Special Article

Challenges to and Lessons Learned from Conducting Palliative Care Research

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Abstract
In response to a 2005 solicitation from the U.S. National Institutes of Health, 16 investigators received funding to test interventions that would reduce the barriers that prevent cancer patients from receiving adequate and appropriate symptom management therapies. Since the awards have been issued, the investigators have met two times and have identified a number of challenges to implementing their respective studies. A survey was conducted that focused on their experiences with hiring and retaining study personnel, gaining Institutional Review Board approval, incurring unexpected costs, challenges to accruing participants, and a listing of standard measures used in the study. The survey was completed online by the Principal Investigator for each project in late 2006 and the initial results were confirmed one year later by resending the initial survey and by a follow-up telephone call. All but one Principal Investigator completed the survey. Obtaining Institutional Review Board approval, hiring and recruiting research personnel, establishing subcontracts, and accruing research subjects were the primary challenges experienced by the investigators. This palliative care solicitation achieved more than its original intent of stimulating research in overcoming barriers to delivering cancer symptom management, palliative care and end-of-life care. From a survey on the challenges and issues that emerged from their projects, grantees were able to identify specific hurdles and their unique solutions that may help other investigators as they plan their program of research. J Pain Symptom Manage 2009;37:387–394.

Key Words
Palliative care, symptom management, end of life, research

Introduction

In 2005, the U.S. National Cancer Institute (NCI) and the U.S. National Institute of Nursing Research (NINR) issued a Request for Applications (RFA) entitled, "Reducing Barriers to the Delivery of Symptom Management and Palliative Care (CA-05-013)."[1] The purpose of the RFA was to solicit grant applications for research directed at developing and testing interventions to reduce or overcome barriers to the delivery of evidence-based symptom management and palliative care to patients suffering from cancer and/or

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treatment-related sequelae. The impetus for this solicitation was based on the recurring problem that was identified from a series of meetings and related publications,[2–5] specifically, that because of a variety of patient, clinician, and health system barriers, cancer patients do not receive adequate, evidence-based symptom management or palliative care throughout the course of their disease. Applications for this RFA were expected to cover the entire cancer trajectory from diagnosis, through survivorship, to end of life and emphasize understudied areas and gaps in the area of symptom management and palliative care. This report describes the background that led to the solicitation and the results of the survey completed by the Principal Investigators who were funded through this announcement.

Response to the Solicitation

Seventy applications were submitted to this call and 16 projects were funded. The projects focused on a variety of barriers, diverse populations, and understudied disease sites along the cancer continuum. Funding for all projects began in September 2005. Depending on the scope of the project and funding mechanism, support ranged from two years (eight projects) to five years (six projects), with two projects funded for three and four years, respectively. Tables 1 and 2 list the grantees, titles of their projects, and selected key characteristics.

One of the requirements of the funded investigators was to attend a yearly meeting at which study plans, findings, and issues of common interest and concern were to be shared and discussed. At the time of this report, two meetings have been conducted, one in September 2006 and one in September 2007. At both meetings, the vast majority of grantees were encountering difficulties in achieving their accrual goals. Most of these difficulties were not related to lack of access to the study population.

To better understand these difficulties, one of the authors (BF) designed and conducted a survey of the grantees, which asked the respondents a series of forced-choice and open-ended questions about their experiences with hiring and retaining study personnel, gaining Institutional Review Board (IRB) approval, incurring unexpected costs, and encountering challenges to accruing participants. A listing of standard measures used in the studies also was obtained. All attendees agreed to participate and noted this as a rare opportunity to collectively capture data on a cohort of investigators studying a similar problem and beginning their projects at the same time. Information from the survey was shared with the NCI official to understand the full range of issues and identify recommendations.

Survey Results

The survey was completed online by the Principal Investigator for each project in late 2006, approximately one year after initiation of the projects. These initial results were confirmed one year later by resending the initial survey and by a follow-up telephone call from one of the co-authors. This was done to capture additional experiences that may have occurred as the projects proceeded and to capture any individual issues at that site not reflected in the written survey. All but one Principal Investigator completed the survey.

