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Dying persons' perspectives on, or experiences of, participating in research: An integrative review.

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Keywords:	Ethics, Hospice Care, Palliative Care, Research Subjects, Research Participation, Terminally Ill
Abstract:	Background: Conducting research with dying persons can be controversial and challenging due to concerns for the vulnerability of the dying and the potential burden on those who participate with the possibility of little benefit. Aim: To conduct an integrative review to answer the question 'What are dying persons' perspectives or experiences of participating in research? Design: A structured integrative review of empirical literature was undertaken. Data Sources: CINAHL Complete, PsycINFO, Medline, Informit and Embase databases were searched for empirical literature published since inception of the databases until February 2017. Results: From 2369 references, 10 papers were included in the review. Six were qualitative studies and the remaining four were quantitative. Analysis revealed four themes: value of research, desire to help, expression of self and participation preferences. Dying persons value research participation, regarding their contribution as important, particularly if it provides an opportunity to help others. Participants perceived that the potential benefits of research can and should be measured in ways other than life

	prolongation or cure. Willingness to participate is influenced by study type or feature and degree of inconvenience. Conclusions: Understanding dying persons' perspectives of research participation will enhance future care of dying persons. It is essential that researchers do not exclude dying persons from clinically relevant research due to their prognosis, fear or burden or perceived vulnerability. The dying should be afforded the opportunity to participate in research with the knowledge it may contribute to science and understanding and improve the care and treatment of others.

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Supplementary data and materials	Is there any content which could be provided as supplementary data which would appear only in the online version of accepted papers? This could include large tables, full search strategies for reviews, additional data etc.	Yes, Table 3 could be included as a Supplementary file, rather than in the published paper
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Title

Dying persons' perspectives on, or experiences of, participating in research: An integrative review

Running Head

Dying persons and research

Abstract

Background: Conducting research with dying persons can be controversial and challenging due to concerns for the vulnerability of the dying and the potential burden on those who participate with the possibility of little benefit.

Aim: To conduct an integrative review to answer the question 'What are dying persons' perspectives or experiences of participating in research?

Design: A structured integrative review of empirical literature was undertaken.

Data Sources: CINAHL Complete, PsycINFO, Medline, Informit and Embase databases were searched for empirical literature published since inception of the databases until February 2017.

Results: From 2369 references, 10 papers were included in the review. Six were qualitative studies and the remaining four were quantitative. Analysis revealed four themes: value of research, desire to help, expression of self and participation preferences. Dying persons value research participation, regarding their contribution as important, particularly if it provides an opportunity to help others. Participants perceived that the potential benefits of research can and should be measured in ways other than life prolongation or cure. Willingness to participate is influenced by study type or feature and degree of inconvenience.

Conclusions: Understanding dying persons' perspectives of research participation will enhance future care of dying persons. It is essential that researchers do not exclude dying persons from clinically relevant research due to their prognosis, fear or burden or perceived vulnerability. The

dying should be afforded the opportunity to participate in research with the knowledge it may contribute to science and understanding and improve the care and treatment of others.

Key Words: Ethics; Hospice Care; Palliative Care; Research Subjects; Research Participation; Terminally Ill

What is already known about the topic?

- Conducting research with dying persons can be controversial and challenging due to concerns for the vulnerability of dying persons and the potential burden that research might impose.
- Access to dying persons for research purposes is limited due to perceived gatekeeping by treating clinicians, managers and policy-makers

What this paper adds

- Dying persons value the opportunity to choose to participate in research, even when there is no hope of cure or life prolongation.
- Vulnerability should not be assumed in the dying person.
- Research participation can be beneficial to the dying person by providing an opportunity to help others, contribute to society, science and future patient care.

Implications for practice, theory or policy

- Dying persons should not be automatically excluded from research due to fear of harm or their perceived vulnerability.
- Dying persons can be invited to participate in research if the research has potential to contribute to science and understanding and inform future patient care.

Introduction

Conducting research with dying persons and/or in hospice or palliative care settings has been described as controversial and challenging [1, 2], with the ethics of such research widely debated [3-7]. There is concern about the actual or potential vulnerability of dying persons [5, 6, 8] and whether those nearing the end of life should be considered 'too vulnerable' to be involved in research [7]. Yet there is evidence that research among vulnerable populations may not be harmful per se, and that there may also be direct benefit to participants [9]. Nonetheless, perceived vulnerability of dying persons results in gatekeeping, where access to dying persons for the purposes of research is limited [6, 9-12]. Denying a person the opportunity to participate in research on the basis of an assumption of vulnerability however, is argued to be paternalistic [13].

