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Compassion and Vigilance: Investigators' Strategies To Manage Ethical Concerns in Palliative and End-of-Life Research

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Abstract

Background: Ethical concerns were identified as a potential barrier to advancing palliative and end-of-life science at the 2004 National Institutes of Health State of the Science Meeting. However, data are lacking about the nature of ethical concerns and strategies for balancing the need to advance science with human subjects protections.
Methods: A qualitative case-study design was used to follow 43 end-of-life studies from proposal development through the review process and implementation. Investigators participated in semi-structured telephone interviews and provided document data regarding their experiences with grant and IRB reviews. Using constant comparative analysis within and across cases, the investigators identified commonly encountered and unique concerns and strategies for managing these concerns.
Findings: Investigator strategies fell into two broad categories: 1) Recruitment and consent strategies related to subject identification and enrollment; and 2) Protocol-related strategies related to the process of data collection. These strategies shared the overarching meta-themes of *compassion,* as evidenced by a heightened sensitivity to the needs of the population, coupled with *vigilance*, as evidenced by close attention to the possible effects of study participation on the participants' well-being, clinical care, and the needs of research staff.
Conclusions: Ethical concerns have led to the development of compassionate and vigilant strategies designed to balance the potential for risk of harm with the need to advance the science of palliative and end-of-life care. These strategies can be used by investigators to address ethical concerns and minimize barriers to the development of palliative and end-of-life care science.

Introduction

The dramatic growth of the aging population in the United States has created a pressing need for expansion of end-of-life care research to explore issues including symptom management, caregiving, treatments, and outcomes.[1–3] Concerns about the ethics of conducting research with patients near the end of life and their family members represent a potential barrier to the advancement of science in this area.[2,4]

The Belmont Report principles of respect for persons (autonomy), beneficence, and justice offer a helpful framework for organizing these ethical concerns.[5] Autonomy-related concerns are focused on the ability to give informed consent. This raises questions about decisional capacity, assent, and proxy decision making.[6,7] Of particular concern is whether individuals near the end of life are able to give voluntary consent to participation or whether they are overly susceptible to undue influence because of their poor health or dependence on treating clinicians.[8,9] Beneficence-related concerns include questions about how to evaluate the risks of participation in palliative and end-of-life research as the risks and potential benefits related to participation may be different for someone who is healthy than for someone near the end of life.[4,6,8,10] Although there may be no direct personal benefit, participants may still find meaning in the act of participating.[11,12] Additionally, researchers need to ensure that clinical needs identified in the course of research are addressed.[9,13,14] Justice-related issues include concerns that fair subject selection and equal opportunity to participate are not possible due to gatekeeping by organizations, clinicians, or family members, which limits investigators' ability to access potential subjects who may be interested in participation.[2,15] Including

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populations with sensory, mobility, or cognitive impairments may necessitate adapting methods to accommodate disease-related limitations to ensure access.[16]

There are minimal data available about how investigators manage the ethical challenges described above. The literature contains accounts of investigators' experiences with recruitment challenges in palliative and end-of-life care research that touch on ethical issues.[15,17–20] However, only a few articles explicitly describe investigators' successful strategies for addressing ethical issues based on first-hand experiences with specific populations or settings.[21–25] These articles make important contributions, but given the wide variations in institutional review board (IRB) evaluation of ethical issues,[26] there is a need for more systematic data about investigators' strategies across the full range of settings and populations where end-of-life research occurs.

Methods

A qualitative, exploratory case study design was used to identify and describe investigators' experiences conducting palliative and end-of-life care studies. Investigators were asked about all phases of the study including proposal submission, grant review, IRB review, and study implementation. Data sources included telephone interviews with the case study investigator as well as relevant document data (e.g., grant reviews, IRB correspondence). Following IRB approval, a certificate of confidentiality was obtained from the National Institutes of Health (NIH). Data collection occurred between August 2009 and July 2010. The focus of this paper is on strategies used to address ethical concerns raised by investigators, IRBs, and external reviewers.

