOL Questionnaire, Missoula-VITAS QOL Index, European Organization for Research and Treatment of Cancer QOL Questionnaire Core 30, Functional Assessment of Cancer Therapy—General, and QODD |
| Functional aspects | Index of Independence in Activities of Daily Living Barthel Index, Physical Self-Maintenance Scale, Rapid Disability Rating Scale, Stanford Health Assessment Questionnaire, and Functional Independence Measure |
| Satisfaction | TIME After-Death Bereaved Family Member Interview, Quality of End-of-Life Care and Satisfaction with Treatment (QUEST), Medical Outcome Study Satisfaction Survey, Family Satisfaction in the Intensive Care Unit, Picker-Commonwealth Survey, and FAMCARE Scale |
| Relationships | Meaning in Life Scale, QODD, and TIME After-Death Bereaved Family Member Interview |
| Decision making and care planning | TIME After-Death Bereaved Family Member Interview, POS, and QUAL-E |
| Continuity and communication | POS, QODD, QUEST, Picker-Commonwealth Survey, Smith-Falvo Patient-Doctor Interaction Scale, and McCusker Scale |
| Family burden and well-being | Caregiver Strain Index, Caregiver Reaction Assessment, Grief Resolution Index, and Anticipatory Grief Scale |
| Quality of death and end-of-life experience | Spiritual Well-Being Scale, Spiritual Perspective Scale, Death Transcendence Scale, POS, QUAL-E, QODD, and TIME After-Death Bereaved Family Member Interview |

[a]See TIME (http://www.chcr.brown.edu/pcoc/toolkit.htm) and end-of-life care and outcomes summary (www.ahrq.gov/clinic/epcsums/eolsum.htm) for additional measures and information.[18,27,30]

end-of-life clinical trials based on data from patient and family/caregiver surveys, focus groups, consensus processes, and intervention studies.[4,21–24,26–31] The domains of symptom management, whole person and maintaining quality of life, functional abilities and aspects, satisfaction, relationships, decision making and care planning, continuity and communication, family burden and well-being, and quality of death and end-of-life experience point to possible outcome endpoints. These domains are not all inclusive and should not be considered essential elements of all trials. Despite knowledge of valued population-level domains, researchers should acknowledge and attempt to assess the individual and personal nature of the dying process, as Danis suggests that, "…we must find measures that indicate whether we are addressing the needs and goals of each dying patient."[32]

The broad range of outcome domains and the mix of perspectives that create comprehensive palliative care plans[33,34] suggest the need for interdisciplinary research teams to define important measures and approaches. The Working Group felt that given the highly subjective nature of many outcomes, interdisciplinary input into outcome measures design is critical.

### *Recommendation: Dying and Death Are Distinctive Entities, and End-of-Life Study Endpoints Should Consider the Unique Dimensions Where Death Is Anticipated Among Participants*

Among the dimensions of palliative care, different priorities and unique aspects exist with the end of life or death. Researchers have sought to develop conceptual models and metrics for essential palliative care domains, focusing substantial attention on measures of a "good death."[20,22,23,28,35–37] The Institute of Medicine (IOM) definition of a good death includes three aspects: that dying be free from avoidable distress and suffering for patients, family, and caregivers; in general accord with patients' and families' wishes; and be reasonably consistent with clinical, cultural, and ethical standards.[19] Even at the end of life, people have priorities that extend beyond just domains of comfort and closures. When conducting palliative care research, we should

understand that people have a "widespread and deeply held desire not to be dead."[38] We recognized that our exploration of appropriate measures needed to include the ambiguity of prognosis and the value people and their families place on the duration of life in concert with QOL and the relief of symptoms. As such, outcomes measurement in clinical trials should account for the distinct dimensions of QOL near the end of life and quality of the dying experience (see Table 1 for some categories of outcomes and examples of measures within each domain), and should consider accounting for survival duration, as appropriate.

### *Recommendation: Interventional Trials Should Consider Outcomes Experienced by Caregivers*

Outcomes assessment in palliative care departs from that in nonpalliative populations in that palliative care extends its responsibility beyond the patient to include caregivers. Research has demonstrated that provision of end-of-life care for patients has an important impact on family members' health and socioeconomic well-being.[4,19,23,39] Among endpoints relevant to caregivers are the dimensions of satisfaction with care, optimizing relationships at the end of life, participation in decision making and care planning, maintenance of continuity and quality of communication, and family burden and well-being.

