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## **Improving the evidence base in palliative care to inform practice and policy: Thinking outside the box**

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### **Abstract**

The adoption of evidence-based hierarchies and research methods from other disciplines may not completely translate to complex palliative care settings. The heterogeneity of the palliative care population, complexity of clinical presentations and fluctuating health states present significant research challenges.

The aim of this narrative review is to explore the debate about the use of current evidence-based approaches for conducting research, such as RCTs and other study designs, in palliative care, and more specifically to (a) describe key myths about palliative care research; (b) highlight substantive challenges of conducting palliative care research, using case illustrations; and (c) propose specific strategies to address some of these challenges.

Myths about research in palliative care revolve around evidence hierarchies, sample heterogeneity, random assignment, participant burden and measurement issues.

Challenges arise because of the complex physical, psychological, existential and spiritual problems faced by patients, families and service providers. These challenges

can be organized according to six general domains: patient, system/organization, context/setting, study design, research team and ethics. A number of approaches for dealing with challenges in conducting research fall into five separate domains: study design, sampling, conceptual, statistical, and measures and outcomes.

Although RCTs have their place whenever possible, alternative designs may offer more feasible research protocols that can be successfully implemented in palliative care.

Therefore, this article highlights 'outside the box' approaches that would benefit both clinicians and researchers in the palliative care field. Ultimately, the selection of research designs is dependent on a clearly articulated research question, which drives the research process.

## **Introduction**

*Each science must develop a set of techniques, methods, procedures and theories, which are appropriate for understanding the characteristics of the subject matter of the discipline*<sup>1</sup>.

To influence clinical practice in palliative care, clinicians need to have access to the "best" evidence. However, acquiring this evidence presents particular problems and the discipline of palliative care urgently requires a wider evidence base. Aoun and Kristjanson<sup>2,3</sup> examined the debate about best evidence within the public health literature. They proposed that similar arguments and concerns exist with respect to the use of current evidence-based approaches for implementing research and evaluating the literature in palliative care.

More recently, Hui and colleagues<sup>4,5</sup> examined the quality, design and scope of the palliative literature in a systematic review of 1,213 articles, spanning two time periods: 6

months in 2004 and 6 months in 2009. The four most common study designs from the evidence hierarchy (Figure 1) were: Case report/series (51%), cross-sectional surveys (18%), qualitative studies (11%), and cohort studies (9%). Randomized controlled trials (RCTs) comprised only 6% of all studies, the majority of which focused on interventions for physical symptoms with a median sample size of only 70 participants. Other aspects of palliative care, including communication, decision making/ethics, education, research methodology, and spirituality represented 5% or less of all RCTs. The authors concluded that there are critical concerns about the current state of knowledge conception with the overall methodological quality of RCTs being poor. The Cochrane systematic reviews in palliative care failed *“to provide good evidence for clinical practice because the primary studies are few in number, small, clinically heterogeneous, and of poor quality and external validity”* (p. 8).

(Insert figure 1 about here)

The most recent Cochrane review on the effectiveness of home palliative care services has raised similar methodological concerns <sup>6</sup>. Based on a review of 23 studies (37,561 patients and 4,042 caregivers), there was strong evidence to demonstrate that these services supported an increased number of patients dying at home and reduced symptom burden, without increasing caregiver grief. However, the evidence was not conclusive on nine other patient and caregiver outcomes due to a number of methodological issues. Therefore, there is a great need for high-quality evidence to

support everyday clinical practice and a need to conduct more studies on caregivers, health care professionals, and psychosocial-spiritual topics in palliative care.

Over the past two decades, numerous concerns regarding methodological issues and debates about the role of evidence-based approaches in palliative care research have been raised<sup>7-21</sup>. The purpose of this narrative review is to further explore the debate about the use of current evidence-based approaches, such as RCTs, for conducting research and evaluating the literature in palliative care, by addressing the following three questions:

- What are some myths about palliative care research?
- What are the challenges of conducting palliative care research?
- What strategies can be used to address these challenges?

We will begin with a description of five myths associated with palliative care research, followed by a summary of specific research challenges and strategies. To illustrate some of the challenges and corresponding strategies, we will present examples of research projects undertaken in different settings at the regional and international levels over the past 10 years.

### **What are some of the myths about palliative care research?**

Five myths that have potentially held back advances in the number, quality and diversity of palliative care research revolve around evidence hierarchies, sample heterogeneity, random assignment, participant burden and measurement issues, respectively.

*Myth 1: RCTs and systematic reviews are the highest (best) level of evidence.*

Palliative care researchers have drawn from many methods outside of the discipline, such as the basic and social sciences, to conduct palliative care research. The adoption of hierarchical frameworks, such as evidence-based medicine, in which RCTs and systematic reviews of RCTs are considered the “gold standard” representing the highest or best levels of evidence <sup>22</sup>, have created significant challenges in palliative care.

In a 25 year retrospective review of their research program, Bruera and Hui <sup>23</sup> suggested that some of their most useful research for patients and families was retrospective. Some of the most important questions either did not receive funding from industry or granting agencies, or were not appropriate for RCTs. Ahmedzai <sup>24</sup> has also suggested that RCTs may not always be appropriate, particularly for unique clinical cases in which urgent decisions need to be made despite a lack of evidence.

*Myth 2: Homogeneous samples are preferred over heterogeneous samples.*

Palliative care patients represent a unique cohort, consisting of multiple disease states and co-morbidities; diverse symptom profiles; fluctuating cognitive and functional status; and broad age ranges. The heterogeneity of this population presents significant research challenges <sup>12, 15</sup>. From a methodological perspective, homogeneous samples are preferred, in an effort to control extraneous variables. From a clinical perspective, however, the use of heterogeneous samples more closely approximates the clinical setting, with the findings being more representative and generalizable to diverse palliative care settings.

*Myth 3: Random assignment ensures group equivalency.*

Random assignment involves the use of a standard method, such as random number generators, for ensuring that each person has an equal chance of being assigned to each intervention. In RCTs, the use of appropriate random assignment procedures can control for the heterogeneity of palliative care populations by evenly distributing this heterogeneity across all groups <sup>12</sup>.

