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Palliative Care Clinical Trials: How nurses are contributing to ethical, integrated and evidence based care of palliative care patients participating in clinical trials.

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Abstract

The aim of this paper is to describe the emerging role of the palliative care clinical trials nurse in an era of evidence based practice and increasing clinical trial activity in palliative care settings across Australia. An overview of the current clinical trials work is provided with a focus on three aspects of clinical trials nursing practice which have significant implications for patients: (1) the consent process; (2) integration of clinical trials into multidisciplinary care, and (3) promotion of evidence based practice in palliative care settings. Clinical trials roles provide palliative care nurses with an opportunity to contribute to clinical research, help expand palliative care's evidence base as well as develop their own research capabilities.

Introduction

Currently there is increasing research activity in palliative care settings in Australia and as a result new clinical research roles have been created. The aim of this paper is to describe the emerging role of the palliative care clinical trials nurse with a focus on:1) management of the consent process, 2) integration with multidisciplinary care, and 3) establishing and building the evidence base in the palliative care setting.

Need to develop the evidence base

In this era of evidence based practice there is a compelling need for processes which support rigorous enquiry and evidence generation. As part of Australia's universal health care system, the Pharmaceutical Benefit Scheme (PBS) ensures that a range of medications are subsidised and available to all who need them. However, many medications commonly used for symptom management in the palliative care population lack the high level evidence required for PBS subsidisation, despite the use of various medications in a palliative care setting often being outside of the manufacturer's recommendations. An example of this is the use of Octeotide in the treatment of malignant bowel obstruction: it is currently not approved for this indication despite widespread clinical use in the palliative care setting. The use of this medication outside of the PBS guidelines has significant cost implications for both inpatient settings and outpatients.

The Palliative Care Clinical Studies Collaborative (PaCCSC) was established in 2006 through funding from the Australian Government Department of Health and Ageing under the National Palliative Care Program to address this evidence gap. Twelve Australian palliative care services are now involved in a number of Phase III PaCCSC clinical medication trials as partner organisations (Table 1). The primary aim of PaCCSC

is to generate research data that will support the listing of these medicines on the Australian Register of Therapeutic Goods and subsequently on the PBS (Table 2), with secondary aims of building the research capacity and evidence base of the palliative care sector through Phase III and IV clinical medication studies. Currently there are six clinical trials underway with the Collaborative's first clinical trial recently successfully completed recruitment (Hardy et al). More detailed information about PaCCSC and its current clinical trials can be found on the Caresearch website (at http://www.caresearch.com.au/caresearch/tabid/97/Default.aspx).

Table 1: Current Partner Organisations

State	Name of Organisation
NSW	Braeside Hospital, Sydney
	Calvary Mater Newcastle, Newcastle
	Calvary Health Care, Sydney
	Sacred Heart Centre, Sydney
Victoria	Peter MacCallum Cancer Institute, Melbourne
	Ballarat Hospital, Ballarat
	St Vincent's Hospital, Melbourne
	The Alfred Hospital, Melbourne
	Austin Health, Melbourne
	Barwon Health, Geelong
Queensland	Mater Health, Brisbane
South Australia	Southern Adelaide Palliative Services, Adelaide

(See http://www.caresearch.com.au/caresearch/tabid/759/Default.aspx)

Table 2: Current Phase 3 Clinical Trials*

Study	**Chief Investigator**
Ketamine for cancer pain	Professor Janet Hardy
Risperidone and Haloperidol for delirium	Associate Professor Meera Agar
Octreotide for vomiting related to malignant bowel obstruction	Professor David Currow
Morphine and Oxycodone for Dyspnoea	
Sertraline for dyspnoea	
Megastrol for appetite	Dr Paul Glare

*All are randomized, double-blinded, placebo controlled trials.

Challenges in Conducting Palliative Care Research

The ethical and methodological considerations of conducting research within palliative care have been well documented (Aoun & Kristjanson, 2005). Despite randomised controlled trials (RCTs) providing high level evidence, it has been suggested that they are often inappropriate in palliative care settings because of the use of a placebo arm (Karim 2000). In the past many palliative care RCT have lacked rigor and power due to high attrition rates, poor design and reporting or failure to adequately recruit (Hudson et al, 2001; Piggott et al 2004; Manchikanti 2008). Given the vulnerability of the palliative care population, many potential trial participants may experience frailty, fatigue, fluctuations in condition and cognitive decline (Whiting & Vickers 2010). These conditions may impact on an individual's decision making capacity and willingness to commit the time and energy research participation requires (Karim, 2000; Dean & McClement, 2002; Seymour et al, 2005; Whiting & Vickers 2010). Further, it is not uncommon for palliative care participants to deteriorate and die during the intervention or the follow up stages of a clinical trial, necessitating sensitive withdrawal and ongoing ethical and safe care of participants and their family. The complexity of these ethical and clinical issues may explain a reluctance of health professionals to refer patients for consideration of inclusion in palliative care studies and a reluctance of families to further burden the patient with this additional task. This well intentioned gate keeping has been frequently cited as a major barrier to participation in palliative care clinical trials (Dean & McClement 2002; White et al 2008; O'Mara et al 2009).