### *Recommendation: Outcomes Assessment Might Also Consider Aspects of Health Care Systems, Delivery, and Society as a Whole*

The conference participants also recognized that outcomes cannot be simply viewed from the vantage of maximal comfort achieved or personal participant gain. From the IOM definition,[19] we recognize that investigators could consider clinician and societal perspectives as complementary to patient-family focused endpoints to provide a more complete evaluation of end-of-life care. The health care system and the larger societal context where our patients live and interact are also within the responsibility of investigators studying clinical interventions. Given the burden of utilization and resulting costs faced by health care delivery systems and society as a whole in caring for patients near the end of life,[40,41] the conference attendees acknowledged that investigators could attempt to incorporate societal perspectives into a complete evaluation of care. Future endeavors might develop both the tools and the means to include such societal perspectives into comprehensive assessments.

### *Recommendation: Intervention Study Endpoints Should Be Guided by a Conceptual Framework Appropriate to the Disease and Treatment Options*

We suggest that researchers frame the evaluation of interventions within a generalized conceptual model using three outcome categories that draw on general palliative research outcome categories: condition-specific outcomes, personal outcomes to the patient, and family/caregiver outcomes (see Table 2). Theoretical models help to frame and identify relationships between core domains and the translation to subjectively valued outcomes of palliative and end-of-life care.[13,20,22,23,28,35–37] Aligning these specific models with disease-specific paradigms may optimally drive selection of variables, analysis, and design (such as issues of equipoise) in palliative care trials. Fixed patient characteristics, such as disease status and demographics, are important in identifying risks for particular palliative needs and for specifications in measurement.

*Table 2*
**Categories and Example of Palliative and End-of-Life Care Outcomes in a Trial of MBO Therapies**

| Condition-related outcomes | Patient-related outcomes | Family related outcomes |
|---|---|---|
| Survival duration | Ability to return home | Caregiving burden |
| Symptoms | QOL (physical, emotional, social, spiritual) | Emotional distress |
| Impairment to eating | Satisfaction with decision making | Financial burden |
| Resource use (hospital days, rehospitalization rates) | Overall patient satisfaction | Family perception of the quality of patient's care |
| Medical expenses | Rating of worth of intervention | Family satisfaction |

Modifiable dimensions, such as symptoms, control of events, social support, beliefs, and economic issues, suggest key targets of palliative and end-of-life interventions. Care system interventions are particularly good targets for process interventions and evaluations.

In our discussion below, we will take the reader through an approach to designing a palliative care outcomes measurement strategy, with examples from our MBO discussion. We begin by categorizing outcome areas as they relate to a clinical trial intervention and consider the types of outcome data that must be collected from the patient and/or caregiver as well as other sources, including chart review and administrative data.

## Sources of Outcomes Data

Palliative care's diverse range of outcomes requires the development of innovative approaches to capture the potential impact of clinical trial interventions. We will focus our attention on measurement approaches for domains most likely affected by an intervention, such as managing symptoms, multidimensional QOL, functional aspects, family well-being, survival duration, and resource use.

### *Recommendation: Researchers Should Collect Data from Multiple Sources in Intervention Trials for Complementary and Comprehensive Outcome Evaluation*

Researchers have a variety of data sources for outcomes assessment among palliative care domains, including chart reviews, administrative data, and patient and family surveys. Chart reviews and administrative sources can provide clinical data, including use of medical interventions (e.g., medications prescribed, surgeries performed), utilization (e.g., emergency department visits, hospital days), and cost. Such objective sources may appear to provide more reliable and rigorous data on intervention outcomes and may sometimes be considered more trustworthy than patients' own reports of their subjective experiences. Acquisition of these data also is not limited by patient ability or willingness to participate as is true with surveys. However, researchers using these sources may miss patient-family valued outcomes in palliative and end-of-life care. Researchers must also account for incomplete data from medical use outside of the trial facilities, necessitating additional data collection from the patient and/or caregiver. For example, to assess the possibility that a patient was taken to an emergency department, researchers might need to ask patients/caregivers, "In the last month how many different times did you have to go to an emergency department?"

