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Special Report

A Strategy To Advance the Evidence Base in Palliative Medicine: Formation of a Palliative Care Research Cooperative Group

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Abstract

Background: Palliative medicine has made rapid progress in establishing its scientific and clinical legitimacy, yet the evidence base to support clinical practice remains deficient in both the quantity and quality of published studies. Historically, the conduct of research in palliative care populations has been impeded by multiple barriers including health care system fragmentation, small number and size of potential sites for recruitment, vulnerability of the population, perceptions of inappropriateness, ethical concerns, and gate-keeping.

Methods: A group of experienced investigators with backgrounds in palliative care research convened to consider developing a research cooperative group as a mechanism for generating high-quality evidence on prioritized, clinically relevant topics in palliative care.

Results: The resulting Palliative Care Research Cooperative (PCRC) agreed on a set of core principles: active, interdisciplinary membership; commitment to shared research purposes; heterogeneity of participating sites; development of research capacity in participating sites; standardization of methodologies, such as consenting and data collection/management; agile response to research requests from government, industry, and investigators; focus on translation; education and training of future palliative care researchers; actionable results that can inform clinical practice and policy. Consensus was achieved on a first collaborative study, a randomized clinical trial of statin discontinuation versus continuation in patients with a prognosis of less than 6 months who are taking statins for primary or secondary prevention. This article describes the formation of the PCRC, highlighting processes and decisions taken to optimize the cooperative group's success.

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Introduction

Methodologically rigorous palliative care research is needed

Extensive research activity has followed the recognition of palliative medicine as a subspecialty; citation trends and new publication channels reflect this collective effort. Between 1970 and 2005, there has been a fourfold increase in palliative care studies as a proportion of all Ovid MEDLINE citations (0.1% versus 0.4%). Palliative care clinical trials comprised 1% of all palliative care literature in 1970; this percentage rose to 7% during 2001–2005. Palliative care clinical trials as a percentage of all clinical trials rose from 0.2% in 1970 to 0.8% in 2001–2005.[1] The International Association of Hospice and Palliative Care website now lists 38 journals specifically dedicated to hospice, palliative, and end-of-life care[2]; increasingly, palliative care-relevant articles are published in general medical, nursing, and social work journals.

Despite a greater volume of published palliative care studies, the majority of palliative care evidence is not derived from randomized controlled trials or other methodologically rigorous studies. While it is possible that other study designs are more appropriate to the palliative care setting, most palliative care articles report case series or nonrandomized trials, creating an imbalance in the sorts of research conducted in this field. A study examining palliative care research articles published from 2003–2005 identified 388 original articles, 8% of which were randomized controlled trials (RCTs) and 2% of which were controlled clinical trials.[3]

Prominent entities, such as the Institute of Medicine (IOM)[4,5] and National Institutes of Health (NIH),[6] have recommended that palliative care research become a national priority in the United States. Many opportunities remain, however, to improve the evidence underlying clinical practice in palliative care and thus to provide more effective patient care. Multiple studies have shown that critical outcomes in palliative care—for example, pain control—have not improved.[1,7,8–10] Poor symptom control may result from inadequacies in care delivery and/or from ineffective clinical management; a more solid evidence base and an effective knowledge translation strategy should remediate this problem.

Perceived barriers to palliative care research

Multiple barriers have deterred clinical trials in palliative care. The population is vulnerable due to symptom and disease burden, psychological and social stressors, and conditions impairing capacity to consent; this vulnerability raises ethical concerns as well as feasibility issues related to research conduct. Fragmentation of the health care system creates problems related to loss to follow-up, data heterogeneity, and nonstandardized procedures. Many provider sites are small and community-based; although clinically proficient, they lack resources, research-relevant skills, and substantial populations for recruitment. Clinicians and caregivers, perceiving research as an intrusion on the sanctity of the end of life, often "shield" patients from research staff.[11]

Standardized research methodologies are virtually nonexistent in palliative care, a field which has historically pursued the "art of medicine," orienting itself more toward compassion than science; this false dichotomy has inhibited research. Uniform research infrastructure, including data collection and management processes, have yet to be instituted across palliative care organizations interested in research. Researchers must battle various antiresearch attitudes in palliative care, such as a belief that research is incompatible with the goals of care.[12,13]