Despite being one of the best approaches for obtaining initial equivalency between different intervention groups, random assignment does not ensure group equivalency. Ineffective randomization procedures, small sample sizes, large within-group heterogeneity, different attrition rates between groups and potential threats to internal validity associated with control groups may create substantial barriers for obtaining and maintaining equivalent groups <sup>25</sup>. Additional approaches to ensure initial group equivalency, such as stratification, matching and increased sample sizes, may be warranted. Cluster sampling or randomization might also be effective when it is more feasible to select intact groups rather than individuals; however, special statistical analyses are needed to adjust for intra-cluster variability and may be less sensitive in detecting individual differences.<sup>25</sup> The use of desirable alternative or delayed interventions for control groups, such as randomized fast-track<sup>52</sup> or wait-list<sup>12</sup> designs, as well as intention-to-treat analysis, may be useful for maintaining group equivalency over time. Fast track or wait list designs ensure that all participants receive the treatment. However, these designs are most appropriate for patients with relatively stable conditions to minimize attrition over time.

*Myth 4: Research can be an additional and unwanted burden on patients and family members.*

Ethical concerns regarding the involvement of vulnerable, medically frail patients and their families in palliative care research are often raised. These concerns revolve around increased patient burden, potential distress and even harm that may be associated with taking part in research <sup>26</sup>; and are often raised by healthcare providers and family members <sup>27</sup>. Less is known about the patients' perspectives.

Hudson et al. <sup>28</sup> point to three levels of gatekeeping - institutional, professional, and patient and family gatekeeping - that have undermined the representativeness of research samples and the ability to generalize from research. According to Sharkey et al. <sup>29</sup>, clinician gate-keeping violates three principles that underpin international ethical guidelines: respect for persons' autonomy; beneficence (a favourable balance of risks and potential benefits); and justice (a fair distribution of the benefits and burdens of research).

In a systematic review, White and Hardy <sup>27</sup> identified eight studies focusing on the views of palliative care patients and their families towards research. Two themes relating to the benefits of participating in research that emerged from this review were the potential for personal gain and altruism. Additional themes included the desire to maintain autonomy and to avoid complex studies. Pessin et al. <sup>30</sup> interviewed 68 advanced cancer patients regarding participation in psychosocial research. Most participants reported no burden associated with participation (75%) and found it to be moderately to highly beneficial (68%). Almost three quarters of participating caregivers



in Hudson's study<sup>31</sup> identified benefits to their dying relative, themselves and for future families in need of palliative care. These findings further contribute to other reports highlighting patients' interest in and enhanced benefits of taking part in research<sup>15, 32</sup>.

*Myth 5: Only factors that can be measured are important.*

The principles of measurement initially evolved from the use of quantitative research designs, in which concepts were operationally defined and evaluated using appropriate outcome measures. With the advent of evidence-based medicine (EBM), the reliance on RCTs and systematic reviews as the highest level of evidence implicitly suggests that only those variables that can be measured are important<sup>33</sup>.

The development of assessment tools and outcome measures in palliative care has grown substantially, which has provided researchers with many options for instrument selection. In most clinical oncology drug trials, quality of life is now included as an outcome measure in trial designs, endorsing the importance of evaluating clinically relevant psychosocial-spiritual outcomes in intervention studies<sup>34</sup>. Accompanying this rapid development, however, researchers are often challenged with selecting an appropriate measure from a plethora of instruments, many of which do not have adequate validity evidence in palliative care settings<sup>35</sup>. The selection of outcome measures that adequately capture complex psychosocial-spiritual concepts is equally challenging<sup>36</sup>. Other approaches for understanding the complexity of patients' and family members' experiences that do not primarily rely on quantitative assessments and measures, including qualitative research methods, can also contribute to the advancement of palliative care<sup>19, 37</sup>. It is also worth pointing out that qualitative studies

provide important preliminary data to inform the development and subsequent validation of quantitative surveys.

### **What are some of the challenges of conducting palliative care research?**

Substantial challenges associated with conducting palliative care research have been previously described in the literature <sup>7-21</sup>. These challenges can be organized according to six general domains, as outlined in Table 1: (a) patient, (b) system/organization, (c) context/setting, (d) study design, (e) research team and (f) ethics.

[Insert Table 1 about here]

Patient factors include varying and unclear definitions for palliative care patients, population heterogeneity, frailty, and fluctuating clinical and cognitive status. In some cases, patient preferences to participate in disease-modifying, rather than symptom management, research, might also hinder recruitment <sup>38</sup>. Organizational factors often relate to complex ethical approval processes, undeveloped research cultures and segregated palliative care services. The limited availability and inherent competitiveness of research funding opportunities may create additional organizational barriers <sup>39, 40</sup>. Each setting has its own unique challenges in which competing clinical demands, opposing styles of practice, limited resources and lack of interest may impede the integration of research agendas within clinical settings. Study design issues revolve around restricted patient eligibility and recruitment, patient attrition, inappropriate randomization, blinding and use of placebos, difficulty controlling for interventions and lack of appropriate outcomes. Recruitment, training, availability and turnover of research

staff can influence research team dynamics. Finally, ethical issues, such as obtaining patient consent, patient safety and inability to withhold treatment, further contribute to these extensive research challenges. Given the fluctuating cognitive status of many palliative patients, the assessment of patients' cognitive status and understanding of their study involvement is paramount in studies where informed consent is required. Researchers need to carefully consider safety issues, targeting an acceptable balance between patient risks and benefits. Further treatments that have low toxicity profiles in non-palliative patients may not be well-tolerated in palliative care populations <sup>41</sup>.

Walshe <sup>21</sup> highlighted several challenges in using standard experimental methods for the evaluation of complex interventions in palliative care:

- Services change with time and are not used or provided consistently. Patients can receive a number of services from various providers at the same time or at different times leading to difficulties in determining the extent and nature of the treatment.
- Randomization or identification of a suitable comparison group is problematic, as there may not be enough providers to recruit from, in addition to the ethical issues regarding withholding services that are already being provided (e.g. when evaluating an existing program). If all patients in the program are already receiving the service, then it may be difficult to find a suitable comparison group outside the program. It would also not be feasible (or ethical) to withhold services from patients within the program.

- The sole use of quantitative experimental approaches gives little information about causation and about why certain effects were or were not observed. They also tend to investigate isolated components of a complex system and not the complicated relationships between components.
- The declining health status of participants leads to difficulties with attrition, retention or interrupted follow up. A high level of attrition prohibits the generation of sufficient data for a powered analysis.