Despite these significant challenges, collaborative clinical trials work is being conducted at across Australian at 12 palliative care centres with over 450 palliative care patients consenting to participate in these studies during since 2008. Given this level of research

activity is therefore timely to articulate the role of the palliative care clinical trials nurse and how it facilitates the recruitment and management of the care needs of participants.

Discussion

Developing the Role and Addressing the Learning Needs of the Palliative Care Clinical Trials Nurse

At the outset, it was determined that the palliative care clinical trials nurses would be integral members of the research teams, the PaCCSC network and the multidisciplinary clinical team. Alongside the Site Investigator, the clinical trials nurse plays a pivotal role in linking the science within the protocols to the reality of complex clinical cultures and individual patient situations. The clinical trials nurse role is broad, with varying responsibilities depending on the site, jurisdiction and the capabilities of the individual nurse (Table 3). Learning needs of the clinical trials nurses include developing knowledge of recruitment and other clinical trial processes, research and ethics concepts, budgeting and financial reporting. Examples of education undertaken to meet these learning needs include International Conference on Harmonisation – Good Clinical Practice training (Therapeutic Goods Administration, 2000) and specific study initiation training prior to commencement of each study at each site. Being part of a larger collaborative such as PaCCSC ensures that each clinical trials nurse, although operating at distinct local sites across a vast country, has ready access to ongoing support, continuing professional development opportunities and a community of practice. The practical support provided by PACCSC ensures the development of required knowledge through the identification of learning needs, training workshops, regular teleconferences and quality assurance processes. This support has been critical to developing the

necessary capabilities to successfully recruit and patients, secure consent, implement the trials and integrate the clinical trial activities into multidisciplinary practice.

Table 3: Overview of the palliative care clinical trials nurse role*

Role	Activities
Coordination	Developing pro-active referral systems, eligibility screening, obtaining informed consent, obtaining study medication, administering study intervention, efficacy and safety assessments, cessation of intervention,+/- withdrawal, follow up period: symptom and safety assessments, adverse event reporting, data collection, entry and management, participation in monitoring activities
Management of Ethical Submissions	Submission of new protocols, submission of amendments to protocols, management of ethics documentation, ensuring compliance with protocols, ethics reporting: adverse events, progress reports
Integration with Multidisciplinary Care	Identification as a member of the multidisciplinary team (MDT), obtaining referrals from MDT and discussing with treating consultant, sharing information obtained from the participant (with their permission) with the MDT, accurate and timely documentation of study processes, referral of patient to other MDT members or services where required, use of palliative care nursing skills and knowledge to support patients and carers
Promotion of evidence based practice and research	Demonstrating ethical and effective study processes, identifying staff knowledge needs, planning and conducting education, sharing information about the progress of each trial with the MDT, highlighting evidence-practice gaps eg the use of off license medications, participating in MDT activities which promote evidence based practice, communicating and celebrating the research activities and achievements
Management/Administration	Managing study budgets and financial reporting, development of systems, processes and resources, recruitment, orientation and coordination of study staff

*Aspects of the role are delegated by the Site Investigator, who accepts overall responsibility for the conduct of the trials and the medical care of participants. Many aspects of the role are completed in collaboration with the Site Investigator, eg adverse event reporting.

The consent process

At the majority of sites, the clinical trials nurse is responsible for actively seeking referrals and obtaining patient consent. The national ethics applications for each clinical trial specified that the clinical trials nurse could obtain consent from participants with the supervision of and delegation by the Site Investigator. Prior to study commencement the clinical trials nurses and investigators are trained in consent procedures for this study, with the opportunity to role play scenarios and develop a consent script to ensure all information is fully covered. Obtaining consent is therefore part of the role of the clinical trials nurse, subject to the requirements of local institutional ethics committees, which may varies from usual clinical trials practice in many jusidictions where consent is usually by a medical practitioner.