Additionally, palliative care is inherently interdisciplinary and multidisciplinary; in practice, it entails collaboration among specialists in medicine, nursing, chaplaincy and spiritual care, psychology, social work, and medical ethics, as well as coordination across settings ranging from inpatient (hospice, hospital) to outpatient (home, clinic, assisted living facility, nursing home). This complexity introduces challenges into the conduct of research, such as the need to coordinate differing research approaches, venues for data collection, and regulatory bodies. Finally, funding for palliative care research is scarce; federal investment is low, and palliative care grant applications are thought to be poorly received and/or not fully understood by NIH study sections.[14]

Cooperative groups in oncology

The cooperative group model, in which investigators work together to conduct large-scale trials in multi-institutional settings, may help overcome recognized barriers to research in palliative care. In oncology, cooperative groups have demonstrated remarkable success but they have also come under intense scrutiny; a recent IOM report drew attention to inefficiencies in and challenges faced by the National Cancer Institute (NCI)-sponsored cooperative groups.[15] Both the successes and the shortcomings of existing cooperative groups provide insights to inform future, collaborative, palliative care research.

Potential for success through the cooperative group model is perhaps best illustrated in pediatric oncology. The NCI has funded cooperative groups in this area since 1956; in 2000, four groups merged into a single Children's Oncology Group (COG). The dramatically improved outcomes for childhood cancer patients— with overall 5-year survival rates increasing from less than 30% in the 1960s to nearly 80% by the late 1990s[16,17]—can largely be attributed to the aggressive, coordinated approach of the COG and its predecessors.[18] By 1996, pediatric cancer clinical trials cooperative groups provided access to latest treatment protocols for nearly 95% of American cancer patients under the age of 15.[19] With the COG's addition of an enhanced remote data entry system, enrollment in COG clinical trials increased by 40%; in 2005, almost 90% of the more than 11,000 newly diagnosed patients registered at COG institutions were enrolled in a COG clinical trial.[20]

The NCI currently funds 10 cooperative groups to develop and coordinate multi-institutional clinical trials, including the Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), and American College of Surgeons Oncology Group. Although the cooperative group model is now well entrenched in oncology, its success in streamlining adult cancer clinical trials is debatable. The 2010 IOM report mentioned above documented that the current process of activating new Phase III clinical trials in NCI cooperative groups averages more than 2 years, and of activating Phase I and II studies typically requires more than 500 days.[15] Many trials, especially those that take longest to open, close after failing to reach accrual goals; of all NCI-funded Phase I–III trials that opened and closed between 2000–2007, 40%–50% failed to meet minimal accrual goals.[21] The report

found the activation path within cooperative groups to be complex, requiring many steps not critical to actual conduct of the study.[22]

To elucidate the barriers faced by cooperative groups, Dilts et al.[23] carefully examined their function using the CALGB as a case study. They identified four types of administrative barriers to trial activation in oncology cooperative groups: (1) procedural barriers, referring to policies or required steps, e.g., that a cooperative group protocol be reviewed by an external agency; (2) structural barriers, created by organizational design, e.g., sites performing research tasks in differing orders; (3) infrastructural barriers, e.g., delays in protocol review; and, (4) synchronicity barriers, i.e., requirements that multiple steps come together before the study be launched.[23] In subsequent work, Dilts and colleagues examined the process of Phase III clinical trial development in the ECOG and identified 481 distinct process steps required for study activation. Trial activation required a mean of 783 days from executive approval and 808 days from initial conception. Study development represented 44% of the total time necessary for Phase II trial activation, and 54% of that for Phase III trials. The most variable aspect of clinical trial development was creation of study forms and preparation for data management, taking, on average, 401 days; compliance with common data elements added another 114 days.[24]

The COG highlights the potential contribution that cooperative groups can make to scientific advancement and outcomes improvement. Certain functions of cooperative groups, such as combining patient populations to more efficiently complete studies, make this structure well-suited to resolving challenges encountered in palliative care research. The multidisciplinary nature of palliative care, and the diversity of care venues including community-based and home settings, present potential hurdles and care must be taken to avoid adding layers of bureaucracy that slow the progress of research.[24]

Cooperative groups in palliative care

Successful research cooperative groups with a palliative care focus exist in Australia (Palliative Care Outcomes Collaborative),[25,26] Canada (Canadian Critical Care Trials Group),[1,27] Europe (European Palliative Care Research Centre),[28] and Sweden (Palliative Care Research Network in Sweden [PANIS]).[29] As yet, the United States does not have a palliative care research cooperative group. The Population-based Palliative Care Research Network (PoPCRN),[30] a hospice practice-based research network centered at the University of Colorado Denver, offers a precedent for a multisite network devoted to research in this field, though it has not regularly pursued randomized clinical trials and lacks infrastructure for pharmaceutical trials. A call to the discipline has underscored the need for a U.S. cooperative group that can spark progress in palliative care research similar to that of our international colleagues.[12]

This article describes the formation of a new palliative care research cooperative group, developed in light of the barriers to research in this field and the challenges and opportunities afforded by a cooperative group structure.