In addition to these challenges, there is the issue of equipoise. One of the key principles of RCTs is a state of clinical equipoise, which means that no preference for any particular treatment arm can occur <sup>42</sup>. However, a state of clinical equipoise is difficult to achieve in studies designed to test complex interventions that are not amenable to blinding, as is possible for RCTs designed to test different medical interventions, such as clinical drug trials. Complex interventions require informed and motivated participants and professionals to engage in the process. In palliative care research, controlling confounding effects, as is the case in clinical drug trials using RCT design are seldom feasible, justifiable or acceptable to the patient. Patients with cancer and their families may not wish to risk reducing the quality of life of their remaining days by participating in a trial with an uncertain outcome. Practitioners may not wish to randomise their patients to treatments in which they lack confidence. Few of them have neutral views about the differences between two or more treatments; hence, clinical equipoise, a requirement of RCTs, may be impossible to achieve. No systematic review has yet integrated the evidence on

participants' and professionals' preferences for particular treatments as modifiers of outcome in randomised trials<sup>42</sup>.

To address these challenges, Walshe<sup>21</sup> proposed the use of case study research. Case study designs are context-driven, rather than method-driven, most commonly being defined by the selected case. This type of research design has the potential to integrate a diversity of quantitative and qualitative methods and data, providing rich understandings from diverse perspectives.

The following three case examples of complex psychological, pharmacological and health services intervention studies, respectively, illustrate several of these methodological challenges, with more details reported on the development and evaluation of Case 3.

#### *Case 1: Dignity Therapy- psychological intervention*

Dignity Therapy is an intervention consisting of interviewing palliative care patients using a series of guided questions about their life and past events that are important to them, resulting in the production of an edited generativity document that could be shared with family members and service providers<sup>43</sup>. A randomized controlled trial to test the effectiveness of dignity therapy for the terminally ill was conducted in Canada, the United States and Australia (n=326), with three comparison groups: the dignity therapy intervention, client centred care and standard care<sup>44</sup>. There were no significant differences between the three groups in terms of the primary outcome of distress. The

authors reported that due to the low base rate of distress within the sample, there was no room for improvement.

However, Nekolaichuk<sup>36</sup> highlighted some substantial impediments for research into psychosocial interventions such as dignity therapy. First, the selection of outcome measures that adequately capture complex psychosocial spiritual concepts is challenging. Some terminally ill patients might be distressed while simultaneously feeling hopeful, and finding meaning in life: Patients have described this apparent paradoxical experience in different ways, including being on an emotional living-dying pendulum<sup>45</sup> or as “latching onto life” in the midst of the possibility of dying<sup>46</sup>. Second, recruitment is often restricted to articulate, cognitively intact patients; therefore, physically frail or highly distressed patients are less likely to participate. A third impediment relates to the lack of standardisation of psychosocial interventions across several sites. Differences exist in care availability and discipline mix between a specialized inpatient tertiary palliative care unit and a home care team. Additionally, some psychosocial spiritual interventions in standard care might help relieve patient distress in the comparison or control groups.

### *Case 2: Ketamine Clinical Drug Trial- pharmacological intervention*

Pharmacological clinical trials were undertaken in 10 Australian palliative care services to test the clinical benefits of a number of drugs, ketamine for pain relief being one of them. The project faced a myriad of protocol and operational issues in all sites. These included complex inclusion/exclusion criteria, as patients needed to be on stable medications for 48 hours; and variations in clinical assessments and pain adjuvant

treatments<sup>47, 48</sup>. Many patients did not complete the study due to disease progression; in some cases, declining conditions made it difficult for patients to swallow tablets.

Several reasons for gate keeping by clinicians included the following:

- The clinical practice not aligning with study protocols.
- The use of placebo not justifiable.
- Patients too unwell to be approached for consent.
- The clinicians' personal beliefs about the medications and time involved.

The following operational issues created additional challenges:

- Patients not under the control of the project chief investigators
- Difficulty maintaining enthusiasm of staff
- Difficulty conducting research in services with no research culture
- Lack of engagement by site investigators
- Staffing issues in recruitment, training and turnover
- Pharmaceutical restrictions in which randomization was restricted to certain days of the week, time restrictions on when scripts needed in pharmacy and lack of availability of drug over weekends

For the 12 months of the ketamine study in Western Australia, 61 people were screened, 7 were randomized, and only 4 completed treatment. Reasons for this low completion rate included patients not meeting inclusion criteria (e.g. patients were already on Ketamine or unstable opioids, undertaking radiotherapy/treatment, having dementia or confusion), deteriorating health or declining to participate. Hardy et al.<sup>49</sup> reported on the national findings of the ketamine study. There were significantly higher

rates of toxicity and other side-effects among the 93 patients given ketamine, compared with the 92 who were given a placebo. Based on the study findings, it was concluded that ketamine did not have a net clinical benefit when used as an adjunct to opioids and standard co-analgesics in cancer pain.

In order to enhance the effectiveness of resources applied to palliative and end of life research, Hagen et al.<sup>41</sup> highlighted several approaches for establishing accrual targets and implementing appropriate interventions if study targets are not reached.

### *Case 3: The Home Alone Study- health service intervention*

This project implemented and evaluated two models of care for terminally-ill people living alone at home, compared to routine care: installing personal alarms and providing extra care aide support<sup>50</sup>. The primary aim was to assess the feasibility of using an RCT approach with this group. A secondary aim was to assess the potential impact of the models of care on the participants' quality of life, symptom distress, anxiety and depression, and perceived benefits and barriers to their use. The challenges of this quantitative approach were numerous:

- The rapidly changing clinical situations meant shifting the timing of measurements and the follow-up session to catch some patients before they died, while other patients survived longer than expected.
- Attrition rates differed between groups as more deaths occurred in the two intervention groups than in the control group.



- Some patients who were randomised to the care aide group did not really need or want this support and care aides were considered more of an intrusion.
- There was wide variation in the degrees of “home aloneness,” as a significant proportion of patients were receiving visits from family and friends either occasionally or regularly, be it for a social visit or to get help with household tasks. This variation confounded the findings in terms of how much informal support each patient was getting over and above the implemented models of care that were randomly allocated. Therefore, this created an impediment to evaluating the effectiveness of interventions using an RCT approach.
- Patient recruitment and attrition were hampered due to limited survival times and clinician gate-keeping during the recruitment period, with only 43 of 330 potential participants completing the study in an 18 month period.