Research participation may provide dying persons opportunities to share their story, reflect upon experiences and contribute to knowledge generation [11]. Recent research of cancer patients' participation in research has demonstrated their willingness to be approached about participation in clinical trials in the hope of improving their own treatment, helping others and contributing to scientific research. This evidence however, did not specifically relate to the perspectives of persons in the last stages of life [12].

Reviews were published in 2010 and 2012, where the goal was to synthesis evidence related to patients' experiences of participation in research [1, 13]. One focused on patients' willingness and participation in clinical trials [1], and the other explored the views of patients (and others) on research participation when receiving end-of-life care [13]. In both reviews patient participants were in various stages of their disease trajectory. This trajectory ranged from immediately after diagnosis, while receiving curative treatment, as well as approaching the end of life [1, 13]. The end-of-life phase, also known as the terminal phase, can last days, weeks or months [14]. This sensitive period, when people are approaching death, is when the question of conducting research to understand the experience is most controversial.

Aim

The aim of this integrative review was to answer the question: *What are dying persons' perspectives or experiences of participating in research?*

Design

A structured integrative review, following Whittemore and Knafl's [15] methodology, was undertaken. This approach was chosen because an integrative review is the broadest type of research review, allowing for the combination of diverse methodologies to enable a comprehensive understanding of problems or phenomena relevant to health care and policy [15]. In contrast to a systematic review in which the randomised clinical trial and hierarchies of evidence are emphasised [16], an integrative review also allows for the combining of data from the theoretical as well as empirical literature [15].

Search methods

A search of Cumulative Index Nursing and Allied Health (CINAHL) Complete, PyscINFO, Medline, Informit and Embase databases was undertaken, using relevant search terms and common Boolean operators (Table 1), since inception of the databases till February, 2017. Inclusion and exclusion criteria were developed and agreed upon by members of the team (Table 2).

Search outcome

A staged screening process was undertaken involving the removal of duplicate references, screening of titles and abstracts, and subsequent full paper review. From the original 2369 references resulting from the search, 23 papers were retrieved for full review, and from these, 15 papers were discarded. The reference lists for the remaining eight papers were scanned for further relevant publications, and an additional two papers were identified that met the inclusion criteria. As a result, 10 papers were included in this integrative review (Figure 1).

Quality appraisal

There is no gold standard by which to appraise quality [15], but given that both qualitative and quantitative papers were included in this integrative review, a research critique framework produced by Caldwell et al. [17], which consists of 11 criteria suitable for assessing quality in both qualitative and quantitative papers, was chosen to evaluate the included papers. Caldwell et al's framework allows researchers to consider quality measures and the methodological strengths and weaknesses of qualitative and quantitative papers simultaneously [17]. Using Caldwell et al's framework, the methodological quality of each included paper was independently assessed by two members of the research team (MB and LB) [17]. Nine of the 10 papers scored 9/11 or higher against the quality criteria and the remaining paper scored 8/11 (Table 3). Whilst quality scores can be used as a criteria for exclusion, in this case, an a priori decision was made not to exclude papers on this basis, but instead to use the quality assessments to describe the quality of the literature in this area.

Data abstraction and synthesis

The purpose of this stage of the review was to reduce the data from each of the included papers and identify common threads. Data from each paper were extracted to create individual evidence tables, detailing key features including author/s, year of publication, country, study design, purpose/aim, setting and sample, data collection methods/measures and findings [15]. This approach enabled succinct organisation of data and ease of comparison between papers. The evidence tables were then used to facilitate constant comparative analysis to identify patterns, commonalities and differences [15]. The process enables the evidence from diverse methodologies to be synthesised to produce a comprehensive portrayal of the topic of concern, and an integrated summation of the phenomenon presented in narrative form [15].

Results

The papers included in this integrative review spanned studies conducted in five countries, and in each of the included papers, participants were identified as having a limited life-expectancy, end-stage disease or receiving palliative or hospice care. Participants included those receiving inpatient care, outpatient care, or those previously involved in a palliative medicine clinical trial. (Table 4).

From the analysis, four themes emerged, (i) The Value of Research, (ii) Desire to Help, (iii) Expression of Self and (iv) Participation Preferences.