Sample selection

Studies selected for potential inclusion were conducted in the U.S. and focused on social or behavioral issues related to terminally or seriously ill patients and/or their families. Studies with active funding were identified using the online NIH database and private foundation websites. Studies presented at professional conferences within the prior year were also eligible for inclusion. Studies were considered ineligible if data collection was completed before 2005. The search was narrowed using the same criteria used at the 2004 NIH State of the Science Consensus Conference on Improving Care of the Dying.[27] Case selection was guided by the principle of maximum variation to locate studies representing a range of funding sources, designs, methods, and participant populations.[28] The sample size was based on qualitative research sampling guidelines regarding scope of the study (focused) and nature of the topic (concrete), and interviews were continued until informational redundancy was achieved.[29–31]

Study procedures

Principal investigators were invited to participate by email. Investigators who agreed to be contacted were screened by phone to confirm case study eligibility. Telephone interviews were conducted by the study team (SH, JC, CN) using a semistructured, open-ended interview guide. Investigators were asked about their experiences with ethical issues during study development, funding, and implementation. Interviews lasted approximately an hour although several took close to two hours. Investigators were invited to submit relevant study documents pertaining to grant or IRB reviews. Interviews were transcribed verbatim, proofed for accuracy and removal of identifying information, and organized by study case using NVivo 8.0.[32]

Analysis

Analysis was performed concurrently with data collection, and interview guides were modified based on ideas or questions that arose during the analysis. Well-established qualitative techniques guided analysis of the case data.[33–35] Each case was analyzed using the following processes: open coding of interview data to inductively identify and label ideas or experiences, followed by examining the document data to locate additional ideas or information that elaborated on or confirmed what was discussed in the interview. Data were coded line by line. Where available, document data were used to confirm key ideas that emerged from the interview. After individual cases were coded, constant comparative analysis across cases was used to identify overarching themes and subthemes related to management strategies.[29] Themes were also compared for similarities and differences. Theoretical memos documented the types of strategies described by investigators. Demographic data about the participants were descriptively analyzed.

Verification of the analysis. To ensure consistency in coding the data, the research team developed a coding dictionary documenting code definitions and coding decisions related to the application of codes. Each interviewer separately coded the first 9 interview transcripts and then discussed differing coding interpretations with the team until consensus was reached. Following the identification of the initial code list, the remaining 34 transcripts were each coded by a primary and a secondary reviewer with discussions at regularly held team meetings. The code list continued to be refined during this process. The team met regularly with an expert methods consultant (KK) who audited the analytical procedures for overall quality.

Sample

Principal investigators for 74 case studies were contacted about participation: 43 (58.1%) agreed to participate; 9 (12.2%) actively refused to participate; 12 (16.2%) passively refused (by not responding to the invitation emails); and 10 (13.5%) were determined to be ineligible. Overall, 43/64 (62.7%) of eligible cases were included in the sample. For three studies, a second investigator also participated in the interview, resulting in a sample of 46 investigators sharing information about their experiences with 43 case studies (Tables 1 and 2).

Strategies specific to palliative and end-of-life care research

The strategies described were largely developed by investigators either in anticipation of potential ethical concerns or as a result of prior research experiences. Few strategies were suggested by IRBs or external reviewers. More-junior investigators described the benefits of working with experts to learn relevant strategies; more-experienced investigators reported a process of building a collection of strategies over

Table 1. Characteristics of Participating Investigators[1]

Investigator sample (n = 43)	
Demographics	*No. (%)*
Female gender	32 (74.4%)
White race	41 (95.3%)
Discipline	
Physician	18 (41.9%)
Nurse	16 (37.2%)
Social scientist	7 (16.3%)
Other	2 (4.7%)
Experience in years	
0 - 5	9 (20.9%)
6- 15	21 (48.8%)
16-25	13 (30.2%)
Number EOL studies	
1-3	12 (27.9%)
4-10	19 (44.2%)
11-30	12 (27.9%)
IRB experience (yes)	12 (27.9%)
Grant review experience (some or lots)	31 (72.1%)

[1]In three instances a second investigator participated in the interview, but demographic data was only collected for the primary interviewee.

time. Table 3 contains a list of strategy categories with exemplar quotes and sample strategies used by investigators.

Recruitment and consent strategies

Consent to contact. Investigators reported that they were generally not allowed by IRBs to directly contact potential study participants "cold," due to concerns about protecting patient confidentiality and a desire to avoid upsetting individuals during a sensitive time. Instead, the investigators had to develop strategies that gave potential participants the option to refuse any contact by the research team. Consent to contact was sometimes obtained by treating clinicians, an approach that protected confidentiality, allowed the clinical partners to confirm study eligibility, and made it possible to screen out individuals perceived to be too distressed to participate. However, clinicians who were unsupportive of the research did not always cooperate in identifying potential participants or presented the study only to a select (potentially biased) population of participants. In some situations, potential participants were sent a letter from either the investigator or a clinical partner indicating someone from the study would be in contact. Depending on the IRB, participants could either opt out of participation (by indicating they did not wish to be contacted) or opt in (meaning investigators were only able to call if the participant provided permission). Opt-outs were perceived as less burdensome for potential participants and more successful than opt-in strategies.