### *Recommendation: Patient-Reported Outcomes Should Be Assessed by Measures That Balance Simplicity, Parsimony, and Psychometric Rigor*

Questionnaires can assess domains of interest through various types of instruments, including single items, symptom-specific batteries of items, generic and condition-specific multidimensional QOL instruments, and after-death family survey tools. The best approach for selecting a questionnaire in a particular trial will partially be dictated by the relevant condition, the intervention, and other practical considerations. Single items may be attractive because they carry a low burden to respondents and responses are easy to report to readers. A number of single items have been validated as global assessments of health status ("How would you rate your overall health?")[42–44] or as screening tools (e.g., for depression, "Over the past two weeks have you frequently felt depressed?"). Single items, however, are limited in that they can assess the patient's experience only very generally, with more in-depth understanding requiring additional questions. In addition, single-item measures generally have more variability, while including more than one question within a measure typically reduces that variability.[45] Health-related quality of life (HRQOL), an increasingly important endpoint of trials in subjects with significant illness, has unique limitations in end-of-life and palliative care research. Functional independence as measured by, say, performance status has been demonstrated to be positively correlated with HRQOL.[46] At the end of life, however, once the assumption of restoration of functioning ends, the relationship disintegrates. The evaluation of HRQOL or therapeutic responses may be very different from a rating of the dying experience.

*Recommendation: Intervention Studies Should Use and Adapt Existing Measures When Appropriate and Expand the Testing of Such Instruments for Validity and Reliability Across Diseases, Settings, and Populations as Part of RCTs*

A number of individual measures have been developed with varying degrees of psychometric rigor and applicability. Many instruments have not been tested beyond narrow populations, conditions, and settings. A useful web-based repository for patient-focused, family-centered instruments was created through a collaborative effort coordinated by Dr. Joan Teno and is called the Toolkit of Instruments to Measure End-of-life care (TIME).[27]

The Toolkit[27] reviewed nearly 1,000 articles published from 1967 through 2000 and selected 293 measures as potentially relevant to end-of-life care research. The Toolkit further recommended 35 measures based on the following characteristics: 1) patient focused, family centered, clinically meaningful, and manageable in their application; 2) reliable, valid, and responsive; 3) user friendly and relevant to quality evaluation and improvement; 4) incorporated both the patient and family perspectives; and 5) examined both the process and outcomes of care. An update from a systematic review of end-of-life care outcome measures[30,47] identified additional instruments and recommended three newer multidimensional measures: the Quality of Life at End of Life (QUAL-E),[48] the Quality of Dying and Death (QODD),[20,49–51] and the Palliative Care Outcome Scale (POS).[52,53]

## Applying Palliative Outcome Domains to Clinical Trials

Clinical researchers faced with a range of potential outcome areas must focus measurement strategy on outcomes that are valued by patients and/or families but also on outcomes, which the intervention being tested might reasonably be expected to impact. Historically, researchers have undervalued the first focus and neglected to measure important QOL and family outcomes. At the same time, it may not be appropriate to include the full range of outcomes in a given clinical trial. Most trials are designed to test interventions targeting specific aspects of a patient's illness experience that may not affect palliative domains far removed from the intervention target. For example, a trial of pharmacological vs. behavioral management of nausea would be hard pressed to affect a patient's spiritual well-being or family burden. At the same time, it is important that researchers consider a broad range of palliative domains and measurement tools and develop a detailed conceptual model for direct and indirect outcomes of the intervention. One organizational strategy we propose is to use three categories of outcomes (see Table 2): condition-related outcomes, person-related outcomes, and family-related outcomes.

*Recommendation: Outcomes Measurement Should Include Attention to Condition-Related Outcomes, Patient-Related Outcomes, and Family-Related Outcomes*

Condition-related outcomes are directly and physiologically related to the disease and/or intervention in question. In the example of nausea, frequency and severity of nausea and vomiting would be the most obvious condition-related outcomes. Impact of nausea and vomiting on other domains, including sleep, energy, and other areas, as well as satisfaction with control of nausea or vomiting specifically, would also be conceptually relevant. Validated, condition-specific measures have been developed for a wide variety of symptoms including pain, dyspnea, nausea, anxiety, and other physical and psychological symptoms, as well as symptom clusters associated with particular disease states.

Patient-related outcomes may include more subjective and value-laden palliative domains that may be impacted more indirectly but that represent a more personal experience of a study intervention than is captured by condition-specific measures. In the nausea management example, researchers may identify broader QOL constructs, such as social and role functioning related to nausea, coping, and perceived control over one's symptoms, as conceptually relevant. Patient satisfaction with the overall treatment, which incorporates not only condition-specific symptom control but also the burdens associated with the intervention, would also represent a patient-related outcome. For clinical trials involving crossover designs (i.e., sequential application of the experimental interventions being compared),

the patient's preference among the treatments is often an excellent way to assess comparative global satisfaction. With other experimental designs, global satisfaction items might ask patients the degree to which going through the intervention was "worth it," whether the patient would choose to continue the treatment, and/or whether the patient would recommend the treatment to others facing the same circumstances.