The Value of Research

Acknowledging that research and the pursuit of new knowledge was an essential part of the workings of a health institution [18], participants responded positively (85%) when asked about researchers and their ability to be honest about research participation [19]. Understanding that their own care was likely informed by research evidence [18], participants affirmed that it was indeed ethical for dying patients to participate in research, and in fact, it was unethical not to include dying patients [20]. Research participation was considered preferable to relying on doctors guessing how to treat terminally ill patients [18]. Participants suggested there was a 'freedom' in being near death, with nothing to lose by voicing their opinion or saying precisely what they wished [18], underpinning their decision to participate. For others, participation in research was contingent on there being no possibility of it delaying their death since for them, life prolongation was seen as a hazard, not a benefit [18].

Desire to help

Desire to help was a dominant theme found in every study included in this integrative review. Participants spoke of the desire to help others, themselves and to aid research or researchers.

Desire to help others

Participants understood it was the knowledge gained from research that guided their treatment, and they wanted others to have the same benefit [18]. In three studies, the desire to help others who may be in a similar position in the future was an important factor in patients' decisions to take part in research [21-23]. In relation to patients with Motor Neurone Disease (MND), Bellamy and colleagues [21] reported that patients made a conscious decision to take part in any research related to MND because they wanted to contribute in ways that raised awareness and knowledge about the disease, in the hope of saving others from going through the same experience [21].

The desire to help others was also reflected in Head and Faul's [19] survey findings, where 76% of patients suggested they would likely participate if the research would benefit others with the same illness in the future. Likewise, White et al.[24] reported that 82% of patients in their study were interested in participating in a trial that was unlikely to help them, but might help others in the future. Some patients said that when they had little time left to live, it was important they used that time to do something of enduring value [18], and one of the perceived benefits of research participation was to feel good about helping others [25].

Desire to help self

Despite their terminal diagnosis, participants maintained a desire to help themselves in ways other than cure. Research participation offered an opportunity to benefit personally [19] and was listed as one of the top three reasons for research participation [22]. For some patients, research participation had the potential to make them feel better [25] and was considered a valuable experience for self [23]. Others suggested participation offered the opportunity to think about issues they had not necessarily considered or discussed [26].

The desire to achieve symptom control rather than cure was identified in two studies [22, 24]. Other potential personal benefits identified by participants included the opportunity to obtain a referral for emotional distress [26] and the belief they would be followed more closely by the clinician team, or perhaps receive better care as a result of participating [19, 25]. Others suggested that participation

might be enjoyable [22], and in a study seeking feedback on various possible research studies, 84% of respondents were interested in a trial of pain medication, 81% expressed interest in a trial of a special mattress, and 79% were interested in a trial of aromatherapy [24], all therapies that participants perceived to have potential to be beneficial.

Desire to contribute to research or help researchers

The desire to contribute to, or advance research was identified as important in several of the included studies. Participants suggested that the importance of research [22], a desire to help the researcher [27] and contribute to scientific knowledge [19, 27] and medical literature [23] influenced research participation. The opportunity to enrich the lives of future patients [23] through research was an important motivation for participation.

Expression of self

Participation in research was considered a positive experience because it offered an opportunity to feel engaged and validated and to express gratitude.

Feeling validated and engaged

The opportunity to participate in research was valued by participants as a way of feeling engaged with the world as a person beyond their illness [21]. Others reported that research participation had made them feel special, offered a way to restore the balance of power and to be seen as an equal human being and was linked to living [21]. Research participation was also seen as a way to think about and reflect on their own lives [23], offering the opportunity to participate in meaningful activity other than being the person living with a life-limiting illness [21] or the dying person [18]. Similar sentiments were expressed by survey participants, with 'sense of purpose' and 'meaning to life' identified as benefits of research participation [25]. Others reported feeling a sense of contribution and appreciated the opportunity for social interaction that came with research participation [26]. In another study, patients welcomed the opportunity to talk with an interested outsider and make

sense of their experiences [27]. This was particularly important for those who reported being unable to talk with others such as their treating team, family or clergy [26].

Expressing Gratitude

Participation also offered an opportunity for participants to have their say, give back to the services that they perceived had been supportive of them during the course of their illness [21], express their gratitude [27] and say thank you for the care they received [21]. Some saw it as their duty to give something back; and that an interview, for example, was the least they could do [27]. 'Because the staff have been good to me' was one of the most frequently stated reasons for participation in research [22].

Participation preferences

Participants in the included studies also provided insights into their preferences for participation. In relation to research recruitment, participants expressed a preference to be approached about research participation by staff familiar to them, with whom relationships had already been established [18, 25], rather than an independent investigator [25]. This approach was preferable as they could avoid the need to explain their situation or problems to a new person, and addressed the concern that an independent researcher may not be able to cope with the issues of dying [18].

