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Developing the Evidence Base for Palliative Care: Formation of the Palliative Care Research Cooperative and Its First Trial

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Abstract

The field of palliative care and hospice has gained accreditation, with a growing cadre of specialists being trained, but there is a dearth of robust research evidence to guide clinical practice. After 2 years of planning, a group of senior investigators convened in January 2010 to explore the possibility of forming a research cooperative group dedicated to advancing the evidence base in palliative care and hospice. The meeting launched the Palliative Care Research Cooperative (PCRC) with an initial national/international membership, and a plan for developing policies and procedures. Proof of the concept for the PCRC is being established through the design, conduct, and dissemination of a multi-site clinical trial targeting a consensually selected, clinically relevant research question: Should patients who are taking statins for primary or secondary prevention, and who have a prognosis of < 6 months, discontinue these medications? A core group of PCRC members have developed the flagship study for the PCRC, evaluating the discontinuation of statin medications in the palliative care setting. Using the proposed trial as a case study, we underscore several approaches to overcoming common research challenges in end-of-life settings, including: 1) study design, to ensure feasibility and timeliness; 2) strategies to overcome barriers to research in this population; 3) data collection and management, to reduce the burden on patients, caregivers, research personnel, and sites while maximizing quality and efficiency; and 4) agenda setting. This article describes the rationale for convening the PCRC and highlights core principles for developing the evidence base in palliative medicine.

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Conflict of Interest Statement

Thomas W LeBlanc, MD, MA, Jean S. Kutner, MD, MSPH, Danielle Ko, MBBS, LLB, Jane L. Wheeler, MSPH, and Amy P. Abernethy, MD disclose no conflicts of interest. Janet Bull, MD discloses conflicts of interest with Medi Pharmaceuticals, Pfizer, and Wyeth.

Keywords

palliative medicine; palliative care; hospice; clinical trial; medication discontinuation

Introduction

The field of palliative medicine (encompassing palliative care and hospice) has made enormous strides in recent years. It was recognized as a medical subspecialty in 2006 by the American Board of Medical Specialties and the Accreditation Council for Graduate Medical Education (ACGME), in 2007 by the American Osteopathic Association, and in October 2008 by the Centers for Medicare & Medicaid Services. There are now 68 ACGME-accredited palliative medicine training programs. The number of hospital-based palliative care and hospice programs has increased steadily, from 632 (15% of hospitals) in 2000 to 1027 (25% of hospitals) in 2003.[1] From 1985 to 2007, the number of hospice programs in the United States increased from 1545 to 4700.[2]

Palliative care research activity has increased commensurately. In 1970, palliative care studies constituted 0.1% of all Ovid Medline citations; by 2005, this proportion had reached 0.4%. Published palliative care clinical trials comprised 1% of all palliative care literature in 1970; from 2001 to 2005, this percentage increased to 7%. Palliative care clinical trials as a percentage of all clinical trials increased from 0.2% in 1970 to 0.8% in 2001 to 2005.[3] The International Association of Hospice and Palliative Care Web site now lists 27 journals specifically dedicated to hospice, palliative, and end-of-life care; a growing number of palliative care-relevant articles are being published in general medical, nursing, and social work journals.

One might expect this rapid growth of interest in palliative care and hospice to be accompanied by the development of strong research capacity, and correspondingly greater productivity. Closer examination deflates this expectation. For example, while the numbers portray a dramatic increase in publications, most articles report on case series, nonrandomized trials, or studies of low methodological quality; few are randomized clinical trials. Despite the insistence of prominent national entities, such as the Institute of Medicine,[4] that palliative care research become a national priority, there remains a dearth of high-quality evidence to inform clinical practice.

United States palliative care and hospice programs have not historically featured research. Barriers to research include vulnerability of a patient population with a short life expectancy and poor functional status, and with high rates of cognitive impairment, comorbidity, and adverse events. This raises feasibility concerns as well as ethical issues regarding patient burden. The small size of many clinical sites makes recruitment difficult. Additional factors include: gate-keeping by clinicians and informal caregivers who, like patients, experience psychosocial distress; scarce and/or dispersed resources to support palliative care research; lack of standard research methodologies; lack of research infrastructure, skills, and capacities in potential trial sites; and various anti-research perceptions, for example, that the conduct of research conflicts with the goals of care.[5,6]

Based on these challenges, the belief that research could (or should) not be conducted in palliative and end-of-life populations has impeded the development of research in palliative care and hospice. The field is now endeavoring to catch up to other disciplines and strengthen its evidence base. In this article we describe: 1) one approach to expediting the development of high-quality research evidence in this area, namely, a national palliative care research cooperative group, and 2) planning for evidence development through this

cooperative group. The development of the first collaborative trial is presented here to illustrate the planning for and early function of a new cooperative group. A more detailed description of the study methodology will be published separately.