Table 3 presents data regarding challenges in institutional approval of the project. Nine of the projects (60%) reported challenges in institutional approval. The issues reported reflect the nature of the projects as clinical research in various community settings and involving multiple sites. The most common issues faced involved consent procedures (such as unfamiliarity of the IRB with psychosocial studies and concern about telephone consents), clinical sites unfamiliar with IRB procedures, delays in IRB meetings, and the complexity of multisite approvals. These issues are important for the future of end-of-life care research, which relies on community hospice programs and multisite research to obtain sufficient numbers of subjects.

Table 3 presents findings related to personnel and the grantee institution on the Barriers projects. Ten of the projects (66%) experienced challenges in recruitment or hiring of personnel, a factor known in clinical research to delay the initiation of the study. Investigators were also asked if there had been changes in personnel as the projects progressed. Nine of the fifteen (60%) had such personnel changes.

Table 1
R21 Projects[a] ($n = 8$)

Title/Investigator	Barrier to Symptom Management/ Palliative Care	Primary Objective
Customizing family's symptom management skills post HSCT/ Eldredge, D. (CA115374)	Transplant recipients and family caregivers feel unprepared to handle complex care	Develop, feasibility test, and pilot test a Symptom Management Toolkit designed to prepare family caregivers with skills to care for post-transplant recipients
Symptom assessment after stem cell transplant/Graham-Pole, J. (CA115982)	Inadequate utilization of standardized symptom reporting methods	Validate and test sensitivity of an electronic visual analog scale to measure pain and anxiety in children and adolescents after stem cell transplant
On our own terms: a lay health advisor pilot study/Hanson, L. (NR009785)	Multiple health care disparities experienced by African Americans	To develop and feasibility test a Lay Health Advisor Intervention (training the advisors and pairing them with patients) to improve treatment for pain and suffering
Telephone counseling for head and neck cancer/Kilbourn, K. (CA115354)	High levels of distress with limited psychosocial and monetary resources	Feasibility of a telephone counseling program to improve symptom management and psychosocial care in newly diagnosed head and neck cancer patients
Use of HIT to improve symptom management in advanced cancer/ Kutner, J. (CA115311)	Inadequate assessment, recognition and communication of pain and symptoms leads to significant distress	Develop and feasibility test a technology-based system for improving symptom management in hospice/palliative care settings
Hospice pain control: developing an opioid order sheet/Murphy, B. (CA115368)	Despite published guidelines and development of standards of care, a substantial number of cancer patients experience uncontrolled pain, particularly at the end of life	Develop and feasibility test an opioid titration order to provide direction to assess pain, generate a treatment plan, and communicate it to the patient
Telehealth symptom management in head and neck cancer/Pfeifer, M. (CA115345)	Ineffective communication between cancer patients and clinicians	Evaluate the efficacy, efficiency, acceptability, and feasibility of a telehealth algorithm to address symptom distress
Patient-centered communication during chemotherapy/Post, D. (CA115388)	Ineffective communication between cancer patients and clinicians	Develop and feasibility test a PDA-based patient communication intervention (symptom monitoring/ communication training) for breast cancer patients undergoing chemotherapy

[a]R21 grants are two-year, exploratory projects, designed to provide preliminary data for larger (R01) projects.

Table 3 also reports findings related to subcontracts. An interesting finding was how common multisite research is in this field, with 10 projects (66%) reporting use of subcontracts to other sites. Of these 10 projects, 70% reported difficulties or delays in establishing the subcontracts. Comments from the survey respondents indicated problems from both the grantee institution as well as subcontractor sites.

Table 3 presents data from survey items related to subject accrual and minority recruitment. Twelve of the projects (80%) reported problems in accrual of subjects. The nature of the problem included several factors, the most common of which was the protectiveness of clinical staff in subject accrual, an important issue in palliative care research. The acuity of the patients and proximity to time of death were other common issues.

Investigators also were asked about experiences in recruitment of minority patients. Fifty-three percent or 8/15 investigators replied that they had been able to recruit

Table 2
R01 Projects ($n = 8$)