Methods

From 2005–2010, a group of senior palliative care investigators, methodologists, and clinicians discussed how best to advance the evidence base in palliative care, with an eye toward developing a coordinated national research effort. Informal conversations culminated in a 1½-day meeting of researchers interested in participating in the formation of a palliative care cooperative group. Possessing expertise in patient-reported outcomes, biostatistics, practice-based research networks, social work, nursing, and psychology, participants represented diverse clinical organizations, the NIH, existing cooperative groups, and international palliative care research networks. All participants funded most of their own travel expenses; those unable to physically attend participated via teleconference. The meeting was held on the University of Colorado Denver Anschutz Medical Campus, January 16–17, 2010. Its purposes were to: (1) define the structure and function of a national interdisciplinary cooperative group in palliative care research and (2) delineate an action plan for developing capacity for collaborative comparative effectiveness research in palliative care.

Funding

Financial support was provided by the National Palliative Care Research Center.

Results

The meeting opened with a goal alignment exercise and brainstorming session, followed by 16 brief presentations with question-and-answer periods (Table 1).

Participants unanimously agreed to form a research cooperative group broadly focused on studies relevant to palliative care, called the Palliative Care Research Cooperative (PCRC). Its mission is to decrease the burden of suffering and to improve outcomes for patients with advanced life-limiting illness and their families. The group delineated core principles that will guide PCRC development (Table 2).

Presentations by Australian and Canadian colleagues described the experiences of two successful cooperative groups. These individuals offered to share their organizations' policies and structures (e.g., bylaws, forms, processes), so that the experiences of established networks might inform PCRC development. Development must address: processes, including those for adding new members, prioritizing research topics, collaboratively developing a protocol, and initiating a clinical trial; governance, including data ownership, data sharing, and dispute resolution; standardization of research procedures, e.g., through data collection forms, recruitment and consenting protocols, inclusion of minorities and women, and standardized human subject protection; data management, covering data collection, transfer, storage, quality assurance, management, aggregation, and extraction; and analysis, including statistical support and reporting. A set of PCRC operating procedures will address these issues. The definition of members' roles, and description of different levels of investigator and site involvement, represent additional topics for clarification.

An initial PCRC membership, comprising all participants in the Denver meeting, was agreed upon. Additional members will be included to extend the reach of the network and the availability of research infrastructure for palliative care investigators. The PCRC will emphasize education through mentoring junior investigators and helping to build skills among staff at research-naïve clinical sites.

Table 1. Palliative Care Research Cooperative January 2010 Meeting Participants and Presentations

Name	*Institution*	*Presentations*
Amy Abernethy (Host)[a]	Duke University Medical Center	Parallel stories from U.S. hospice and palliative care and lessons learned; Moving from outcomes to data collection
Ethan Basch	Memorial Sloan Kettering Cancer Center	Adverse events as outcomes, or vice versa?
Janet Bull	Four Seasons	What does cooperative research require? And offer?
David Cella	Northwestern University Medical Center	
Charlie Cleeland[a]	M.D. Anderson Cancer Center	Current and previous initiatives for joint research in palliative care and symptom management; outcomes measurement in disadvantaged and underserved populations
David Currow[a]	Flinders University (Adelaide, Australia)	Australian model for a palliative care clinical studies collaborative
Diane Fairclough[a]	University of Colorado Denver Medical Center	
Laura Hanson[a]	University of North Carolina, Chapel Hill	What does cooperative research require? And offer?
Josh Hauser[a]	Northwestern University Medical Center	
Paul Hutson	University of Wisconsin	
Jean Kutner (Host)[a]	Univ. of Colorado Denver Medical Center	What makes a population-based research network?
Linda Lloyd[a]	San Diego Hospice and The Institute for Palliative Medicine	
Janelle McCallum	Denver Hospice	
Jeri Miller[a]	National Institutes of Health	
R. Sean Morrison[a]	Mount Sinai School of Medicine	National Palliative Care Research Center and The Pepper Center
Ann O'Mara[a]	National Institutes of Health	A Brief History of the Oncology Cooperative Groups; IRB Issues; National initiatives related to PRO's and other palliative care-related outcomes
Shirley Otis-Green[a]	City of Hope	City of Hope palliative care research and education
Steve Pantilat	University of California at San Francisco	
Russ Portenoy	Beth Israel Medical Center	
Christine Ritchie[a]	University of Alabama at Birmingham	Research at the UAB School of Medicine Center for Palliative Care
Graeme Rocker[a]	Dalhousie University	Canadian model for a palliative care clinical studies collaborative
Jeff Sloan[a]	Mayo Clinic	PRO Advances in Palliative Care
David West[a]	University of Colorado Denver	
Jane Wheeler[a]	Duke University Medical Center	
Yousuf Zafar[a]	Duke University Medical Center	