Throughout the consent process the clinical trials nurse applies knowledge of ethical research principles and regulations around consent to individual situations, with a dynamic counterpoise between the philosophies of beneficence, nonmaleficence and respect for individual autonomy (Hopkinson et al 2005; National Health and Research Council, Australian Research Council & Australian Vice-Chancellors' Committee, 2007; White et al 2008). The clinical trials nurse gives information about the study and assesses the impact of symptoms, illness and individual characteristics on the patient's capacity to receive and understand the information.

There are often marked variances between patients' capacity to make decisions and willingness to participate in clinical trials. In the interactions with Mr D (Case Study 1) and Mr R (Case Study 2) the clinical trials nurse assessed their capacity, eligibility and willingness to consider the Ketamine study and responded appropriately to each (Refer

Table 4). Care was taken to honestly and sensitively explain that symptoms may not be relieved during the study, recognising that for many patients hope of relief plays a part in their decision to participate in clinical trials. In Mr D's case, he was both willing and eligible to participate, and had the capacity to give consent, whilst it became evident during the pre-consent process that Mr R may not be either eligible or capable of giving an informed consent. As Mr R indicated he did not want to participate, confirmation of his capacity was not sought. These case studies illustrate the complexity of the interactions between the clinical trials nurse and each patient during the consent process, and the need for ethical, transparent and clinically skilled interactions.

Transparency around the consent process is achieved through optimal communication, both verbal and written, with the patient, their family and the multidisciplinary team: all interactions between the clinical trials nurse and the patient are documented in the patient's medical record, and a copy of the written consent form placed in the clinical file. Through these means the nurse models ethical research practice in the consent process, ensures it is open to scrutiny, ensures that the multi-disciplinary team is kept informed of the process and promotes the continuance of referrals (White et al 2008; Whiting & Vickers 2010).

Table 4: Case Studies Mr D and Mr R – Obtaining informed consent

Stages in consent process	**Case study – Mr D**	**Case Study - Mr R**
Referral	Mr D, an 81 year gentleman with metastatic lung cancer with poorly managed pain, AKPS 60. He was referred for consideration for inclusion in the Ketamine study (Hardy et al) by the medical registrar.	Mr R, a 76 year old gentleman with metastatic colorectal cancer, AKPS 50 was referred for consideration in the Ketamine study (Hardy et al) by the medical registrar.
Physician confirmation	The treating Physician was aware of the referral and happy for the patient to be approached about the study.	The treating Physician was aware of the referral and happy for the patient to be approached about the study.
Approaching the patient	The clinical trials nurse approached Mr D introduced herself and her role. Mr D was alert, and willing to discuss the study. The clinical trials nurse spent approximately 15 minutes with Mr D getting to know his circumstances.	The clinical trials nurse approached Mr R introduced herself and her role. Mr R was alert but appeared dishevelled. He agreed to discuss the study. The clinical trials nurse spent time with Mr R getting to know his circumstances, but quickly noticed that Mr R was distractible and fidgety.
Assessing the symptom	Mr D gave a clear description of the location, quality and intensity of his pain, and gave a numerical rating score (NRS) of 5/10 on average over the previous 24 hours. Mr D's level of pain meant that in relation to the symptom under investigation he was eligible to participate.	Mr R stated that he had pain in his back, but he was not able to give a NRS. Due to Mr R's difficulty scoring his pain it was not yet clear if he was eligible to participate in the study.
Checking it is OK to continue	Mr D stated he wanted to hear about the study.	The nurse asked Mr R if he wanted anything for pain. Mr R stated he did not want anything for pain at that time and

		he was willing to hear more about the study.
Explaining the study in detail	The nurse explained the purpose, duration and type of intervention, the assessments required, and what was meant by a placebo controlled trial and what implications this would have for his pain management. Mr D was informed that the study was voluntary and his personal details would be confidential. Mr D was offered the written information sheet.	The nurse started explaining the study in more detail to Mr R, but before all the information was given Mr R made a statement about participation.
Gauging the patient's response	Mr D took the written information sheet, and requested that the nurse speak with his wife, son and GP about the study.	Mr R said: "Yes, yes, I'll do it, anything so as get rid of this pain". The nurse explained that participation would not guarantee that pain would be relieved, and again outlined the placebo-controlled nature of the study. Mr R said "Oh, no, then I don't want the study, I want to just have the medication".
Assessing capacity	The nurse assessed Mr D's capacity to understand the implications of the study throughout their discussion. Her assessment was that Mr D understood the information and was able to give informed consent. A Mini-Mental assessment was completed to confirm capacity to consent: Mr D scored 27/30.	The nurse assessed Mr R's capacity to understand the implications of the study throughout their discussion. Her assessment was that Mr R was having difficulty understanding the implications of participation, and may not have the capacity to give an informed consent. A Mini-Mental assessment was not completed as Mr R declined participation.
Communicating	Mr D was thanked for agreeing to participate in the study,	The clinical trials nurse acknowledged the impact of the