Systematic Development of an Evidence Base

The relative newness of the field of palliative medicine, its recent growth, its burgeoning interest in research, and recognition of an evidence gap in palliative care and hospice create an opportunity to take a planned, systematic approach to evidence development. The operative question is how best to amass a substantial body of high-quality, robust research evidence to support clinical practice in palliative care and hospice. A successful approach must carefully and proactively address various considerations, including: 1) elements of study design, such as definition of study population, outcomes, methods, and analyses; 2) strategies for overcoming research barriers, to ensure timely, successful, and efficient completion of studies; 3) strategies for data collection and management that are both feasible and reliable across diverse clinical settings; and 4) definition and prioritization of appropriate, sufficiently important research questions. We briefly discuss each of these issues, not as sequential stages of development, but rather as domains of work that synergistically inform one another.

1. Study Design

Efficiency, feasibility, and timeliness are essential as we endeavor to strengthen the evidence base for palliative care and hospice. A variety of study designs should be considered when selecting methods that will answer the research question efficiently and rigorously. Some research questions can be definitively resolved without a randomized trial, while other important clinical dilemmas require trials with large sample size, tightly controlled design, and coordinated data collection.

Experimental design must be matched to the importance and urgency of the clinical question. When patient safety or substantial health care expense is involved, adequately powered randomized trials may be needed to supply sufficient clarity and precision. Less burdensome, more efficient, and lower-cost study designs, such as observational trials and secondary data analyses, are prudent when an inaccurate outcome is less risky.

2. Overcoming Research Barriers

Barriers to research in palliative care populations have been clearly described,[5,6] as well as methods for overcoming them.[7] These methods include: development of a recruitment protocol to standardize enrollment processes; employment of dedicated research staff; use of simplified consent documents and proxy consenting; role-play training for recruitment and enrollment visits, using standardized wording; proactively defined plans to address gate-keeping; continuous study performance monitoring and quality assessment; and multi-institutional studies to provide sufficient samples.[8] Minimizing participant burden is important for accruing and retaining study participants; offering research home visits and enhancing meaning to patients (eg, framing research participation as a legacy) may facilitate enrollment.

3. Data Methods

Careful data collection is crucial in a field that has not historically focused on data nor instituted data-related processes. Because many palliative care providers, especially community-based ones, lack resources to invest in full-scale data infrastructure, collaborative approaches are a good option in this field. Centralized, secure data servers facilitate the timely deposition of data, allow for interim analyses, facilitate monitoring of

accrual, and help construct a robust data set, which can be used to answer future research questions expediently and support multiple studies over time, thereby maximizing the return on research investment. When data systems accommodate community and academic organizations as well as diverse care venues (eg, hospital, home, or hospice), the data gathered will most appropriately reflect the broad health care continuum within which palliative care is practiced.

4. Agenda Setting

Agenda setting involves prioritizing the research question (high-impact, answerable), study design (feasible, efficient), and implementation timeline (completion, dissemination). Responsibility for specific tasks must be appropriately delegated. Prioritization should be based on: impact in terms of cost or key outcomes; revolutionary, innovative, or practice-changing nature; timeframe; and/or surrounding urgency or controversy.

Developing the Palliative Care Research Cooperative

Senior investigators in palliative care and hospice met in January 2010 to initiate a national/international research collaboration. The purposes of the meeting, which was the capstone to several years of ongoing discussion and 2 years of active planning, were to define the structure and function of a national interdisciplinary cooperative group devoted to palliative care research, and to articulate an action plan to develop capacity for collaborative comparative effectiveness research (CER). Participants represented oncology, cardiology, geriatrics, general internal medicine, psychology, neurology, pulmonary medicine, social work, nursing, and public health. Outcomes of the meeting were: 1) commitment among participants to establish a cooperative group, the “Palliative Care Research Cooperative” (PCRC); 2) decision to launch and demonstrate the PCRC through a multi-site clinical trial; and 3) consensus on the research question to be addressed through that trial.

Evidence suggests that successful cooperative groups need an early accomplishment in order to cement their existence, propel further development, secure commitment among sites to continue participation, and generate enthusiasm.[9] The newly formed PCRC selected an initial research topic that is compelling and that can be addressed in the context of a manageable clinical trial within a short timeframe: a CER study to determine the impact of continuing versus discontinuing HMG coenzyme A reductase inhibitor lipid-lowering agents (also known as statins) among palliative care patients who have a life expectancy of > 1 month but < 6 months.