Title/Investigator	Barrier to Symptom Management and Palliative Care	Primary Objective
Reducing barriers to pain and fatigue management/Ferrell, B. (CA115323)	Lack of interventions that integrate known patient, clinician and system barriers	Test the effect of a model titled "Passport to Comfort" to address patient, professional, and system barriers to relieve pain and fatigue
Cancer pain in elders: promoting evidence-based practices (EBPs) in hospices/Herr, K. (CA115363)	Poor utilization of clinical practice guidelines for pain management and patient/caregiver noncompliance with the treatment plan	To evaluate the effect of Translating Research into Practice (TRIP-Cancer), which promotes the use of evidence by health care providers, to improve pain management in elders receiving hospice care
Reducing symptom barriers among American Indians/Hodge, F. (CA115358)	Lack of information regarding American Indians' perception of symptoms, management, and the cultural constructs	Clarify/define the cultural constructs of cancer-related symptoms, develop, and test a culturally appropriate program to overcome barriers
RCT of FFGT in palliative care and bereavement/Kissane, D. (CA115329)	Families avoid discussions regarding death and dying	Determine the efficacy and frequency of FFGT in preventing complicated bereavement/depression compared with standard palliative care in families at high risk for complicated grief
TeleCare management of pain and depression of cancer/Kroenke, K. (CA115369)	Pain and depression often go unrecognized or undertreated	Determine if an automated home-based symptom monitoring by phone or internet with a telephone-based nurse care management is more effective than usual care in improving depression and pain
Overcoming barriers to depression recognition in cancer/Passik, S. (CA115349)	Efficacious interventions to treat depression are available but not used due to lack of recognition, patient reporting, and limited clinician time	To examine the impact of depression screening results when made available to patients with lung cancer, physicians, both, or neither
Caregivers' strengths-skills: managing older CA patients' symptoms/Raveis, V. (CA115315)	Limited resources and access to health care	Evaluate the efficacy of a short-term problem-solving skills training program during the cancer survivorship period
Weekly symptom telemanagement in advanced lung cancer/Yount, S. (CA115361)	Unrecognized and poorly managed symptoms due to lack of patient reporting, clinician assessment, and limited time	Determine whether a system combining computer and interactive voice response identifies clinically significant symptoms and enhances their management in patients with advanced lung cancer

minority subjects. The most common recruitment strategy was having research staff attend clinics/rounds.

The projects used a variety of methods in their research designs, as illustrated in Table 3. As directed by the initial NCI/NINR RFA, all projects had to be testing interventions and 10 of the projects involved randomized trials. Patient interviews were common as was abstraction of chart data. Interestingly, eight projects (53%) reported monitoring the fidelity of a clinical intervention included in the study.

The final question asked the investigators to describe the measurement tools used in the study. The intent of this question was to determine if there was common use of established tools that might facilitate comparing data across studies. The response to this question was very informative, as common use of a few established tools was not reported. A total of 80 different scales were reported across the 15 projects and only nine tools were used in more than one site. Among the 80 scales, 12 had never been published or had been

Table 3
Challenges and Methods in Palliative Care Research

Challenges in institutional approval of project ($n = 15$)		
Did you experience challenge in the institutional approval of your project?	Yes: 9	No: 6
Personnel ($n = 15$)		
Did you experience challenges in recruitment or hiring of study personnel?	Yes: 10	No: 5
Have there been any key personnel leave the project or change institutions?	Yes: 6	No: 9
Inclusion of subcontracts ($n = 15$)		
Does your project involve subcontracts?	Yes: 10	No: 5
Have you had difficulty or delays in establishing the subcontracts? ($n = 10$)	Yes: 7	No: 3
Research subjects accrual ($n = 15$)		
Have you had problems regarding accrual of subjects?	Yes: 12	No: 3
Have you been able to recruit minority patients as you projected?	Yes: 8	No: 7

Recruitment Methods	Number of Respondents
Staff attend clinic/rounding in clinical setting	11
Depend on clinical staff referrals	9
Flyers/written materials	9
Attendance at multidisciplinary meetings	8
Direct contact with potential subjects via phone	5
Home visits	2

Methods Used in Study Design	Number of Respondents
Clinical intervention	10
Randomized trial	10
In-person interviews	9
Medical record abstraction	9
Focus groups	8
Assessment of fidelity of intervention	8
Telephone interviews	6
Mailed surveys	4

designed specifically for the project. This finding indicates that there is little uniformity in measures and significant use of project-initiated scales.

Discussion

The ability to follow a cohort of 16 investigators involved in similar research that began at the same time is a rare opportunity and has resulted in rich qualitative data. These data reveal multiple challenges experienced by the investigators. Some are well known when conducting symptom and palliative care research and others were unforeseen yet provide valuable lessons for investigators, the funding agency and grant reviewers. These issues are of special importance in symptom and palliative care research. In addition, the varied and innovative methodological approaches implemented by this cohort of investigators can contribute to the growing science of symptom management and palliative and end-of-life care.