acceptance of the patient's decision	and given information about the assessments that were required to confirm his eligibility. Once eligibility was confirmed Mr D was informed when the study intervention would start.	pain on Mr R, advised him that she would inform his medical team about his decision, and thanked him for taking the time to consider the study.
Obtaining written consent	Mr D signed the consent form, and a copy was given to him, and another copy placed in the clinical file.	Written consent was not sought from Mr R.
Communicating with the team and documenting the consent process	The nurse informed the site investigator and the medical and nursing team of Mr D's consent to participate. All aspects of their discussion were documented in the clinical file.	The discussion was documented by the nurse in the clinical file, and the medical and nursing team informed of his response, current pain and cognitive symptoms.
Outcome	Mr D commenced the Ketamine study the next day. He withdrew on Day 3 because he was experiencing side effects that were not acceptable to him. The nurse completed weekly follow up visits for 3 weeks During this time Mr D's condition deteriorated and he died less than four weeks after participation.	Overnight Mr R became more unwell, developing a chest infection and delirium. He continued to deteriorate and died 18 days later.

Integration with multidisciplinary care

Specialist palliative care is generally delivered by multidisciplinary teams (MDT) who are configured to address the unique needs of each patient and their families (Palliative Care Service Provision in Australia: A Planning Guide, 2006, p.8). These teams work within the World Health Organisation (2003) definition of palliative care, which emphasises impeccable assessment, relief of symptoms and distress, holism, quality of life and acceptance of dying as a normal process. These principles and the advanced illness and complexity of needs for many palliative care patients demand that the clinical trial nurses develop strategies to meet the needs of participants, their families, the MDT and the study and that there is sound integration between each element.

Communication

With the Site Investigator, the clinical trials nurse is responsible for communicating the purpose, rationale, protocols and progress of each study to the MDT members. Developing communication and a collaborative relationship with members of the MDT is critical to integrating clinical trials as another element of usual palliative care practice. Regular attendance and input into the MDT meetings, adding to the clinical documentation, developing relevant clinical trials information resources and verbal communication helps build collaboration and encourages members of the MDT to refer all potentially eligible patients for consideration of recruitment into a clinical trials. The team are then aware when the patient goes onto participate and of their response to the study intervention. It also enables the team to consider and come to agreement about how the patients' care will be managed once the trial has been completed.

Continuum of care

Whilst caring for a patient during their participation in a clinical trial it is inevitable that the nurse will recognise or be privy to patient or family needs or concerns, which may or may not be related to the symptom under investigation. The clinical trials nurse has a responsibility to refer to the MDT or other appropriate health professional to ensure the need is met. Examples include reporting an elevated temperature or blood sugar level to the team, or a more complex situation where the requirement for confidentiality requires the nurse to consider how to promote optimal care of the patient or family whilst ensuring ethical research practice. In the case study of Mrs M and her husband, the nurse became aware that Mr M was experiencing great distress about his wife's condition when he consented to complete a caregiver quality of life questionnaire during Mrs M's participation in the Octreotide study (Refer Table 5). After acknowledging his distress and seeking his permission to share his responses with the team, the nurse ensured supportive interventions were initiated by appropriate team members.

Table 5: Case Study Mrs and Mr M

Mrs M was referred to the Octreotide study, to which she consented and participated. Her husband Mr M consented to participate in the caregiver quality of life questionnaire. When the nurse read Mr M's questionnaire, she noted that he reported high levels of stress, guilt, frustration and insomnia, and felt unsupported by his family. The clinical trials nurse spent time talking with Mr M about his responses and acknowledged what he was feeling. This discussion confirmed to the nurse that Mr M was experiencing a high level of distress. She asked for his permission to communicate this to the team so that more support could be provided. Mr M agreed, and the nurse then spoke with his consultant and documented her discussion with Mr M. The consultant then liaised with the social worker and bereavement counselor to provide more intensive support for Mr M.