[a]Participated in-person vs. via videoconferencing.
IRB, Institutional Review Board.

Dilts et al. [23] underscored the importance of an early "win" for maintaining initial momentum and setting an enduring, productive course for a cooperative group. PCRC founding members therefore decided to launch the PCRC with a demonstration clinical trial that is straightforward to implement and possible to complete within a short timeframe—but also likely to definitively answer an important clinical question. The group chose discontinuation of medications for comorbid chronic disease, among patients with advanced life-limiting illness, as a compelling and clinically meaningful issue, one arising frequently in practice, and one for which genuine clinical uncertainty exists.

The first trial, envisioned as a step toward operationalizing a theoretical framework for managing comorbid illnesses at the end of life,[31,32] is a medication discontinuation trial focused on statins. Among the most prescribed medications in the world, statins are commonly encountered in palliative care. Because more than 25% of Medicare beneficiaries take a statin,[33] any change in prescribing practice could dramatically impact health resource utilization. While the benefit of statins for patients with cardiovascular risk, but without a defined short survival prognosis, is well-demonstrated,[34–36] the benefit versus cost/risk of this medication in patients with an estimated prognosis of less than 6 months remains unknown. Statins can contribute to illness burden. Up to 8% of patients taking statins report gastrointestinal side effects[37]; myopathy is the most common serious adverse effect.[35,38,39] Conversely, the safety of statin discontinuation is a critical concern; observational studies suggest that 1-year mortality may be higher in acute myocardial infarction survivors whose statins

Table 2. Palliative Care Research Cooperative Group Core Principles

- *Active interdisciplinary membership,* with an understanding that membership decisions will reflect an inclusive rather than exclusive orientation.
- *Commitment to shared research purposes*, including development of meaningful and sustainable palliative care research, patient-focused inquiries and methods, and use of measurable outcomes valued by patients, investigators, regulators, and funders.
- *Heterogeneity of sites*, i.e., participation of sites with diverse skills, demographics, practice patterns, and healthcare delivery systems, to ensure the PCRC's ability to meet the needs of diverse research studies.
- *Development of research capacity* in participating sites, to upskill sites through increasing their knowledge of research methodology.
- *Standardization of methodologies*, such as study procedures, consenting, and data collection and management.
- *Agility*, i.e., ability to respond efficiently to requests of investigators, government sponsors, and industry.
- *Responsiveness* to regulatory and ethical requirements, including human subject protections.
- Focus on *translation*, i.e., connecting innovative ideas with clinically relevant and measurable outcomes; rapid implementation of research results to effect change.
- Engagement in *education*, to energize and train future researchers in palliative care.
- Generation of *actionable results* that can inform health policy.

PCRC, Palliative Care Research Cooperative.

are discontinued.[40] The effect of statin discontinuation on other outcomes important in palliative care, such as patient burden, quality of life, and performance status, is also unclear. Although an enlarging literature, predominantly in palliative care journals, supports discontinuation of medications, specifically statins, in end-stage disease,[41] the balance of medication efficacy versus burden has yet to be defined in clinical studies.

With statin discontinuation as the agreed topic for a PCRC demonstration trial,[32] members worked together to develop an application for a federal grant, submitted to the NIH in March 2010; the National Institute of Nursing Research has awarded funding.

Discussion

The need for a concerted approach to evidence development in palliative care is well accepted. What has been less clear is the best way to develop that evidence base given the barriers to research in palliative care, disparate pockets of research expertise, and a majority of clinical sites not conversant with research processes. A cooperative group framework may help overcome many obstacles to palliative care research, such as lack of standardized definitions and processes, small populations in clinical trial sites, and uneven distribution of expertise.