Participants also expressed their preferences for types of studies they would participate in. In relation to clinical trials, even when the clinical trial was unlikely to help them, participants in the study by White et al. [24] remained consistently positive about participation, if the trial was likely to help others in the future (82%), might help symptoms but not help the cancer (88%), when the clinical trial is quick and easy (94%), or when the doctors were very keen for the patient to participate (84%). In relation to placebo-controlled randomised trials however, Terry et al. [18] found that participants reported concerns based on the assumption that those in the placebo arm of a trial

would suffer worse outcomes or receive no active treatment. Hence, active comparator trials were more acceptable to patients [18].

Willingness to participate according to the level of burden associated with studies was explored in two studies. Willingness to participate reduced with increasing burden, where burden was related to invasiveness of treatment and level of commitment. Ross and Cornbleet [22] measured willingness of participants to participate in three hypothetical studies. Factors that would reduce willingness to participate included a dislike of blood tests, uncertainty about the drug, lack of appeal for the proposed therapy, the burden of record keeping, that the study would upset them, and that they didn't have the associated condition or a need to talk [22]. Willingness to participate was also explored by White et al. [24] in relation to the level of study invasiveness. The majority of participants were interested in less invasive studies such as pain education research, trialling a special mattress or aromatherapy. As the degree of uncertainty or invasiveness increased, willingness to participate decreased. For example, more than half of respondents stated they were not interested in trialling a new oral 'pain killer' of unknown benefit, and even less were interested in trialling an injection, epidural or spinal stimulator designed to reduce pain [24].

Participants' willingness to tolerate inconvenience daily, weekly and monthly was also measured by White et al. [24]. Approximately one third of participants were willing to tolerate extra hospital visits, answer questions or complete a questionnaire, have extra blood tests or scans or take extra tablets, once a week. Participants were less willing to tolerate daily interventions, and more than one third reported that they would not be willing over any timeframe to have extra injections as part of a trial [24].

Discussion

In the past, researchers have avoided research with vulnerable populations such as dying persons, because of the prevailing perception that it would be too burdensome or perhaps even unethical [9, 28]. The dominant ethical principle associated with the question of research involving dying persons is

respect [29]. Respect in this context is about protecting the life, health, privacy, and dignity of the human subject of research [30] and recognising that each human being has value, autonomy, and the capacity to make decisions for him or herself [29]. With this in mind, researchers and clinicians should work to ensure dying persons are afforded the same level of respect and autonomy as others, including the opportunity to participate in research. To deny dying persons this opportunity on the basis of their life-limiting illness denies their right to autonomy. Evidence from this review demonstrates that dying persons not only value the opportunity to participate in research but regard their contribution as important to themselves and others.

The evidence in this review also challenges assumptions related to recruitment. A common requirement of institutional review boards is that recruitment is undertaken via an independent third party to avoid potential coercion [8]. However, consistent with previous research [25, 31], this review suggests that dying persons may prefer to be approached about research by a member of their treating team with whom a relationship is already established. A way forward is for institutional review boards to allow recruitment by members of the patient's treating team, where other measures, such as a silent opt-out process, in which potential participants can decline through inaction is in place [32].

Whilst not the focus of this review, of note is the inherent sampling bias of studies included in this review. By the very nature of research regarding participation preferences, the perspectives of dying persons who chose not to participate, are not included in this review. Where information about reasons for declining to participate are provided, the reasons vary, suggesting at the very least, that dying persons do maintain autonomy in decision-making when it comes to research participation, and can and do refuse to participate in research for reasons other than just their terminal illness.

How benefit is defined is also an important consideration in research involving dying persons. Institutional review boards are mandated to ensure that there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research [30].

Hence, when dying persons are considered, any research that does not seek to improve their condition or benefit the person in some way may be considered unethical. This review has shown that benefit can and should be measured in ways other than life prolongation or cure. Altruism, and the desire to be of help were dominant themes to emerge from this review, and similarly reflected in other research involving patient cohorts with significant illness [9, 10, 13]. Making a contribution to society, helping others and advancing research should also be considered benefits from research for the individual participant [4, 9, 12, 33].

The need for a concerted approach to expand evidence to underpin palliative and end-of-life care is well documented [34]. The benefits of enhancing healthcare through research are obvious, yet in palliative and end-of-life care, the reluctance and perceived difficulty of conducting research has meant that care provided to dying persons may be less likely to be based on research evidence [9]. Although research with dying persons may be seen as more challenging, researchers can work to overcome these challenges in order to ensure that care provided to dying persons is underpinned by research evidence [9].