Table 2. Characteristics of the Case Research Studies

Case studies (n = 43)	
Study methodology	
Mixed methods	19 (44%)
Qualitative	10 (26%)
Quantitative	13 (30%)
Study design	
Descriptive	26 (60.5%)
Intervention	17 (39.5%)
Funding source	
Federally funded	26 (61%)
Private foundation	13 (30%)
Other/none	4 (9%)
Study documentation provided (yes)	24 (57%)

Initial contact. Investigators reported that the timing of the initial approach had to be carefully considered. In some cases this required the development of fairly broad eligibility criteria that allowed participants to decide when they felt ready to participate, even if it had been many months after the event under study (e.g., the death of a loved one). Investigators reported that they often employed multiple recruitment approaches within the same study, depending on the study site and other unique factors; and several described the importance of modifying recruitment strategies when accrual was slow. When a referral was received, a rapid response was often critical to avoid losing a potential subject due to declining health.

Consent process and forms. Whereas IRBs were perceived as emphasizing the use of standardized language and providing comprehensive details about risks and benefits in consent forms, investigators focused more on presenting information in ways that reduced burden, prevented distress, and fit the needs of a population already under duress. When possible, investigators obtained waivers of documentation of written consent from the IRB so that consent could be obtained verbally by phone or in person. Alternate versions of the consent form were provided by some investigators, such as a one-page summary or brochure that provided an overview of the study's purpose and what participation would entail. Several investigators described modifying the approach to obtaining consent so participants had the opportunity to ask questions about the study prior to enrollment (e.g., reading the consent form out loud at a deliberate, unhurried pace). Some obtained IRB approval for witnessed consent to help ensure physically impaired persons were able to participate even if they were unable to sign a form. Other investigators inserted language in the consent document describing the intent to report symptoms to clinicians in the event that clinical care was needed. A related strategy was providing examples of the most sensitive research questions in the consent form, so that participants who chose to consent were fully aware of the nature of the study questions.

Decisional capacity. Patients nearing the end of life may lack decisional capacity or may experience fluctuating and/or declining capacity. Investigators therefore stressed that it was important to have clear plans to assess capacity at the time of consent. In some studies, participants who lacked capacity were excluded from participation altogether. In other research it was important to include participants who lacked capacity to ensure the representativeness of the sample, as loss of capacity is common near the end of life.[36] For these studies, investigators described working with the IRB to determine who was viewed as an appropriate proxy and developing a plan to obtain assent either verbally or in writing from

Table 3. Recruitment, Consent, and Protocol-Related Strategies with Exemplar Participant Quotes and Sample Strategies