Designing a Clinical Trial

Choice of Research Question: Agenda Setting

The first task after achieving agreement on PCRC principles (Table 1) was to define a research question that was compelling and clinically important but also feasible to complete within a short timeframe. Palliative Care Research Cooperative investigators agreed that the prevalence and impact of the targeted clinical scenario must be sufficient to warrant the demands of a randomized clinical trial, including expense, investigator time and resources, and patient and family contributions of time, energy, and emotional resources.

Among the most prescribed medications in the world, statins are commonplace in palliative care. Given that > 80% of individuals will die of a chronic life-limiting illness, and that > 25% of Medicare beneficiaries are on a statin, a rational approach to medication discontinuation in this population has the potential to produce dramatic health care savings and reduce patient burden.[10]

The risks and costs of statins versus their benefits remains a genuine clinical uncertainty for palliative care and hospice patients. Multiple studies support long-term statin use for prevention of nonfatal myocardial infarction (MI) and stroke in patients with cardiovascular risk,[11] or for the prevention of recurrent MI in those with known coronary artery disease.[12] Benefits have been clearly shown for patients who live the 3 to 6 years required to observe meaningful risk reduction.[13] Observational studies suggest that there may be higher 1-year mortality in survivors of acute MI whose statins are discontinued.[14]

An enlarging literature,[15] predominantly published in palliative care journals, supports the discontinuation of medications, specifically statins, in end-stage disease. In 2005, Vollrath et al[16] proposed that statins be discontinued in this setting, given increased risk of adverse side effects and little evidence of benefit. During the intervening 5 years, this clinical question has not been answered. Stevenson et al[17] highlighted that the number needed to treat soars while the number needed to harm plummets as patients approach death; these trends have not yet been quantified. Statins do entail burden. Up to 8% of patients taking statins report gastrointestinal effects such as nausea, vomiting, and abdominal pain.[12,18] The most serious adverse effect, myopathy ranging from mild myalgia (1%–7%) to rhabdomyolysis (0%–0.005%),[12,19] is more common in older patients who have metabolic disturbances, renal and hepatic compromise, or polypharmacy, characteristic of the palliative care population.[20]

At the January 2010 PCRC planning meeting, participants concurred that genuine equipoise exists surrounding continuation versus discontinuation of statins, and that, given the prevalence of statin use, this issue is of considerable importance. They unanimously agreed to launch the PCRC with a medication discontinuation trial focused on statins.

While statins are neither the most controversial nor the most costly medication in palliative care and hospice, they are among the most prescribed, and are a source of controversy in the field. By aiming to clarify this issue in an evidence-based fashion, this trial is designed to provide proof of concept for the PCRC, and also pave the way for future medication discontinuation studies where controversy exists, side effects can be severe, and costs to individuals and society are high. The impact of discontinuation studies on the United States health care budget could be substantial. In completing and disseminating results of this statin discontinuation trial, the PCRC could take the first step toward developing a systematically researched, evidence-based approach to discontinuation of unnecessary medications in the palliative care population. Dramatic health care savings, reduction in patient burden, and protection of quality of life could result from this research agenda, provided the studies find medication discontinuation to be safe.

Study Design

Implementation and analysis parameters must match the research question at hand, balancing quality and rigor against efficiency and expediency. While the randomized controlled trial (RCT) remains the gold standard of clinical research, other study designs may be more appropriate to certain research questions. For example, retrospective studies analyzing data in the 5% Medicare random sample data set may be the most reasonable way to answer questions surrounding health care utilization of patients with specific clinical characteristics. A CER approach, in which the relative impact of available treatment options is studied in the context of real-world clinical practice, will maximize the likelihood of generating clinically meaningful results that can be readily translated into clinical practice. For the statin discontinuation trial, and to demonstrate that the PCRC can function effectively, participating investigators agreed that a large-scale RCT, within a CER framework, offered the most definitive yet feasible study design.

A core group of investigators then proceeded to develop the plan for a multi-site CER study of discontinuing versus continuing statin medications in palliative care patients with limited prognosis. Eligible participants are adults with a life-limiting illness who are on statins for primary or secondary prevention of cardiovascular events. The primary outcome is survival (ie, time to death), an easily measured endpoint that minimizes data collection burden on sites, and secondary outcomes focus on polypharmacy, quality of life, and patient experience. The hypothesis is that discontinuing statins will not influence survival or overall quality of life, but will improve statin-related symptoms and decrease polypharmacy. Cost-effectiveness, while not a primary outcome, will also be measured.