Strengths and Limitations

A key strength of this review was the focus on research conducted with dying persons, specifically identified in the included manuscripts as either dying, terminal, terminally ill, having a short prognosis or receiving end-stage palliative care. This is an important distinction from other systematic reviews, where patients with cancer and other life-limiting diagnoses were included, but where death was not imminent and the focus of care was cure.

The integrative review design enabled research evidence derived from diverse methodologies to be synthesised, providing a comprehensive understanding of dying persons' perspectives on, or experiences of, participating in research. This is critically important because assumptions made by clinicians and treating teams have historically limited access to dying persons for the purposes of

research but this review provides evidence that gatekeeping may not necessarily be in the best interests of the dying person.

There are several limitations to this review. The database search retrieved numerous research publications about studies reporting on patients' perceptions and/or experience of research participation, except the participant populations were not specifically described as dying. Rather, many included patients receiving curative and palliative care, where the findings are not separated. Hence, even though these papers may have had findings relevant to this review, they were excluded. As stated earlier, the findings of this review represent the views of those who participated in the ten included studies, and the perspectives of those who declined participation is not as well understood.

Conclusion

Previous reviews have explored clinical trial participation by dying persons, others have included participants with a life-limiting diagnosis, at various stages of their disease trajectory including immediately after diagnosis. This integrative review is the first to synthesise evidence related to dying persons' perspectives on or experiences of participating in research. Given the expectation that care is evidence-based, understanding dying persons' perspectives of research participation will enhance the future care of dying persons, if it is conducted with sensitivity and respect. Therefore it is essential that researchers do not exclude dying persons from clinically relevant research, as a result of their prognosis, fear of burden or perceived vulnerability.

Rather, dying persons should be afforded the same opportunities as those seeking active treatment to participate in and contribute to research, where appropriate, with the knowledge that even if the research cannot result in an improvement to their condition, benefit may be measured in other ways, including contributing to the body of research evidence that informs the care of others. Researchers should be encouraged to undertake research involving those nearing the end of life if the intended research has the potential to contribute to science and understanding and inform future patient care.

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Declarations

Authorship

Study Design: MJB, MB & AMH

Data collection and synthesis: MJB, LB

Manuscript preparation: MJB, MB, AMH, LB

All authors approve the final version of the manuscript

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Declaration of conflicts of interest.

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this manuscript.

Table 1. Search strategy

dying OR “end of life” OR palliative OR terminal OR hospice OR person OR patient	Searched with AND
participant OR subject OR inpatient OR resident OR client	
involve* OR experience* OR perspective* OR perce* OR attitude* OR feel* OR reflect* OR satisfact*	
participa* OR subject OR involv*	
“research participation” OR “research subject*” OR research	

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Published in English	Secondary research including systematic reviews, literature reviews and integrative reviews
Reports primary research	Letters, Commentary, Editorials and opinion pieces
Subjects/participants were adult (18 years or older)	Subjects/participants where the age of participants was not determinable and/or where subjects/participants were not acknowledged as dying, terminal, terminally ill, acknowledged as having a short prognosis, receiving palliative care
Subjects/participants were identified or acknowledged as dying, terminal, terminally ill, acknowledged as having a short prognosis, receiving palliative care	
Where multiple subject/participant groups were included, the findings for each group were reported separately	

Table 3. Quality Appraisal

Authors & Year	Quality Appraisal*		Critical Appraisal Comments
	Appraisal 1	Appraisal 2	
Bellamy, Gott & Frey 2011	11/11	11/11	
Gysels, Shipman & Higginson 2008	11/11	11/11	
Head & Faul 2007	10/11	11/11	Ethical issues not specifically detailed or addressed.
Perkins, Barclay & Booth 2008	9/11	9/11	Literature review not comprehensive. Methodology identified, just justification of chosen method not comprehensive.
Pessin, Galietta, Nelson, Brescia, Rosenfeld & Breitbart 2008	10/11	10/11	Ethical issues identified but could warranted from further detail.
Ross & Cornbleet 2003	9/11	9/11	Rationale for questionnaire and evidence of testing of the questionnaire not provided. No conclusion provided
Siu, Leung, Liu & Leung 2013	8/11	10/11	The literature review has a medical focus, hence not comprehensive. The process for analysis is not detailed. Discussion not comprehensive, and lacked sufficient link with other literature. Some grammatical errors in the paper.
Terry, Olson, Ravenscroft, Wilss & Boulton-Lewis 2006	9/11	11/11	Aim is reported differently between abstract and the body of the paper. Literature review is brief
White, Hardy, Gilshenan, Charles & Ross Pinkerton 2008	11/11	11/11	
Williams, Shuster, Clay & Burgio 2006	11/11	11/11	