Investigators

Obtaining IRB approval, hiring and recruiting research personnel, establishing subcontracts, and accruing research subjects were the primary challenges experienced by the investigators. Though these challenges occur independently, they can also be interrelated. Subject accrual is a well-known challenge, primarily due to the serious nature of the subjects' illness or symptom burden, and close proximity to death. Moreover, once enrolled, there is high attrition due to declining medical status, resulting in large amounts of missing data. In an effort to offset this challenge, many of the investigators conducted their research in multiple sites. Consequently, many encountered significant delays in IRB approval and establishing subcontracts. Though anticipated, very few investigators encountered delays or challenges due to the new federal regulations pertaining to the privacy of personal health information (Health Insurance portability and Accountability Act [HIPAA] regulations).

Herr (Table 2) involved 16 community-based hospices in three states in the Midwest. Overall, it took 12 months to obtain IRB approval for the 16 sites. Issues encountered included hospices who never participated in federal research requiring application for a Federal Wide Assurance,[6] local IRBs who met quarterly vs. monthly, and sites that lacked access to a local IRB. The complexity of involving multiple sites can be mitigated by obtaining as much information as possible about each site, such as their IRB process, previous involvement with federal research, and developing plans for meeting individual accrual goals. In many institutions, investigators cannot obtain IRB approval until their funding has been secured, and it is important to determine this early in the process.

The dilemma of how to streamline IRB reviews in the context of multisite research is becoming ever more critical. The beginning of the modern IRB system is relatively new, dating back to the mid-1960s.[7] At that time, the role of IRBs was primarily focused on local investigator-initiated single-site studies. As data from this survey show, many IRBs as currently configured are not equipped to efficiently review multisite research projects. Newer approaches, including regional ethics organizations and web-based programs for cooperative IRB review, are emerging as possible solutions.[8]

Because of the high symptom and disease burden, palliative care clinicians focus their attention on patient comfort and naturally protect their patients. Consequently, offering a clinical study to this population may be perceived as placing undue burden on the patient. In this survey, staff gatekeeping of the patients was another challenge to subject accrual. Clinic or hospital staff would not recommend eligible patients for the study because of the perception that they were too ill or tired or participation would add time and burden to the patient's care. In response to this challenge, clinical institutions are using patient navigators to minimize barriers and increase minority accrual to clinical trials. One example of this is an NCI-funded project, "Cancer Disparities Research Partnership Program." Dr. David Kahn, one of the investigators involved in the project, realized the patient navigators had biases against clinical trial participation similar to the patients they were trying to recruit.[9] Educating the staff and patients about the nature of the study, time and effort involved, and associated risks and benefits can ease the perceived burden of the research. Despite these challenges, this group of investigators did use strategies to decrease burden to their subjects. These included avoiding long assessment periods, unnecessary documentation, and overlong project duration, all of which have been documented in the literature as lessons learned.[10]

Other factors can contribute to the difficulty in conducting supportive care and behavioral research: lack of familiarity with supportive and behavioral research by the sites and local IRBs, prioritization of research involving cancer treatment, and a lack of understanding of the importance of the research to be conducted. Each of these was encountered by one or more of the investigators. In a study conducted by Crowley and Casarett to determine the feasibility of using screening questions to identify patients interested in participating in research, patients were less likely to believe symptom-related research would provide potential benefit (10%) compared to disease-modifying research (33%).[11]

In addition to facing these challenges, the investigators were asked to consider vulnerable populations, such as children, the elderly, racial and ethnic minorities, and individuals of lower socioeconomic status. These underrepresented populations face numerous barriers to participation in clinical trials, including lack of education about clinical trials, lack of provider referral, perceived harms of clinical trial participation, time commitment and loss of income, transportation, mistrust of research and the medical system, and inadequate health insurance.[12] The investigators developed innovative projects to include these populations and address the barriers to palliative care and symptom management in the context of the known barriers to participation in clinical trials.

The funded projects emphasized the research gaps in symptom management and palliative and end-of-life care. Despite increased clinician education, the development of standards of care, published guidelines, and published patient, clinician, and system barriers, pain and cancer/treatment-related symptoms continue to be under- or poorly-treated. Several investigators addressed these issues.