### **What strategies can be used to address some of the challenges in conducting research?**

A number of approaches for dealing with these challenges in conducting research are summarized in Table 2, based on reports in the literature. As shown in this table, these approaches can be divided into five separate domains: (a) study design, (b) sampling, (c) conceptual, (d) statistical analysis and (e) measures and outcomes.

[Insert Table 2 about here]

#### *(a) Study Design*

In terms of study design, specific strategies targeting RCTs have been proposed. These include general suggestions for designing a clinical trial <sup>51</sup>, as well as the use of randomized fast-track trials, in which the comparison (control) group is offered the intervention at the end of the normal randomized trial <sup>52</sup>. The use of enrichment design strategies, in which targeted strategies are used to select participants based on the presence or absence of specific markers, are being used more frequently in clinical drug trials <sup>53, 54</sup>. These designs are most appropriate when the new targeted agent's mechanism of action is well known. Crossover designs, which require fewer patients, and "N of 1" studies, which individualize treatments, can provide meaningful comparisons in which patients serve as their own controls. Both of these designs are most appropriate for patients with relatively stable disease and can supplement other RCT designs. Davis and Mitchell<sup>55</sup> provide a more detailed discussion of these alternatives to the classic RCT, highlighting their strengths and weaknesses.

Others have advocated for the use of research designs other than RCTs <sup>9, 19</sup>, including case study <sup>21</sup>, action research <sup>56</sup>, discourse analysis <sup>57</sup>, narrative research <sup>58</sup> and mixed method designs <sup>59</sup>. The most recent update of the Medical Research Council Framework in the United Kingdom <sup>60</sup> recommended using mixed methods to develop and evaluate complex interventions by combining qualitative and quantitative approaches: "Wherever possible, evidence should be combined from a variety of sources that do not share the same weaknesses" (p. 980). The following is an example of how mixed methods have added value when used in developing and evaluating the models of care for terminally ill people who live alone (The Home Alone study mentioned in the previous section).

The first phase of this study consisted of scoping the problem in three large community-based palliative care services in Australia. This was achieved by analysis of services records of 721 home alone clients, where the demographic and clinical profiles, the services provided, hospitalisations and place of death were ascertained <sup>61</sup>. This was followed by in-depth interviews with a small number of patients and service providers to assess unmet needs and gaps in service provision <sup>62, 63</sup>. Based on these findings, a questionnaire was then developed and posted to 90 service providers to identify their priorities and recommendations for models of care/ interventions. In the second phase, two of the recommended models of care were implemented using a three-armed RCT approach: installing personal alarm systems (arm 1), providing extra care aide support (arm 2) and providing standard care (arm 3) <sup>50</sup>. This was followed by in-depth interviews with patients and service providers to assess barriers to and benefits of the two models of care <sup>63</sup>.

The findings from the qualitative interviews revealed that both models of care could meet the physical and psychosocial support needs for home alone patients towards the end of their lives. By providing a safer, more secure environment through the use of either the personal alarm or the care aide support, patients were able to continue their activities of daily living with a degree of independence, while remaining at home <sup>63</sup>. This example is a useful illustration of the value of mixed methods design where insights gained from qualitative (described here) and quantitative (described in previous section) approaches complemented each other to provide a more in-depth understanding of the evaluated intervention.

*(b) Sampling*

Specific strategies to address sampling concerns have focused on the development of conceptual frameworks for defining the palliative care population<sup>64, 65, 83</sup>, as well as the collection and reporting of minimum data sets for reporting patient characteristics in the study findings<sup>66-69</sup>. The development of a taxonomy to guide clinical trial recruitment<sup>51</sup> and the use of administrative databases to assess study feasibility<sup>67, 70</sup> have also been proposed to improve patient recruitment.

*(c) Conceptual*

Conceptual strategies have focused on approaches for building research capacity<sup>8</sup>, through the development of innovative partnerships; multidisciplinary research teams involving researchers, clinicians, basic scientists and social scientists<sup>8, 71</sup>; and international collaborations<sup>8, 72, 73</sup>. Some have emphasized the importance of progressing in incremental steps<sup>8</sup> and the use of different frameworks for assessing evidence, such as equity-based frameworks<sup>3</sup> or Jonas' <sup>74</sup> concept of an "evidence house." Jonas offers a compelling argument for considering an "evidence house," rather than an evidence hierarchy, consisting of many "rooms" or types of research methods that may equally be used as evidence for research, depending upon the purpose.

*(d) Statistical Analysis*

Statistical analysis of palliative care findings may present substantive challenges. Preston and colleagues identified three key areas as being potentially problematic for statistical analyses in palliative and end-of-life care research: missing data, attrition and response shifts<sup>75</sup>. In a review of 18 clinical trials (n=1214), Hui et al.<sup>76</sup> described a median attrition rate of 28% and 44% for primary and end-of-study outcomes, respectively. The two main reasons for attrition were patient withdrawal, most commonly

due to high symptom burden, and clinical deterioration. Other statistical analysis issues that need to be considered include the importance of clinical relevancy (minimal clinically important differences) <sup>77, 78</sup> as opposed to purely statistical significance of findings; regression towards the mean for extreme scores <sup>25</sup>; and the shape and variance of the sample distribution in relation to the expected normal population distribution.<sup>25</sup>

Statistical approaches have largely focused on strategies for dealing with missing data and attrition, as illustrated through palliative care case presentations <sup>79, 80</sup>. Based on a consultation workshop with experts in statistical methods in palliative and end-of-life care, specific recommendations for managing missing data and attrition have also been proposed <sup>75</sup>.

#### *(e) Measures and Outcomes*

The selection of appropriate measures and outcomes continues to be problematic due to the diversity of available tools, and, in many cases, limited reliability and validity evidence in palliative care settings. Varying scale formats and instrument time frames can complicate score interpretation, particularly with cross study comparisons. One approach for addressing these issues is the use of standard measures for recording clinical outcomes <sup>8</sup>, which could then be used as a framework for research designs and program evaluation. The development and validation of the Edmonton Classification System for Cancer Pain (ECS-CP) illustrates this approach <sup>70, 81</sup>. The requirement for patient consent was waived by the ethics review boards, as all of the study variables were part of routine assessments in clinical practice. Thus, all patients admitted to the palliative care services were included in the study designs.