Other concepts that may be applicable include assessing "hope" or "will to live" as related to survivorship and goals, especially as an influence to participation in phase I trials or as a covariate to trial participation and assessment of personal benefit. Assessing expectations or beliefs in different treatment arms may also be considered as a mediator to determining personal outcomes. Another possibility is assessing "the bottom-line" as a threshold or subject-defined construct to capture the overall assessment of an RCT treatment effect. These types of items integrate a wide variety of patient-, treatment-, and trial-related factors and may be useful in capturing aspects of the global patient experience that are difficult to measure using other instruments.

The third category of outcome measures involves the family and/or caregiver perspective. Caregivers are important sources of outcome data for three reasons. First, interventions affect caregivers in important ways and this impact may differ dramatically across treatment categories. In the MBO trial, for example, described below, the aspects of caregiver burden in providing postoperative care for surgery patients (e.g., wound management, ostomy care) are different in scope from those for medically managed patients (e.g., managing ongoing or recurrent obstructive symptoms, managing nasogastric drainage) and should be addressed in family-related outcomes assessment. Second, as the individuals closest to the patient, caregivers are likely in the best position to act as surrogate respondents in cases where the patient is unable to provide data due to progressive illness or mental incapacity. Studies examining patient-proxy concordance suggest that overall congruence between patient and proxy evaluations is moderate, with more observable areas (e.g., physical function, vomiting) having higher agreement and more subjective areas (e.g., pain, QOL) having less agreement.[54] While caregivers may not be ideal substitutes for patients' own responses, given caregivers' investment in patient well-being and the role patients expect them to play in their care and in decision making,[55,56] caregivers will continue to be relied upon to provide surrogate data for patients unable to respond.

Caregivers are important sources of information about the final days/weeks of the patient's life, usually when the patient is too ill to respond, and can reflect on the extent to which the patient's end-of-life experience matched his or her conception of a "good death." Such data are usually collected from after-death interviews, typically conducted anywhere from weeks[57] to a year or more[36] after the patient's death. After-death interviews have been used to assess many aspects of the patient's dying experience and a number of instruments are currently available to achieve this goal (see Table 1).

### *Example of Considerations in Selecting Outcomes for an RCT for MBO*

An RCT comparing surgical vs. medical management of MBO provides an excellent example of how applying a palliative care framework leads to substantially different outcomes measurement design than may be the traditional norm for clinical trials. Patients with MBO have a median life expectancy of approximately three months depending on diagnosis and prior functional status, and initial medical (rather than surgical) management is often associated with short-term clinical improvement.[58] Recurrence, however, is frequent and is associated with inability to eat, severe symptoms, rehospitalization, and other morbidity as well as mortality. Early surgical intervention is associated with an initial risk of surgical complications and mortality, as well as postoperative discomfort, the risk of complications (e.g., infection, wound dehiscence due to malnutrition), and an extended hospital stay during the postoperative period. However, if successful, early surgical intervention enables a patient to resume eating, and the patient may go home with his or her physical symptoms controlled for a period of time, although subsequent recurrence (range, 10%–50%) and repeated hospitalizations with consequent morbidity and mortality can still occur.[59] Symptoms related to MBO

depend on the location of the obstruction and may include constipation, bloating, nausea and/or vomiting, and pain. Some condition-related outcomes for the MBO trial that result from the condition, as well as its treatment, are listed in Table 2.

The two different therapeutic approaches compared in the trial may also carry important personal meaning for patients approaching the end of life based on the quality of the palliative outcomes described above. Patients may regard time at home with family as an outcome to be cherished, or, alternatively, avoided if it means dependency on loved ones or family memories of a terminally ill, rather than robust, patient. The ability to eat carries great importance to many individuals, even at the final stages of illness. The sense of being a "whole person" near the end of life varies across individuals and across cultures, and measuring the extent to which medical or surgical treatment of MBO permitted individuals to retain that sense may be important to assess. Finally, caregivers are likely to be differentially affected depending on whether a surgical or medical approach is used. Physical caregiving burdens, emotional stress associated with patient experience of symptoms, and caregiver perceptions about how the chosen management approach affected their relationship with their loved one are all relevant clinical trial outcomes. In sum, conceptualizing medical and surgical treatment outcomes for MBO within a palliative framework permits the researcher to develop outcome measures that reflect the patient's perspective when determining the benefits of the respective interventions.