To advance palliative care and symptom management, it is essential to not only develop evidence-based interventions but to ensure their dissemination into practice and see them used appropriately. This can be particularly challenging in home and hospice settings, which is where several of the investigators chose to conduct their research.

These investigators met many of these challenges, demonstrated flexibility and persevered. Becoming aware of many of the potential challenges will help investigators identify insurmountable problems and quickly move to another approach to prevent significant delays. In several situations, the solutions and options came from outside the institution. For example, because of unforeseeable delays

in starting projects and accruing participants, two of the R01 investigators have negotiated with NIH to restructure their budgets and will have an additional year to complete their work.

The Funding Agency

The early findings from this one time solicitation can serve to assist funding agencies in their development of future initiatives for palliative care research, as well as to guide potential applicants when interacting with a funding agency. As learned from this cohort of investigators, the feasibility for conducting these types of studies is a significant challenge. Investigators should carefully consider funding mechanisms, such as the NIH Exploratory Grant Mechanism (R21),[13] which are specifically designed to support feasibility and pilot studies, before embarking on a larger more long-term project.

Although this RFA included a special review panel to evaluate the scientific merit of the applications, this is not always feasible. In the absence of a special review panel, it is imperative that the investigator request, at the time of submission, the expertise needed to review the application. As the field matures and more qualified reviewers are available to review applications, standard study sections will become populated with adequate numbers of reviewers who are knowledgeable and sensitive to the issues facing palliative care researchers.

When applying for NIH support, a very important consideration is to contact the Program Director, particularly when there is a specific solicitation. By taking the time to discuss the relevance of the particular project to the goals and objectives of the solicitation, the investigator will get a better sense of how to shape the application so that it is responsive to the solicitation.

Investigators seeking R01 funding for their palliative care research projects are not required to cite a specific solicitation on their applications. However, speaking with a Program Director remains critically important. Because palliative and end-of-life issues cut across the expertise and resources of several NCI divisions, no single unit within NCI has been designated as the focal point for palliative care research. The NCI web site can help investigators find information and the most appropriate Program Director. Using the term "palliative care," a recent search of the NCI web site identified six "Best Bet" links and another 625 links to a variety of documents and reports.[14] Among the six "Best Bet" links, two are particularly informative for investigators. The link entitled "Funding Opportunities in Symptom Management and Palliative Care Research"[15] will yield a listing of all NIH funding opportunities related to this area of research. The other link, entitled "Cancer Research Portfolio: Palliative Care Research Projects,"[16] lists all current NCI-funded projects, the Principal Investigator(s), and the NCI Program Director assigned to the project. A cursory review of the 168 funded projects yielded five different Program Directors in three different divisions managing these grants.

Grant Reviewers

Applications that were submitted in response to this solicitation (CA-05-013) were reviewed by a special panel of scientists with expertise in symptom management, palliative and end-of-life care, health services research, as well as statistical methodology. The standard criteria of significance, approach, innovation, investigator qualifications, and environment were used to evaluate the applications. Despite the expertise of the study section, nowhere in the review criteria would the reviewers have been able to predict the unique hurdles and challenges that these investigators would later encounter. It is imperative that study sections/reviewers are available to evaluate palliative care and symptom management research who consider its unique challenges, as seen with this RFA.

Next Steps

Of the eight R21 investigators, several have indicated that their projects are not feasible for a larger (R01) study, with poor patient accrual being the major reason. This finding, although not optimistic, is the main point of R21 projects, to determine feasibility and obtain pilot data. At the last annual meeting, several investigators, whose projects include similar populations, are collaborating on a project for their next study.

This palliative care solicitation achieved more than its original intent of stimulating research in overcoming barriers to delivering cancer symptom management, palliative care

and end-of-life care. From a survey on the challenges and issues that emerged from their projects, grantees were able to identify specific hurdles and their unique solutions that may help junior investigators as they plan their program of research.

In addition, other issues emerged from the survey, specifically, the need to include instrument development, as evidenced by the considerable diversity in assessment tools used in this survey. Finally, when evaluating budgets, reviewers and funding agencies should take into account the additional time and staff required to address accrual difficulties and high rates of attrition.

These investigators learned significant lessons, which will enhance their future research efforts. By having the opportunity to share challenges as well as accomplishments, the investigators learned a variety of lessons and engaged in a rare opportunity to be supported and mentored.

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