The study population was defined based on: the clinical question, prevalence of the targeted condition, clinical populations of the sites, feasibility, and desire to approximate a real-world clinical population—a CER principle that ensures translatability and generalizability of results. Eligibility criteria were intentionally broad; participants must: 1) be aged > 18 years; 2) have a progressive life-limiting illness; 3) have life expectancy of < 6 months but > 1 month; 4) exhibit declining functional status, defined as reduction in the Australia-modified Karnofsky Performance Status score[21] to < 80% in the previous 3 months; 5) have been taking a statin medication for primary or secondary prevention of cardiovascular disease for ≥ 3 months; 6) provide informed consent; 7) have intact cognitive status (ie, a Short Portable Mental Status Questionnaire score[22] of ≥ 6; and 8) speak and read English at grade 5 level or higher. The study uses the standard Medicare prognostic criteria for hospice eligibility as a proxy for life expectancy, but does not require participants to forgo disease-focused treatments, resuscitation, or life support. Treating physicians must document the participant's progressive life-limiting illness, provide anticipated prognosis, and answer "no" to the question "Would you be surprised if this patient died within the next 6 months?"[23,24]

Exclusion criteria were: 1) primary physician unwilling to have patient enrolled; 2) known active cardiovascular disease or sufficient risk of active cardiovascular disease to require ongoing therapy with statin drugs, in the opinion of the treating physician; and 3) myositis, liver function test abnormalities of > 2.5 times the upper limit of normal (ULN), creatine kinase abnormalities of > 2.5 times ULN, or other contraindications to continuing statins. These criteria resulted from interdisciplinary discussion among PCRC members in geriatrics, palliative care and hospice, and cardiology.

Eleven academic and community-based clinical sites were selected based on investigator interest, relevance of the study to their populations, and ability to recruit. Participants will be inpatients and outpatients (ie, clinic or home care).

Confirmation of Design Elements

Before committing financial and patient resources to a large-scale CER trial, it is critical to ensure that study results will inform clinical practice. To this end, a large-scale survey of palliative care and hospice practitioners was formulated. Questions focused on the central issue of discontinuing statin treatment, current clinical practice, and study design features that would provide clinically useful evidence. The institutional review board (IRB)-approved survey will be distributed to palliative care and hospice clinicians via the major professional organization; results will be used to update the study protocol.

Overcoming Research Barriers

Research barriers in palliative care clinical trials can be anticipated both in general and with respect to the specific study protocol. An example of the former is difficulty retaining the study sample given the short average life expectancy of palliative care patients, and of the

latter is the potential unwillingness of clinicians to allow their patients to participate in a study of statin discontinuation. Below we describe some of the ways in which consideration of potential research barriers informed the study design and protocol.

To ensure feasibility, this first PCRC study was created with an intentionally simple design —a straightforward, unblinded, 2-arm RCT. Eligibility criteria are broad in order to enable recruitment of a large number of palliative care patients across multiple sites in a short time period. The total enrollment target is large (N = 1200) in order to accommodate a realistic drop-out rate and still supply sufficient power to detect a meaningful decrease in survival time (primary endpoint and safety concern). Projections were made to determine the feasibility of recruiting this sample size; targeted study sites have adequate numbers of potentially eligible patients plus experience with recruitment into palliative care protocols. Expert statisticians contributed to the design, outcomes, and sample size. Because their continued engagement is critical to the success of this study and the PCRC, they must be well informed of rationale, progress, and obstacles; statistical input and independent data safety monitoring are fundamental.

Recruitment processes will be patterned after a recruitment protocol demonstrated by 2 PCRC investigators in a large, Australian palliative care trial.[7] Distinctive features of this protocol are: screening and recruitment algorithms, which will be developed for each site; key messages for the recruitment visit; use of supporting study diagrams; recruitment scripting and role playing with site-based study staff, with periodically repeated role plays to ensure consistency; and simplified consent language. Weekly teleconferences including investigators and site-based clinical research coordinators will enable discussion of recruitment, sharing of experiences, and provision of constructive advice on recruitment hurdles. Recruitment metrics will be monitored monthly and will include rates of screening, eligibility, randomization, study completion, and study withdrawal; progress will be presented in a monthly PCRC newsletter.

Other issues related to sample size pertain to this specific study. For example, in a statin discontinuation trial, some patients may consent, but withdraw after being randomized to the discontinuation arm. Study plans include close monitoring of withdrawal from the study, examination of reasons for withdrawal, and enactment of proactive participant retention strategies, as appropriate. The study withdrawal rate may itself provide valuable information about patients' desires, perceptions of benefit and risk, and emotional reactions to medication discontinuation.