The development of minimum datasets for describing research studies could further facilitate multi-site collaborations and cross-study comparisons. As an example, Currow and colleagues<sup>82</sup> have proposed a generalizability framework for classifying palliative care research, consisting of five domains: (a) patient and caregiver, (b) professional, (c) service, (d) health and social policy, and (e) research. Within each domain, core and optional data elements that could potentially influence generalizability of findings are proposed.

## **Conclusion**

This narrative review highlighted some of the potential myths and challenges associated with conducting palliative care research, accompanied by some effective “out of the box” strategies for designing studies in this complex field. Although RCTs and systematic reviews represent an important source of evidence, they may not always be appropriate for certain research questions and palliative care settings. Research designs need to take into account the unique qualities and culture of each setting. Whenever possible, pilot feasibility studies need to be conducted to determine whether or not a particular setting is appropriate for the proposed research. The integration of routine assessments into clinical practice and the maintenance of clinical administrative databases can complement the development of clinically-based research programs.

The realities of conducting research in complex, palliative care settings will continue to challenge researchers. The ideal principles of research methodologies and study designs, many of which originated from other disciplines, are not readily transferable to palliative care. Researchers will continue to be confronted with difficult decisions, often

weighing research ideals with clinical realities. There are a number of ongoing issues, which will continue to challenge researchers in this area, in line with the following dichotomies:

- individual versus population-based focus
- homogeneous (e.g. single tumour group, specific palliative care setting or stage of cancer) versus heterogeneous samples (e.g. multiple disease states, different illness courses, diverse symptom profiles)
- single versus multiple interventions
- outcome versus process

A summary of these dichotomies and corresponding questions appears in Table 3.

[Insert Table 3 about here]

Ultimately, it is the research question, which is clearly articulated and clinically relevant, that provides a guiding framework for developing the research design and conducting the study. Future work needs to address how we grade studies in palliative care to guide practice, when most studies are at a lower level of evidence than RCTs and systematic reviews. If studies are to be fairly and accurately graded for the development of evidence-based guidelines, a new system for classifying evidence is warranted<sup>2</sup>.

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## References

1. Howard GS. Dare we develop a human science? Notre Dame, Indiana: Academic Publications; 1986; p. 208.
2. Aoun S, Kristjanson L. Evidence in palliative care research: How should it be gathered? *Medical Journal of Australia*. 2005; 183(5):264-6.
3. Aoun S, Kristjanson L. Challenging the framework for evidence in palliative care research. *Palliative Medicine*. 2005; 19(6):461-5.
4. Hui D, Arthur J, Dalal S, Bruera E. Quality of the supportive and palliative oncology literature: a focused analysis on randomized controlled trials. *Supportive Care in Cancer*. 2012; 20(8):1779-1785. DOI:10.1007/s00520-011-1275-9.
5. Hui D, Parsons H, Damani S, Fulton S, Liu J, Evans A, et al. Quantity, Design, and Scope of the Palliative Oncology Literature. *The Oncologist*. 2011; 16(5):694-703. DOI:10.1634/theoncologist.2010-0397.
6. Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. *Cochrane Database of Systematic Reviews*. 2013; 6:CD007760. DOI:10.1002/14651858.CD007760.pub2.
7. Beaver K, Luker K, Woods S. Conducting research with the terminally ill: Challenges and considerations. *International Journal of Palliative Nursing*. 1999; 5(1):13-17.
8. Bennett M, Davies E, Higginson IJ. Review: Delivering research in end-of-life care: problems, pitfalls and future priorities. *Palliative Medicine*. 2010; 24(5):456-461. DOI:10.1177/0269216310366064.
9. Corner J. Is there a research paradigm for palliative care? *Palliative Medicine*. 1996; 10(3):201-8.
10. Davies B, Reimer JC, Brown P, Martens N. Challenges of conducting research in palliative care. *Omega (Westport)*. 1995; 31(4):263-73.
11. Evans C, Harding R, Higginson IJ, MORECare obo. 'Best practice' in developing and evaluating palliative and end-of-life care services: A meta-synthesis of research methods for the MORECare project. *Palliative Medicine*. 2013; DOI:10.1177/0269216312467489.
12. Grande GE, Todd CJ. Why are trials in palliative care so difficult? *Palliative Medicine*. 2000; 14(1):69-74.
13. Higginson IJ. Evidence based palliative care. *BMJ*. 1999; 319(7208):462-463. DOI:10.1136/bmj.319.7208.462.
14. Jordhøy M, Kaasa S, Fayers P, Ovreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. *Palliative Medicine*. 1999; 13(4):299-310.
15. Kaasa S, Hjermstad MJ, Loge JH. Methodological and structural challenges in palliative care research: how have we fared in the last decades? *Palliative Medicine*. 2006; 20(8):727-34. DOI:10.1177/0269216306072620.
16. Keeley D. Rigorous assessment of palliative care revisited. *BMJ*. 1999; 319(7223):1447-1448. DOI:10.1136/bmj.319.7223.1447.
17. Keeley P, Waterhouse E, Noble S. The evidence base of palliative medicine: is inpatient palliative medicine evidence-based? *Palliative Medicine*. 2007; 21(7):623-627. DOI:10.1177/0269216307082657.