Strategy focus	*Strategy categories*	*Exemplar participant quotes*	*Sample strategies*
Recruitment and consent strategies	*Consent to contact:* Strategies for accessing the population through the use of intermediaries or opt-out/opt-in system	"We approached their nurse before we approached the patient to see if there was any reason why they felt like this was not a good time or a good situation to approach the patient from their perspective as a clinician" P023C "We initially would get information from the hospice staff. They would talk to patients and families, get their consent to give us information, consent to contact, and then we would follow up. Then one hospice said, 'Why don't we kind of turn that around and we will inform the patient that we are participating with you in this study, and we will ask them to sign the form if they are not okay with us giving you information.' So it actually worked very well." N057J	(a) Establish partnerships with clinicians to assist in verifying participant eligibility and appropriateness for study. (b) Obtain consent to contact through clinical or community partners (allows potential participants to opt out or opt in without interacting with researcher. (c) Prepare letter of introduction that will be sent to potential participants by clinical or community partners indicating their support of the study that also clarifies right to refuse participation but does not imply participant should participate.
	Initial Contact: Approaches to establishing a relationship with potential participants before inviting participation.	"When I contacted subjects about participating, I sent them a letter explaining the study and I sent them an opt-out card. When I didn't hear back within a certain amount of time, I called them on the telephone and gave them a lot of information about what I would be expecting and also, you know, when they would ask, How have other people done with this? Sort of just walked them through what other people's experiences had been without obviously divulging any personal information." P009S "The turnaround time was crucial. From the time that I got the phone call that someone was interested, I called them back within 48 hours, and I was in their home as soon as they would allow it." N003J	(a) Use caring and sensitive language in materials. (b) Set time frame for contact with sensitivity to potential participant's situation. (c) Provide opt-out postcard or phone number to call to opt out with initial letter of information. (d) Share experiences of other participants when describing study. (e) Be prepared to respond quickly to interest in participation. (f) Promise participant that data collection will be stopped if they appear tired or upset.
	Consent process and forms: Strategies related to the process of obtaining consent including the use of surrogates and the approach to ensuring informed consent.	"Patients consented for themselves whenever possible, and then if they were not able to consent and not able to understand what was happening at the time, we needed to go to surrogate consent." P002C "I repeat things at least twice, verbally and then in writing, and I actually read the consent even though the person says, "Oh yes, I want to do it." I always have a story explaining to them whey I want to read them the formal document. I purposely read every word and try not at all to give the impression of being rushed." I007S	(a) Request waiver of informed consent or waver of documentation of informed consent when appropriate to minimize what is asked of participants. (b) Provide alternate forms of consent form that are readable and simplified to supplement (but not replace) the IRB-required version. (c) Read consent form out loud, slowly, to help ensure participants fully understand and have time to process information. (d) Provide examples of the most sensitive study questions in the consent form so participants who agree to participate more fully understand nature of study.

(*continued*)

Table 3. (Continued)

Strategy focus	*Strategy categories*	*Exemplar participant quotes*	*Sample strategies*
	Decisional capacity: Approaches to assessing the capacity to consent to participation and identifying appropriate surrogates.	"And initially we also had a requirement in there that there was 'no noted cognitive impairment' for consenting to the study, but we modified that so that we can enroll hospice patients who are no longer able to provide an informed consent, but can assent to the study itself.'' N013J "We used the [IRB] screening tool, so we were prepared to deal with capacity issues to make informed consent. We had a whole piece on assent as well. If we decided that there was someone that wanted to participate, but we were questioning their capacity to give informed consent, we had the whole assent piece in place." N033S	(a) Assess decisional capacity at time of enrollment if population is anticipated to be impaired. (b) Proactively establish standards and procedures for proxy consent, witness consent, and assent with IRB.
Protocol related strategies	*Approaching a Potentially Sensitive Topic:* Strategies to gently approach a delicate topic.	"We were at great pains to make sure the interviews were all done in ways that were very sensitive and we used language that gave people an opportunity to not answer or [indicate that certain topics did not apply to them] – all those kinds of things." N069J "We are very careful in the way that we word our consent form and our questionnaires to try and make it clear that individual patients and families may find that some of these questions don't apply to them, and to sort of give them that psychological out or psychological protection if this is stressful for them." N013J	(a) Use "may not apply" qualifiers to give participants a psychological "out" in consent form and interview. (b) Use broad, open-ended questions that expand focus and allow participant to decide what aspects of question are applicable to their situation. (c) Be sensitive and responsive to cues of discomfort or hesitation. (d) Back away from or skip sensitive questions if responses to preliminary questions suggest discomfort or a lack of awareness.
	Use of language: Selecting language to avoid inadvertently disclosing prognosis or other information that participants may not already know, or may choose not to recognize. Includes recruitment, consent, and data collection documents or speech.	"We are very cautious to kind of tread lightly and ask questions in a way that does not presuppose that they are aware of their prognosis.'' N064S "We never talk about end of life in our studies. We talk about serious illness." N069J	(a) Avoid charged terms including terminal, death, dying, and end of life. (b) Use terms such as advanced illness, critically ill, seriously ill, palliative care, or life-limiting disease. (c) Use language employed by participant and follow their lead on what terms are acceptable. (d) Avoid language that conveys or discloses prognostic information.