Participant burden due to extensive study assessments and questionnaires is a well-documented obstacle to palliative care research.[25,26] Assessment instruments used in the statin discontinuation trial are therefore chosen with an eye toward minimizing participant burden; measures focus on the trial's specific aims and extraneous information will not be collected. Independent variables will be measured at baseline only. The goal of the primary analysis is to ensure that withdrawing statins is not a safety risk; therefore, the main outcome is death. Secondary outcomes include quality of life, psychological distress (eg, anxiety or depression), other symptoms, polypharmacy, and satisfaction with care; major cardiac events and cause of death will also be monitored. Dependent variables will be measured at baseline, 2 weeks, 4 weeks, and then every 4 weeks until death or 6 months, with the exceptions being survival and performance status, which will be monitored weekly (and do not involve the patient in data collection). Follow-up will continue for a maximum of 6 months.

Clinician gate-keeping and noncooperation are barriers rooted in organizational culture. To avert these possible obstacles, each site principal investigator will communicate with local

stakeholders (eg, oncologists, cardiologists, and palliative care teams) to generate interest and buy-in. Site-based clinical research coordinators will have IRB-approved printed information sheets to distribute to clinicians during clinic hours; they will be reachable via pager, will be available for discussions with patients at clinician request, and will visit patients at home if needed.

Data Collection and Management

Dilts et al[27] have conducted extensive work to identify factors that promote the demise or success of research cooperative groups. Though they focused on cancer, many of their findings pertain to palliative care. One area of development that contributes to enduring success in a cooperative group, while central to efficient study conduct and completion, is data collection and data management. Hence, this first PCRC study focuses on the creation of data forms, databases, data management procedures, and quality checks. Data management will be centralized at one of the partnering institutions. We will use a combination of centralized and decentralized data entry that minimizes on-site burden but allows timely monitoring of study performance. A limited proportion of the data (ie, enrollment, randomization, adverse events, withdrawal, and death) will be entered by the site-based clinical research coordinator into a central, Web-based database hosted on a secure server. Data provided by study participants on paper questionnaires will be sent for centralized data entry. Each site will receive a notebook detailing all study-specific data management procedures. Study data will be collected on 2-part forms, one part to be sent to the data coordinating center after site-based quality control procedures, and the other part for local documentation. Data collection forms will be designed to minimize patient-identifying information. Identifying information necessary for patient contact will be maintained in a separate database at the study site.

Centralized coordination of data management is intended to facilitate site participation, streamline processes, ensure consistency of methods, and identify potential problems early, for remediation. Monthly reports will summarize accrual, completeness of follow-up, and data quality. A regularly run query program will check for missing data, perform other data checks, and generate data clarification forms that will be sent electronically to the sites. Sites will review the data clarification forms, make appropriate changes, and return the forms to the coordinating site. Tracking of queries in the database will be facilitated by an electronic flagging system. An independent data safety monitoring board will conduct interim data reviews throughout the accrual process to ensure patient safety.

Summary

While research in palliative care and hospice is fraught with challenges, barriers to clinical trials in this population can and must be overcome in order to build an evidence base to support clinical practice. A national research cooperative group, the PCRC offers a potentially viable structure for advancing research in this field. Devoting careful attention to study design, research barriers, data collection and management, and choice of topic, the PCRC has designed a multi-site clinical trial to answer a clinically relevant research question expediently, while positioning the group for further studies in a medication discontinuation agenda.

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Table 1

Founding Principles of the PCRC

The PCRC will be:
• An interdisciplinary group whose mission is to decrease the burden of suffering among patients and their families.
• Committed to developing meaningful, sustainable palliative care research, which is patient-focused and uses measurable outcomes valued by patients, colleagues, regulators, and funders embedded in practice.
• Able to efficiently respond to research requests from independent investigators, government sponsors, and industries.
• Comprised of sites of varied skills, demographics, practice patterns, and health care delivery systems, so as to be able to match study sites to the needs of particular research studies.
• Prepared to help build study sites' ability to increase their knowledge of research methodology, and of how to protect human subjects.
• Willing to formulate standardized procedures, data collection methods, and management strategies.
• Responsive to regulatory and ethical requirements.
• Able to connect innovative ideas with clinically relevant, measurable outcomes and rapidly implement them to create change.
• Engaged in energizing and training future generations of palliative care researchers.
• Willing to provide actionable research findings to inform health policy.

Abbreviation: PCRC, Palliative Care Research Cooperative.