18. McQuay H, Moore A. Need for rigorous assessment of palliative care. *BMJ*. 1994; 309(6965):1315-1316. DOI:10.1136/bmj.309.6965.1315.
19. Payne S, Turner J. Research methodologies in palliative care: a bibliometric analysis. *Palliative Medicine*. 2008; 22(4):336-342. DOI:10.1177/0269216308090072.
20. Rinck G, van den Bos G, Kleijnen J, de Haes H, Schadé E, Veenhof C. Methodologic issues in effectiveness research on palliative cancer care: a systematic review. *Journal of Clinical Oncology*. 1997; 15(4):1697-707.
21. Walshe C. The evaluation of complex interventions in palliative care: An exploration of the potential of case study research strategies. *Palliative Medicine*. 2011; 25(8):774-781. DOI:10.1177/0269216311419883.
22. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996; 312(7023):71-2.
23. Bruera E, Hui D. Palliative care research: Lessons learned by our team over the last 25 years. *Palliative Medicine*. 2013; DOI:10.1177/0269216313477177.
24. Ahmedzai S. Evidence-based medicine in palliative care: a systematic mistake? *Progress in Palliative Care*. 1997; 5(3):97-99.
25. Gall M, Gall J, Borg W. Educational research: An introduction. . 7th ed. Boston: Allyn & Bacon; 2003.
26. Emanuel EJ, Fairclough DL, Wolfe P, Emanuel LL. Talking with terminally ill patients and their caregivers about death, dying, and bereavement: Is it stressful? is it helpful? *Archives of Internal Medicine*. 2004; 164(18):1999-2004. DOI:10.1001/archinte.164.18.1999.
27. White C, Hardy J. What do palliative care patients and their relatives think about research in palliative care?—a systematic review. *Supportive Care in Cancer*. 2010; 18(8):905-911. DOI:10.1007/s00520-009-0724-1.
28. Hudson P, Aranda S, Kristjanson L, Quinn K. Minimising gate-keeping in palliative care research. *European Journal of Palliative Care*. 2005; 12(4):165-169.
29. Sharkey K, Savulescu J, Aranda S, Schofield P. Clinician gate-keeping in clinical research is not ethically defensible: an analysis. *Journal of Medical Ethics*. 2010; 36(6):363-366. DOI:10.1136/jme.2009.031716.
30. Pessin H, Galietta M, Nelson CJ, Brescia R, Rosenfeld B, Breitbart W. Burden and benefit of psychosocial research at the end of life. *Journal of Palliative Medicine*. 2008; 11(4):627-32. DOI:10.1089/jpm.2007.9923.
31. Hudson P. The experience of research participation for family caregivers of palliative care cancer patients. *International Journal of Palliative Nursing*. 2003; 9(3):120-3.
32. Ross C, Cornbleet M. Attitudes of patients and staff to research in a specialist palliative care unit. *Palliative Medicine*. 2003; 17(6):491-7.
33. Williams DD, Garner J. The case against "the evidence": a different perspective on evidence-based medicine. *British Journal of Psychiatry*. 2002; 180:8-12.
34. Staquet M, Hays R, Fayers P. Assessing quality of life in clinical trials: Methods and practice. 2<sup>nd</sup> ed: Oxford University Press; 2005.
35. De Roo M, Leemans K, Claessen S, Cohen J, Pasma HRW, Deliëns L, et al. Quality Indicators for Palliative Care: Update of a Systematic Review. *Journal of Pain and Symptom Management*. In press; (0) DOI:10.1016/j.jpainsymman.2012.09.013.

36. Nekolaichuk C. Dignity therapy for patients who are terminally ill. *The Lancet Oncology*. 2011; 12(8):712-713. DOI:10.1016/S1470-2045(11)70185-1.
37. Audrey S. Qualitative research in evidence-based medicine: Improving decision-making and participation in randomized controlled trials of cancer treatments. *Palliative Medicine*. 2011; 25(8):758-765. DOI:10.1177/0269216311419548.
38. Crowley R, Casarett D. Patients' willingness to participate in symptom-related and disease-modifying research: results of a research screening initiative in a palliative care clinic. *Cancer*. 2003; 97(9):2327-33. DOI:10.1002/cncr.11329.
39. Gelfman LP, Morrison RS. Research funding for palliative medicine. *J Palliat Med*. 2008; 11(1):36-43. DOI:10.1089/jpm.2006.0231.
40. Hui D, Reddy A, Parsons HA, Bruera E. Reporting of funding sources and conflict of interest in the supportive and palliative oncology literature. *J Pain Symptom Manage*. 2012; 44(3):421-30. DOI:10.1016/j.jpainsymman.2011.09.016.
41. Davis MP, Kirkova J, Lagman R, Walsh D, Karafa M. Intolerance to mirtazapine in advanced cancer. *J Pain Symptom Manage*. 2011; 42(3):e4-7. DOI:10.1016/j.jpainsymman.2011.05.002.
42. King M. The effects of patients' and practitioners' preferences on randomized clinical trials. *Palliative medicine*. 2000; 14(6):539.
43. Chochinov H, Hack T, Hassard T, Kristjanson L, McClement S, Harlos M. Dignity Therapy: A Novel Psychotherapeutic Intervention for Patients Near the End of Life. *Journal of Clinical Oncology*. 2005; 23(24):5520-5525. DOI:10.1200/jco.2005.08.391.
44. Chochinov H, Kristjanson L, Breitbart W, McClement S, Hack T, Hassard T, et al. Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial. *The Lancet Oncology*. 2011; 12(8):753-762. DOI:10.1016/S1470-2045(11)70153-X.
45. Sand L, Olsson M, Strang P. Coping strategies in the presence of one's own impending death from cancer. *J Pain Symptom Manage*. 2009; 37(1):13-22. DOI:10.1016/j.jpainsymman.2008.01.013.
46. Saeteren B, Lindstrom UA, Naden D. Latching onto life: living in the area of tension between the possibility of life and the necessity of death. *J Clin Nurs*. 2011; 20(5-6):811-8. DOI:10.1111/j.1365-2702.2010.03212.x.
47. Shelby-James T, for the Palliative Care Clinical Studies Collaborative (PaCCSC). Internal study report. Daw Park, South Australia: Flinders University; January 2010.
48. Currow DC, Agar MR, Abernethy AP. Tackling the Challenges of Clinical Trials in Palliative Care. *Pharmaceutical Medicine*. 2011; 25(1):7-15.
49. Hardy J, Quinn S, Fazekas B, Plummer J, Eckermann S, Agar M, et al. Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain. *Journal of Clinical Oncology*. 2012; 30(29):3611-3617. DOI:10.1200/jco.2012.42.1081.
50. Aoun S, O'Connor M, Breen L, Deas K, Skett K. Testing models of care for terminally ill people who live alone at home: is a randomised controlled trial the best approach? *Health & Social Care in the Community*. 2013; 21(2):181-190. DOI:10.1111/hsc.12002.
51. Hagen N, Wu J, Stiles C. A Proposed Taxonomy of Terms to Guide the Clinical Trial Recruitment Process. *Journal of Pain and Symptom Management*. 2010; 40(1):102-110. DOI:10.1016/j.jpainsymman.2009.11.324.