(*continued*)

Table 3. (Continued)

Strategy focus	*Strategy categories*	*Exemplar participant quotes*	*Sample strategies*
	Working with clinicians: Strategies that include working with clinicians as consultants, screeners, or to address physical or emotional symptoms identified during the study.	"We work closely with the oncologist. We get a list from them of the patients who meet criteria, and then we ask them if there are any specific patients that they feel might be harmed by us approaching them. Actually, they will often have helpful information. They might say, you know, 'This person is so ill – I don't think they are going to make it [through] the whole study.' Or they may give us a heads up that this is a very fragile patient who uses a lot of denial and even if approached to be involved in a study like this will freak out or something like that." N006S "Any symptoms rated as severe– and we used a four, none, mild, moderate, severe Likert scale for assessing severity of symptoms– by the patient would be reported to the patient's primary nurse and documented in the medical record, and that was acceptable to the study section and to the IRB." N047C	(a) Before approaching patients, seek input from clinicians about whether they are well enough to participate or if the approach should be on another day (or not at all). (b) Let participants know distressing physical or emotional symptoms will be reported to treating clinicians. (c) Pass clinical questions on to team or encourage participant to follow up with clinicians. (d) Do not interfere with clinical care.
	Flexible methods: A strategy that involves modifying data collection procedures to accommodate participant's physical, emotional, or other needs.	"So, that's part of what we have been working with, is creating it so it is still rigorous in trying to get at the same issues, but being flexible to recognize this is not a pharmaceutical trial and that 72 hours is not nearly as important as making sure that somebody will talk to you." N013J "One of them had an experience on a telephone call where the patient was really very, very short of breath, having a very difficult time getting through the interview, and part of what we had done to adjust for any of those kinds of things was to say we can stop at any point. We can call back and finish the interview later today. We can call tomorrow. I mean we were very flexible in how we presented the interview." N033S	(a) Track and avoid holidays, birthdays, death anniversary. (b) Anticipate need to reschedule or prematurely end data collection based on participant's needs. (c) Check in frequently during data collection and stop if participant fatigued or upset. (d) Compensate regardless of whether participant completed surveys/interview. (e) Minimize number, length, and complexity of survey instruments and interviews. (f) Allow participants to talk as long as they need. (g) Drop surveys or data collection time-points to minimize burden. (h) Conduct data collection at location most convenient to participant. (i) Conduct data collection by phone or in person depending on participant preferences. (j) Let participant control who is in the room (especially if a patient).

(*continued*)

Table 3. (Continued)

Strategy focus	*Strategy categories*	*Exemplar participant quotes*	*Sample strategies*
	Backup protocols: Plans that address situations where the participant identifies or appears to be experiencing physical, emotional, or spiritual harm. Formalized as part of the study protocol.	"We have a procedure for, if we upset anybody, they can get counseling resources. If there are any red flags, if somebody expresses during the intervention that they are thinking of suicide, we have a procedure to handle that. That's all well spelled out. We have a plan in place for all of the studies like this that could upset somebody or where we could learn something about them." P006C "We tell them in the consent form that if you tell us about untreated symptoms or severe distress, we will let your treatment providers know. No one has ever objected." N064S	(a) Develop guidelines regarding participant behavior, comments, or scores on measure that serve as triggers for enacting backup plan. (b) Train data collectors how to respond if participant is distressed or at risk of self-harm. (c) Create backup plan to detect underlying, preexisting problem or issues related to data collection. (d) Use data safety and monitoring plans to identify at-risk participants. (e) Develop contingency plans to include referrals or direct contact with mental health or psychiatric services.
	Research staff strategies: Ways to support the research staff who engage in challenging, emotionally laden work during the study.	"We have had conference calls devoted solely to the research staff talking about what it is like emotionally to work with this patient population that are moderated or led by our social workers…. If you want to have a sustainable, retainable, standardized research staff, you have to address this, just as we do on clinical teams. We think about burnout. We talk about it. We talk about self-care. You have to do the same with research team." N047C "Whenever [the research assistant] has any concerns or whenever they just need to process – that is another thing. That's a big one for me and anyone working on this: Do they know what they are getting into before they start working on the study? So [my] providing support in that way is a big thing." N042J	(a) Hire more than one research assistant to do data collection to ensure peer support is available. (b) Ensure resources are readily available for research staff who may require support, including access to team members with appropriate background to provide support. (c) Screen staff carefully and hire individuals with relevant expertise, familiarity with population, and ability to think on their feet. (d) Provide in-depth training to staff to prepare for work with population. (e) Regularly and deliberately provide emotional support to research staff to help process the difficult work and manage feelings about population through planned team meetings and the use of professional counselors.

impaired participants. Investigators reported widely varied IRB policies about the participation of persons with decisional impairment, but in most settings, proxy consent was permitted by either a strictly defined legally authorized representative or a more loosely defined surrogate (such as a family member or domestic partner).