## *Practical and Conceptual Challenges to Outcomes Measurement*

Patients entering palliative care trials are by definition facing limited life expectancy and progressive illness characterized by decreased energy and attention span, and high rates of cognitive impairment. The anticipated morbidity over the course of a trial may limit participants' ability to report their subjective experience.[60–63] For researchers, numerous decisions need to be made, including whether to include and/or how to prioritize patient-reported data as a measured outcome, timing of initial evaluation, the length (in terms of number of items and/or time required to complete) of the evaluation, and when evaluations will be repeated.

### *Recommendation: Outcomes Assessment in Palliative Care Should Minimize Respondent Burden*

While outcomes measurement would ideally center on patient and family reports of their own subjective experiences, a number of practical considerations often limit investigators' ability to elicit this information. Clinical researchers need to examine in detail the clinical course, including the range in trajectory toward death, that patients entering a clinical trial are expected to have and to make adjustments as needed in the assessment strategy. In the MBO trial, for example, upon admission to the hospital patients may be so sick as to preclude an in-depth initial interview. Delaying the baseline interview by 24 to 48 hours might improve our ability to obtain patient-reported data, although it would likely impact on the data collected, as symptoms often improve following initiation of treatment and recall bias may distort the report. Given that a delay between enrollment and baseline evaluation would be expected to occur equally across the randomized groups, improvement would not be expected to bias the results. However, documenting and comparing the length of delay between study groups would help to assess whether response bias may have occurred.

Survey instrument length and question ordering are other important considerations in the design of patient-reported outcome assessments. Few data are currently available on appropriate survey instrument length in a palliative population, and MBO panel members reported survey administration times in their own trials of as little as 10 minutes and as long as 60 minutes. However, there is general agreement that patients who are weak or suffering from pain, nausea, or other symptoms may not be able to tolerate a lengthy interview. This limitation may force the researcher to pare down the measurement domains to those that are most essential to the trial, choose measurement tools that validly capture each domain with as few questions as possible, or both. In addition, if patient endurance is a major concern, the researcher may choose to

order the highest priority items near the beginning of the survey instrument to maximize response rates for those items.

*Recommendation: Strategies for Handling Nonresponse Due to Progressive Illness and/or Death Should Be an Integral Part of Study Design*

In contrast to the situation with less ill populations, missing data ("loss to follow-up") in palliative populations are typically not due to random events (e.g., due to a patient moving out of state or disconnecting his telephone) but to progressive illness or death, which may in turn be related to the study intervention. In traditional clinical trials, death may be regarded as the ultimate adverse health outcome, being reported on its own as a mortality statistic or being assigned a QOL value of "0."[64] In palliative care populations, however, where progressive disability and death are expected, weighting deaths as equivalent to zero QOL may not be sufficient.[65] For some determinations, such as quality-adjusted life years, other states of health may be considered worse than death and assigned negative numbers for computation. In excluding missing data due to death or progressive illness from both the numerator and denominator during data analysis (a common practice), an investigator risks missing important intervention effects. A few researchers have proposed assigning death a nonzero QOL value based on complex statistical methods.[66] While each of these approaches has its underlying assumptions and limitations, given the high rate of loss of follow-up data due to death or progressive illness, researchers should work with a statistician to plan in advance which approach is most appropriate given their research goals.

Timing and frequency of follow-up evaluation are important. Researchers need to estimate a sufficiently long time interval from baseline to identify intergroup differences in clinical outcomes, but at the same time not so long an interval that disease trajectory, leading to progressive disability and/or death, would preclude follow-up data collection for many or most participants. In the MBO trial, for example, the researcher might develop a patient survey plan that includes interviews in the early period following initiation of the surgical or medical intervention (e.g., two weeks following study entry) and limits patient follow-up surveys to three months following study entry, at which point approximately half of study participants would have died.