52. Higginson IJ, Booth S. The randomized fast-track trial in palliative care: Role, utility and ethics in the evaluation of interventions in palliative care? *Palliative Medicine*. 2011; 25(8):741-747. DOI:10.1177/0269216311421835.
53. Mandrekar SJ, Sargent DJ. All-comers versus enrichment design strategy in phase II trials. *J Thorac Oncol*. 2011; 6(4):658-60. DOI:10.1097/JTO.0b013e31820e17cb.
54. Wang SJ, Hung HM. Adaptive enrichment with subpopulation selection at interim: methodologies, applications and design considerations. *Contemp Clin Trials*. 2013; 36(2):673-81. DOI:10.1016/j.cct.2013.09.008.
55. Davis MP, Mitchell GK. Topics in research: structuring studies in palliative care. *Curr Opin Support Palliat Care*. 2012; 6(4):483-9. DOI:10.1097/SPC.0b013e32835843d7.
56. Froggatt K, Hockley J. Action research in palliative care: Defining an evaluation methodology. *Palliative Medicine*. 2011; 25(8):782-787. DOI:10.1177/0269216311420483.
57. O'Connor M, Payne S. Discourse analysis: examining the potential for research in palliative care. *Palliative Medicine*. 2006; 20(8):829-834. DOI:10.1177/0269216306072348.
58. Bingley A, Thomas C, Brown J, Reeve J, Payne S. Developing narrative research in supportive and palliative care: the focus on illness narratives. *Palliative Medicine*. 2008; 22(5):653-658. DOI:10.1177/0269216308089842.
59. Farquhar M, Ewing G, Booth S. Using mixed methods to develop and evaluate complex interventions in palliative care research. *Palliative Medicine*. 2011; 25(8):748-757. DOI:10.1177/0269216311417919.
60. Craig P, Dieppe P, McIntyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008; 337 DOI:10.1136/bmj.a1655.
61. Aoun S, Kristjanson L, Currow D, Skett K, Oldham L, Yates P. Terminally-ill people living alone without a caregiver: an Australian national scoping study of palliative care needs. *Palliative Medicine*. 2007; 21(1):29-34. DOI:10.1177/0269216306073198.
62. Aoun S, Kristjanson LJ, Oldham L, Currow D. A qualitative investigation of the palliative care needs of terminally ill people who live alone. *Collegian*. 2008; 15(1):3-9.
63. Aoun S, O'Connor M, Skett K, Deas K, Smith J. Do models of care designed for terminally ill 'home alone' people improve their end-of-life experience? A patient perspective. *Health & Social Care in the Community*. 2012; 20(6):599-606. DOI:10.1111/j.1365-2524.2012.01074.x.
64. McNamara B, Rosenwax L, Holman CDJ. A Method for Defining and Estimating the Palliative Care Population. *Journal of Pain and Symptom Management*. 2006; 32(1):5-12. DOI:10.1016/j.jpainsymman.2005.12.018.
65. Van Mechelen W, Aertgeerts B, De Ceulaer K, Thoosen B, Vermandere M, Warmenhoven F, et al. Defining the palliative care patient: A systematic review. *Palliative Medicine*. 2013; 27(3):197-208. DOI:10.1177/0269216311435268.
66. Casarett D, Teno J, Higginson IJ. How Should Nations Measure the Quality of End-of-Life Care for Older Adults? Recommendations for an International Minimum Data Set. *Journal of the American Geriatrics Society*. 2006; 54(11):1765-1771. DOI:10.1111/j.1532-5415.2006.00925.x.

67. Currow D, Shelby-James T, Agar M, Plummer J, Rowett D, Glare P, et al. Planning phase III multi-site clinical trials in palliative care: the role of consecutive cohort audits to identify potential participant populations. *Supportive Care in Cancer*. 2010; 18(12):1571-1579. DOI:10.1007/s00520-009-0780-6.
68. Kaasa S, Caraceni A. Palliative Cancer Care Research. *Palliative Medicine*. 2010; 24(3):259-260. DOI:10.1177/0269216310362852.
69. Sigurdardottir K, Oldervoll L, Hjermstad MJ, Kaasa S, Knudsen A, Løhre E, et al. How Are Palliative Care Cancer Populations Characterized in Randomized Controlled Trials? A Literature Review. *Journal of Pain and Symptom Management*. In press; (0) DOI:10.1016/j.jpainsymman.2013.06.005.
70. Fainsinger R, Baracos V, Fassbender K, Nekolaichuk C, Watanabe S, Quan H. Using a Comprehensive Palliative Care Program Database to Plan Research Trials in Palliative Care. OA45. Abstracts of the 7th World Research Congress of the European Association for Palliative Care (EAPC). Trondheim, Norway. *Palliative Medicine*. 2012; 26(4):384-674. DOI:10.1177/0269216312446391.
71. Froggatt K, Field D, Bailey C, Krishnasamy M. Qualitative research in palliative care 1990-1999: a descriptive review. *International Journal of Palliative Nursing*. 2003; 9(3):98-104.
72. Kaasa S. Editorial: Palliative care research – time to intensify international collaboration. *Palliative Medicine*. 2008; 22(4):301-302. DOI:10.1177/0269216308091918.
73. Kaasa S, Radbruch L. Palliative care research – priorities and the way forward. *European Journal of Cancer*. 2008; 44(8):1175-1179. DOI:10.1016/j.ejca.2008.02.036.
74. Jonas WB. The evidence house: how to build an inclusive base for complementary medicine. *The Western Journal of Medicine*. 2001; 175(2):79-80.
75. Preston N, Fayers P, Walters S, Pilling M, Grande GE, Short V, et al. Recommendations for managing missing data, attrition and response shift in palliative and end-of-life care research: Part of the MORECare research method guidance on statistical issues. *Palliative Medicine*. 2013; DOI:10.1177/0269216313486952.
76. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. *Cancer*. 2013; 119(5):1098-105. DOI:10.1002/cncr.27854.
77. Bedard G, Zeng L, Zhang L, Lauzon N, Holden L, Tsao M, et al. Minimal clinically important differences in the edmonton symptom assessment system in patients with advanced cancer. *J Pain Symptom Manage*. 2013; 46(2):192-200. DOI:10.1016/j.jpainsymman.2012.07.022.
78. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001; 94(2):149-58.
79. Fielding S, Fayers PM, Loge JH, Jordhøy MS, Kaasa S. Methods for handling missing data in palliative care research. *Palliative Medicine*. 2006; 20(8):791-798. DOI:10.1177/0269216306072555.
80. Palmer JL. Analysis of missing data in palliative care studies. *Journal of Pain and Symptom Management*. 2004; 28(6):612-618. DOI:10.1016/j.jpainsymman.2004.02.026.