Systematic assessment

Care of the patient may be enhanced through the use of validated assessment tools. For example, assessment tools for delirium are not currently routinely used in palliative care clinical practice, despite the prevalence, seriousness, under-recognition and distressing nature of delirium in this population (Lawlor et al 2000; Agar & Lawlor 2008; Bruera et al 2009). The 'Risperidone for delirium' study (Agar et al) uses the Memorial Delirium Assessment Scale (MDAS) (Breitbart et al 1997; Lawlor et al 2000) and the Nursing Delirium Screening Scale (NuDESC) (Gaudreau 2005) to assess both eligibility and response during the study intervention period. Several delirium evaluation instruments exist, however this study requires tools which allow repeated assessments and measured change in severity over time (Agar et al). The MDAS is a brief, valid and reliable tool for assessing delirium severity in advanced cancer patients, and was developed to be consistent with DSM IV criteria (Breitbart et al 1997; Lawlor et al 2000). The MDAS is performed at eligibility (eligibility requires a score of >7) and daily between 8 am and 12 midday using information from the preceding 24 hour period. The Nu-DESC is a simple to use 5 item validated screening tool which enables continuous assessment of fluctuating delirium symptoms (Gaudreau 2005). A score of at least 1 in one of items 2 (altered communication), 3 (altered behaviour) or 4 (illusions/hallucinations) is required for a patient to be eligible; in addition it is the primary outcome measure of targeted delirium symptoms in the study. The NuDESC score is obtained at the end of each nursing shift by ward nursing staff, and also at 8am and 4pm by the clinical trials nurse, to determine the dose titration of the study medication.

Both tools contribute to systematic assessment and documentation of the symptoms of delirium for patients being both screened and participating in the study. Appropriate

interventions such as modification or treatment of precipitating factors and reassurance and explanation to the patient and family are then facilitated by communication between the clinical trials nurse, the Site Investigator and the MDT. Systematic assessment is likely to contribute to better understanding of complex symptoms under investigation and the experience of individual patients at participating sites.

Thus through optimal communication, assessment and promotion of care of participants clinical trials nurses achieve congruence with the philosophy of palliative care and integrate clinical trial activities into routine multidisciplinary care.

Establishing and Building the Evidence Base

Integration of clinical trial practice with multidisciplinary care also has the potential to influence care of patients who do not participate. There is some evidence that patients treated at hospitals participating in clinical trials have better outcomes than patients at hospitals which do not (Majumdar et al 2008). Majumdar et al hypothesised that clinical trial activity:

> "…has been developed to ensure that trial subjects receive safe, high-quality, protocol-driven care from highly trained research personnel overseen by experienced and well-informed investigators…these same elements could induce beneficial changes in the hospital environment, thereby leading to better processes and outcomes of care for patients treated outside the trial setting" (pp. 657- 658)

Although this effect was demonstrated in the acute cardiac setting using the outcomes of in-hospital mortality and use of guideline-indicated care, there is potential for a similar effect within palliative care settings. It is not within the scope of this paper to show this

effect, however there are a number of processes undertaken by clinical trials nurses that are likely to implement and establish the evidence-base at participating sites, including:

- Communicating the rationale for each clinical trial to the MDT
- Highlighting evidence-practice gaps
- Conducting audits on the local use of study medications when used "off-study"
- Integrating validated assessment tools into usual clinical practice
- Contributing to review of local medication policies and protocols
- Participation in journal clubs and research forums
- Delivering education on research and evidence-based practice

It is likely that these activities contribute to cultures which value questioning, reflective practice and evidence based practice, which has implications for all patients treated at the site (Janni et al 2006; Majumdar et al 2008). Working within the clinical trials role also develops participating nurses' knowledge and skills in research and evidence-based practice. This professional development is likely to have implications in the volume and quality of these nurses' future contribution to the generation of palliative care evidence.

Conclusion

The establishment of the PaCCSC clinical trials nurse role at across over a dozen Australian sites and completion of the first large RCT by the collaborative is testimony that recruiting palliative care patients to well designed RCT is feasible. The contribution of the clinical trials nurse in facilitating successful implementation of these clinical trial protocols cannot be underestimated. Managing the consent process with often very unwell patients, integrating clinical trials into usual multidisciplinary care, and

establishing and building the evidence base at participating sites are all important aspects of the PaCCSC clinical trials nursing role. Clinical trials nurse roles have the potential to improve the research capacity of the palliative care sector and outcomes for patients requiring palliative care. There is also the potential to contribute to future intervention development and/or take the next step to become independent researchers.

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