Protocol strategies

Approaching a potentially sensitive topic. Investigators described using a very active approach to data collection that involved constant monitoring and adjustment during data collection. The primary motivation behind this strategy was to be sensitive to the emotional needs of the patient or caregiver. This sensitivity included avoiding challenging the patient's understanding of his or her condition and caution about inadvertently imposing the investigator's values on the situation. Investigators described starting the survey or interview with nonthreatening topics to build trust and with probing questions to assess participants' willingness to engage in conversation about more sensitive topics such as diagnoses or prognoses. Interviews were diplomatically ended or specific items skipped if a participant signaled he or she was uncomfortable with the questions or was unwilling to respond. Other investigators described using very broad questions that allowed the participant to decide what if any aspects of the interview questions or survey items were relevant to their situation. Additional strategies included giving participants as much time as needed to reflect on emotional experiences both during and after the interview and concluding the interview with something more upbeat. Finally, some investigators reported that they reminded people frequently of their right to refuse to answer questions or to withdraw from the study at any time. For studies with more than one data collection time point, investigators described assigning the same team member to a participant for each time point to help build rapport as well as minimize the burden of getting used to a new person and style.

Use of language. Investigators considered the use of language to be very important in developing consent documents, recruitment materials, and data collection materials, and described numerous strategies to avoid inadvertently disclosing prognostic or diagnostic information to participants. These strategies included inserting language in the consent form or study materials indicating that "some of these questions may not apply to you" to allow participants who were troubled by certain words or phrases to maintain the belief that this language was not relevant to their situation. Investigators described "echoing" language, meaning they used certain terms and phrases only when first used by participants rather than risk using language that could be distressing. Specific terms that were commonly avoided in written materials and in conversation included "terminal," "death," "dying," and "end of life." More general terms such as "advanced illness," "seriously ill," "critically ill," "life-threatening," and "palliative care" were generally viewed as preferable, though there was no universal agreement about the acceptability of these terms. Some investigators reported that IRBs were not as sensitive about the use of language as they were themselves and provided examples of IRBs requiring the use of terms that investigators felt to be too direct and potentially upsetting.

Working with clinicians. Investigators who did data collection in clinical settings worked closely with the clinical team to avoid interfering with care and to ensure that physicians, nurses, and other members of the treatment team thought it was appropriate to approach patients for participation. In some situations, that meant postponing data collection based on either the clinician's opinion about the patient's ability to participate or on what was happening during that day's appointment.

Flexible methods. Being sensitive to the needs of participants required creativity and flexibility. Investigators reported being flexible about the timing of data collection or intervention based on the needs of the participant and careful tracking to ensure they avoided contacting participants on personally meaningful dates such as holidays, birthdays, or the date of death anniversary. Data collection time points were delayed or dropped if necessary to minimize burden despite the impact on scientific rigor. Missing data were dealt with in the analytic phase. In designing the study, investigators were careful to minimize the number, length, and complexity of instruments. Participants were allowed to decide whether they wished to be interviewed by phone or in person, whether they wished to read survey questions or have the items read out loud, where they preferred data collection to occur, and who they wanted in the room. Investigators described using real-time feedback to determine whether the participant was fatigued or upset, even if it resulted in terminating data collection prematurely.

Backup protocols. Investigators were very clear that they were engaging with participants as researchers rather than clinicians but described feeling a strong sense of responsibility to intervene when participants seemed to be emotionally or physically distressed. Backup protocols consisting of contingency plans for addressing participant distress were viewed favorably by most investigators and even required by some IRBs as an acceptable way to minimize risk. A backup protocol could be triggered when a study participant was observed to be in distress as a result of study participation (e.g., emotional distress) or due to an underlying, preexisting condition (e.g., untreated pain). The distress was recognized both through the use of objective "cut points" on study instruments and with more subjective observations. Some backup protocols involved asking the patient to share information with his or her clinician (for less urgent issues), notifying the participant's clinical care providers about the concern, providing a list of community resources, directly referring the patient to a resource such as mental health services, or delivering mental health services crisis intervention through experts affiliated with the research team. Confidentiality concerns were mitigated by notifying participants during the consent process about the existence of backup protocols. For many, the use of backup plans, such as reporting high levels of symptom distress in an observational study, represented a tradeoff with scientific rigor that was viewed as methodologically challenging but ethically necessary.