81. Fainsinger R, Nekolaichuk C, Lawlor P, Hagen N, Bercovitch M, Fisch M, et al. An international multicentre validation study of a pain classification system for cancer patients. *European Journal of Cancer*. 2010; 46(16):2896-2904. DOI:10.1016/j.ejca.2010.04.017.
82. Currow DC, Wheeler JL, Glare PA, Kaasa S, Abernethy AP. A framework for generalizability in palliative care. *J Pain Symptom Manage*. 2009; 37(3):373-86. DOI:10.1016/j.jpainsymman.2008.03.020.
83. Hui D, Mori M, Parsons HA, Kim SH, Li Z, Damani S, et al. The lack of standard definitions in the supportive and palliative oncology literature. *J Pain Symptom Manage*. 2012; 43(3):582-92. DOI:10.1016/j.jpainsymman.2011.04.016.

**Table 1. Challenges of conducting palliative care research**

Domain	Challenge	References
Patient	• defining the palliative care patient (timing, terminology)	8, 64, 65, 83
	• heterogeneity of the population	12, 15, 20
	• frailty	7
	• unpredictable clinical course and declining health	15
	• increased prevalence of cognitive impairment, particularly with advancing disease	15
	• individual patient preferences to participate in disease-modifying rather than symptom management research	38
System or organization	• complicated or complex processes for obtaining ethical and administrative approval for research studies	7
	• undeveloped research culture or lack of awareness of relevancy of research	9
	• service delivery of palliative care services, which is not integrated or which has undergone substantial change	47, 48
	• funding challenges	39, 40
Context or setting	• gatekeeping by clinicians or family members	28, 29
	• clinical practice does not align with protocols	47, 48
	• increased workload for clinicians (e.g. medical assessments by clinicians required)	47, 48
	• limited or unavailable staff on weekends (research and clinical staff)	47, 48
	• lack of engagement by site investigators	47, 48
Study design	• Patient eligibility and recruitment	10, 14, 20
	○ complex inclusion and exclusion criteria, which may prevent many patients from being eligible for the study	20
	○ recruitment of “super patients”	20
	• Patient attrition	
	○ high attrition rates due to progressive disease	14, 20, 75, 76
	○ dealing with missing data	75, 79, 80
• Randomization	12	
	○ patients unwillingness to be part of a comparison group	

	• Blinding and use of placebos	12
	○ use of placebo cannot be justified	
	• Interventions	
	○ patients in control arm or comparison arm may perform better due to participation in study or benefit of intervention	20
	○ difficulty standardizing complex interventions, particularly psychosocial spiritual interventions	12, 20
	○ difficulty controlling for non-specific therapeutic factors, such as the therapeutic relationship	36
	○ difficulty designing appropriate interventions due to lack of understanding of complex pathophysiology	12
	• Selection of appropriate outcomes	10, 20, 35
	○ lack of appropriate outcome measures that adequately capture complex concepts such as psychosocial spiritual issues	
Research team	• recruitment, training and turnover of research staff	10
	• lack of specific training of research staff in clinical trials	47, 48
	• lack of availability of research staff over weekends	47, 48
Ethics	• obtaining patient consent & patient safety	12
	• unable to withhold treatment	12

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**Table 2. Strategies for dealing with challenges in conducting palliative care research**

Domain	Strategy	References
Study design	• Specific strategies for RCTs	
	○ randomized fast-track or wait list trial	12, 52
	○ additional strategies for designing a clinical trial	51
	○ enrichment design strategies	53, 54
	○ crossover design	55
	○ “N of 1” design	55
	○ Cluster randomization/sampling	25, 55
	• use of study designs other than RCTs	9, 19
	○ case study	21
	○ action research	56
○ discourse analysis	57	
○ narrative research	58	
○ mixed method (quantitative and qualitative)	59, 60	
	• use of multicentre data collection sites	8, 15
	• linking data sets	8
Sampling	• standardizing the definition of the palliative care patient	64, 65
	• collection and reporting of minimum data sets	66-69
	• taxonomy to guide clinical trial recruitment	51
	• use of administrative databases to assess study feasibility	67, 70
Conceptual	• innovative partnerships	8, 71
	• multidisciplinary research teams, involving researchers (including basic scientists, social scientists) and clinicians	8, 71
	• building research capacity, including international collaborations	8, 72, 73
	• progressing in incremental steps	8
	• different frameworks for assessing evidence	
	○ equity-based framework	3
	○ evidence house	74
Statistical	• handling missing data, attrition and response	75, 76, 79, 80

Analysis	shifts	
	• reporting minimal clinically important differences	77, 78
	• regression towards the mean	25
	• shape and variance of the sample distribution	25
Measures and Outcomes	• recording clinical outcomes using standard measures	8, 70, 81
	• development of minimum data sets	82

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**Table 3. Research Dichotomies**

Dichotomy	Sample Questions
Individual vs. population-based focus	<ul style="list-style-type: none"><li>• What is the purpose of the research?</li><li>• How important is it that the findings be generalizable to other settings?</li><li>• How can these findings be applied in a clinical setting?</li><li>• What impact will this study have on individual patients and/or families?</li></ul>
Homogeneous vs. heterogeneous samples	<ul style="list-style-type: none"><li>• How important is it to obtain a homogeneous sample (e.g. single disease and/or tumour group)? How might this restriction limit the generalizability of the findings to other palliative care patients?</li><li>• How will other extraneous variables, inherent with heterogeneous samples, potentially impact the findings?</li><li>• How many of these extraneous variables can be controlled?</li></ul>
Single vs. multiple interventions	<ul style="list-style-type: none"><li>• How can a single intervention be studied, while controlling for other confounding variables and clinical interventions which are part of standard practice?</li><li>• Is it ethically appropriate to withhold treatment from some patients, during the study intervention?</li></ul>
Outcome vs. process	<ul style="list-style-type: none"><li>• What outcomes are most appropriate and relevant?</li><li>• Are there quality indicators available for measuring these outcomes? What are the psychometric properties of these indicators? How appropriate are these indicators for palliative care settings?</li><li>• What approaches could be used to capture patients' and family members' experiences, which may not be adequately measured with a quality indicator?</li></ul>

**Figure 1: The hierarchy of evidence (levels I - IV)** <sup>74</sup>