Cooperative groups have met with varying levels of success. The PCRC is endeavoring to learn from the experiences of other cooperative groups. Likely to support its success are: the coalescence of a sizeable group of committed, experienced investigators who have a history of and commitment to working together; agreement on the cooperative group's purposes, parameters, and first steps; a pragmatic approach focused on prioritizing studies and efficiently generating results that can be applied to current clinical practice, and; a design intended to support learning-through-doing and iterative adaptation. Streamlining research activation processes and minimizing the layers of bureaucracy will help to avoid the roadblocks and delays encountered by other cooperative groups. Dilts et al.[23,24] suggest several procedures for overcoming barriers, which the PCRC plans to adopt: process mapping, to identify and eliminate those steps that do not add value to the protocol; inclusion of operational complexity, alongside scientific merit, in study review criteria, and; reducing study activation time through changes to concept or protocol. Because studies that fare poorly on initial scientific review exhibit disappointing long-term success, they suggest winnowing out these unlikely-to-succeed projects in favor of other, potentially more productive, endeavors. A focus on practicality, feasibility, and efficiency is key to timely completion of collaborative studies.

Overall, palliative care is ripe for research development but under-resourced for research infrastructure and not savvy in research processes. Hence, a PCRC data collection strategy must be pragmatic, inexpensive, and convenient in community-based as well as academic settings. To allow for participation of smaller and nonacademic sites, total costs of research need to be minimized through choice of study design and methodology; funding will likely need to be secured from the NIH, to sufficiently support infrastructure development and studies. Care should be taken to identify best items, instruments, measures, and outcomes – matched to the research question and to practical considerations. By incorporating expertise in patient-reported outcomes at the outset, the PCRC is making a commitment to research that directly addresses the concerns of people with complex and/or life-limiting illness. The most consistent hurdle to palliative care clinical trials is participant recruitment; hence, the first PCRC trial will incorporate a careful recruitment program based upon prior successful models in palliative care.[42] Other concerns requiring careful attention are participant burden, clarity of outcomes, data management, missing data, and ethical issues.

Challenges that may limit the success of the PCRC group approach include: (1) its inherent risk, in that we cannot know in advance if the PCRC is a feasible structure; (2) the possibility that unique vulnerabilities of the population and human subjects protections concerns may limit feasibility of a multisite approach; (3) the possibility of lack of funding; (4) the possibility that only large research institutions will participate, thereby potentially limiting the generalizability of results, failing to build research capacity more broadly, and omitting valuable perspectives from agenda setting and prioritization; (5) the need for strong leadership, balanced

against the need for broad-based participation; (6) the potential for unanticipated problems to impede the organization's function; and (7) the potential for individual goals to overshadow collaborative intentions.

Our proactive responses to these limitations are as follows. (1,2) Inherent risk is a necessary condition, but not a reason to forego the opportunity, provided we take conscious steps to make the PCRC feasible. (3) Funding constraints are a valid concern, and one reason for creating the PCRC. We argue that studies conducted in this collaborative, multi-institutional context, as part of a larger national agenda, have a better chance of securing funding than do stand-alone and/or single-institution studies. (4) The group is committed to inclusion of diverse sites, and regular discussion of membership, with strategies developed to promote heterogeneity of research participants. (5) The first PCRC trial highlights the need for a core team of leaders on any given study, yet this functional requirement does not obviate the participation of multiple other members. A focus on the core principles of active interdisciplinary participation and commitment will remind those most active in the PCRC to continue to reach out and engage additional members. (6) Unanticipated problems are best resolved by a governance committee and/or steering committee. Structures will be created that can expeditiously work through roadblocks, with a focus on timeliness, research completion, delivery, and translation. (7) PCRC investigators have made a group commitment to monitor and remedy such problems.

Through a deliberated and inclusive process, the PCRC was established and the first study protocol submitted for funding to the NIH. Our next steps include developing a 5-year agenda of studies, drafting standard operating procedures, and cultivating collaborative relations with professional associations, potential funders, and relevant national entities. We welcome input from our colleagues both within and outside palliative care. The field of palliative care will require novel approaches to evidence development; the PCRC seeks to fill an important void in current research, and to prepare future investigators to advance the field and contribute to the evidence base, toward the ultimate goal of improving care for patients with life-threatening illness.

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