The challenge of obtaining patient responses in a compromised palliative care population requires consideration of whether data sources other than direct patient-reported outcomes should be selected as the primary study outcome.[67–71] Meaningful conclusions from patient-reported outcomes may be precluded if a large number of patients are too ill at study entry to complete a baseline interview and/or if there is an exceedingly high rate of dropout (due to death or incapacity). Alternatives to patient surveys include caregivers as surrogate respondents, recognizing that surrogates are more accurate at estimating observable patient variables (e.g., ability to ambulate or toilet oneself) than subjective patient experiences (e.g., pain or QOL). Reliance on caregivers as proxy respondents in a high percentage of cases might raise doubts about the validity of study findings.

The concern about patient nonresponse was especially important in discussions regarding an MBO trial where a substantial number of patients were anticipated to be unable to complete baseline or follow-up assessments even if measures were designed specifically to limit instrument length and time burdens. The Working Group sought a primary outcome that was patient centered (i.e., includes domains of known importance to MBO patients), but also an outcome that did not rely on patient responses alone. The Working Group arrived at two potential indicators of patient "good days" following study enrollment: 1) days out of the hospital without a nasogastric tube, and 2) days out of the hospital with little or no nausea (this latter outcome would require limited patient-reported data). We believed that these outcomes capture elements important to patients—time at home, comfort, relief from invasive interventions, survival duration—while minimizing the risk of patient nonresponse associated with lengthy patient survey instruments.

*Recommendation: Researchers Should Anticipate Different Results in Some Measures as Death Approaches and Plan Secondary Endpoints Accordingly*

Researchers using QOL as a palliative outcome measure should be aware of the concept

of *frame shift* or *response shift* in which the generally positive correlation between physical functional independence and QOL appears to disintegrate in patients who are near the end of life.[72] In some patients, as physical health worsens, the relative importance of physical health may pale compared to other domains, such as social and spiritual health. As a result, the person's global evaluation of life quality may be remarkably preserved even in the face of clear physical deterioration. While a philosophical discussion about how such adaptation should be interpreted is beyond the scope of this discussion, it is important that researchers be aware that global QOL ratings may be preserved (or relatively nonresponsive to physical decline) even as patients are close to death.

Planned secondary patient outcome measures might include QOL (including symptoms), satisfaction with the assigned intervention, survival duration, days out of the hospital, and resource use (e.g., hospital days, ICU days, and medical expenses). Additional outcomes may include after-death surveys of caregiver burden, satisfaction measures with the assigned intervention, and perception of the quality of the patient's dying experience.

Given the range of potentially relevant outcomes, the researcher needs to identify "primary" and "secondary" study endpoints. The prioritization process is important for two main reasons. First, part of the conceptual basis for outcome measure selection is identifying a conceptual hierarchy of valuation of the outcomes to patient, caregiver, and/or the health care system. Selecting a primary outcome measure informs those interpreting the trial's results of the investigator's a priori commitment to an outcome that is considered most important in demonstrating the investigational interventions. Second, determination of a primary study outcome enables statisticians to determine the number of trial participants required to detect a prespecified difference (i.e., effect size) between the experimental groups at a given type I error rate (i.e., $\alpha$ or the false positive rate) and power (i.e., one minus the false negative rate or the probability of rejecting the null hypothesis when it is indeed false). For instance, a power analysis might state that "a sample size of 80 (40 per group) will provide at least 80% power (given $\alpha = 0.05$) to detect relatively small group differences (effect sizes of 0.30 or greater) with regard to the primary outcome." Inclusion of multiple outcomes within the primary analysis typically requires adjustments in the power calculations (e.g., a multiple comparison adjustment such as a Bonferroni correction[73]) and often necessitates a larger sample size. Also, specifying detection of small differences generally increases the number of needed subjects to attain a statistically significant result between groups.

## Conclusion

Palliative care faces a major challenge in building a base of research evidence to support a role consistent with other medical subspecialties. Just as other fields have progressively developed and refined research methodologies to meet the particular research needs of their fields, palliative care must develop a set of research approaches that will yield valid answers to important clinical questions. The unique features of palliative care require new conceptual models and additional measurement tools to augment those traditionally used in clinical trials research. While some work has been conducted in this area, numerous theoretical and measurement issues remain unresolved. The expert conference on which this article was based was designed as a step to address the work ahead. Based on substantial interest from public and private research funding organizations, the Working Group expects that opportunities for funding of both outcomes measurement research and RCTs in palliative care will only increase. Further, as quality of care assessment, reimbursement, and other policy decisions depend on evidence, research in palliative and end-of-life care will need to consider and be responsive to societal and health policy trends and the need to measure the quality, effectiveness, and efficiency of care.[2,3,28,47]

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