Research staff strategies. Many investigators expressed concerns that research with seriously ill and dying populations is challenging and emotionally laden. Therefore, hiring research staff who had previously worked with the

study population in some capacity was highly valued. This helped ensure consent was sensitively obtained and it provided some reassurance that research staff had the necessary clinical expertise to be responsive to signs of distress. When it was not possible to hire staff with prior experience, investigators described careful training plans to develop the necessary skills. Additionally, investigators expressed concerns that it was not realistic to expect staff to fully understand the existential implications of doing research with seriously ill and dying populations, so applicants were carefully screened for their ability to manage stress. Investigators also described providing research staff with emotional support to help process their reactions to what they were hearing or observing during the course of data collection. When possible, more than one data collector was hired to provide a natural outlet for staff to informally share experiences. Strategies included encouraged research staff to journal and do additional reading about grief and bereavement; holding team meetings (including via phone for multisite studies) to process emotions and discuss challenging participants; including professional counselors in team meetings; referring to counselors for individual sessions; encouraging the use of alternative therapies for self-care; facilitating access to an expert consultant; and forming a project staff support group. In the best case scenario, funding was built into the study budget to provide some of these services.

Meta-themes

The strategies described above share the common, overarching meta-themes of *compassion* and *vigilance*. The concept of compassion was reflected in strategies that represented heightened sensitivity to the needs of the population such as allowing extra time to solicit consent, gently building up to sensitive questions, developing backup protocols, careful attention to the use of language, and methodological flexibility. Compassion was coupled with exercising heightened vigilance during every step of the research process about the possible effects of study participation on the participants' emotional and physical well-being, ensuring the research did not interfere with clinical care, and being attentive to the emotional needs of research staff. Investigators were fully committed to protecting human subjects and creative in the development of strategies to mitigate the potential risk of harm.

Discussion

Palliative and end-of-life investigators described a range of strategies sharing the underlying themes of compassion and vigilance that minimize ethical concerns in the course of recruiting, consenting, and conducting research with seriously ill patients and their family members. The strategies described by investigators reflect efforts to balance the principles of respect for patient autonomy, beneficence, and justice with the goal of minimizing negative outcomes related to research participation.[37]

However, achieving a balance among these ethical principles often necessitates methodological and ethical tradeoffs. Most investigators reported that they obtained consent from treating clinicians prior to contacting potential participants, and several expressed the belief that this approach helps minimize the risk of harm and facilitates research by allowing clinicians to screen out patients who are too distressed or otherwise inappropriate for research. However, clinicians who are opposed to the research may act as gatekeepers and impede recruitment, limiting the applicability of study findings, or may leave patients feeling pressured to participate.[7,15,37,38] Remaining flexible about study procedures allows investigators to meet the needs of seriously ill patients and potentially bereaved family members and increases opportunities for participation.[6,37] However, being too flexible can result in a loss of generalizability and power,[15] which limits the value of the research.

Investigators proposing research with seriously ill patients and family members need to anticipate challenges such as these and proactively plan to minimize the impact of tradeoffs by building in procedures to reduce the effects of gatekeeping, developing alternative recruitment sites, crafting backup protocols to manage distressing symptoms, and devising plans for managing missing data.[6] If investigators are not attentive to these challenges in the course of the study design, it could impact the success of projects and ultimately raise concerns about the validity of this area of science.[7] These concerns also suggest it is important that IRB applications and grant proposals be reviewed by individuals with appropriate expertise who are able to evaluate whether proposed studies are both sensitive to the needs of the population and address potential methodological limitations that could impact the usefulness of study findings.

A key limitation of this study is that the findings represent only the experiences of those investigators who agreed to be interviewed. Although efforts were made to include research that reflected a broad array of end-of-life and palliative care issues, the experiences and perceptions of the study participants may be different from those of people not invited or unwilling to participate in the study. Additionally, the investigators who were interviewed were on average a highly experienced group of researchers who developed strategies over time through a program of research, and newer investigators may not be as adept at managing ethical concerns.

Findings suggest that investigators who do research with seriously ill patients and family members are creative in managing ethical concerns through compassionate and vigilant strategies. The identification of commonly used, successful strategies may be useful in developing evidence-based standards for evaluating research with palliative and end-of-life care populations. Although IRBs vary in their interpretation of federal policy for the protection of human subjects and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), many of these strategies can be adapted to fit local conditions in order to address ethical concerns and minimize barriers to the development of palliative and end-of-life care science.

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Author Disclosure Statement

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