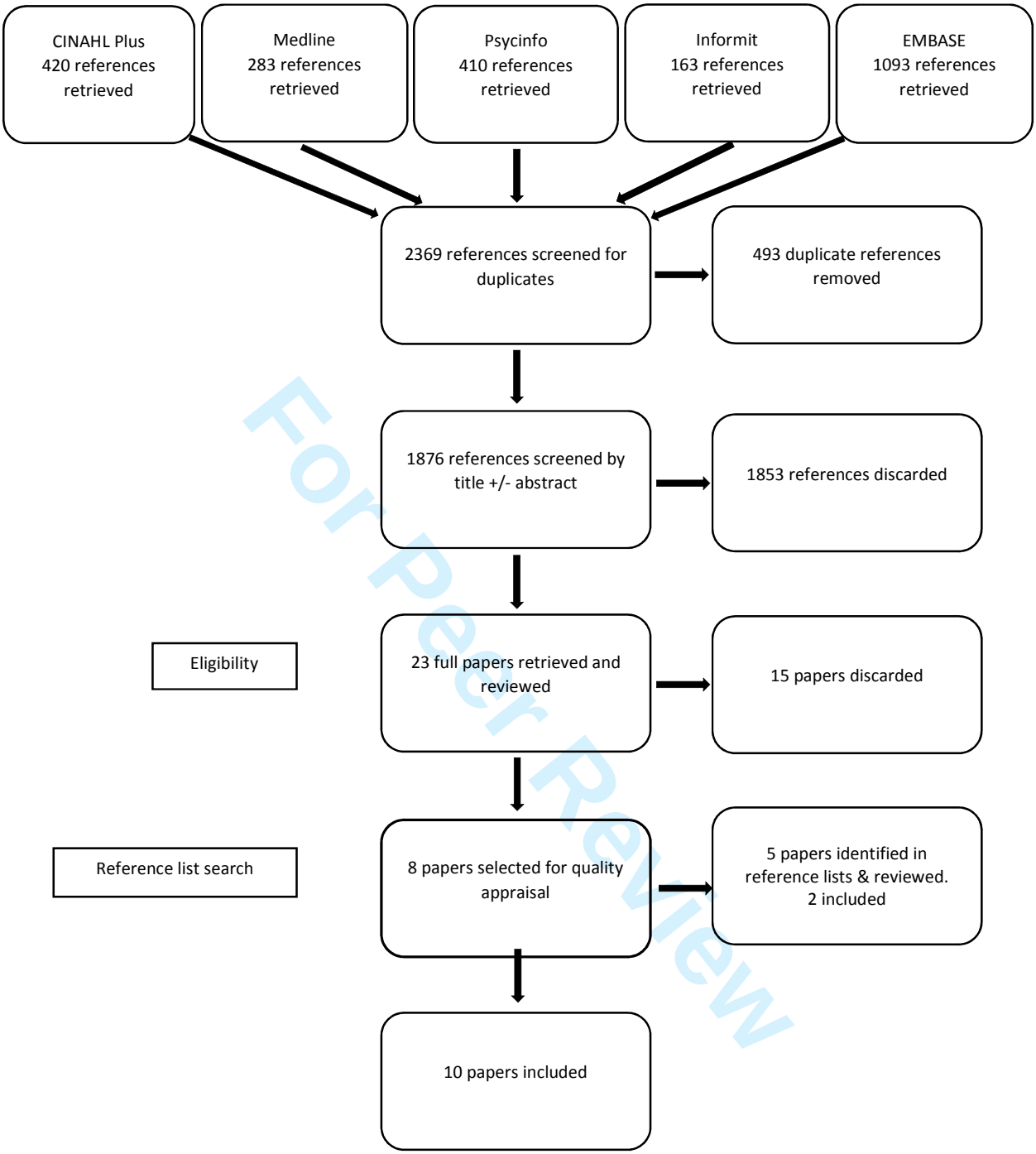
**11 step quality appraisal framework from Caldwell, Henshaw and Taylor (2011) used*

Table 4. Papers included in this review

Authors & Year	Setting	Objective/Research Questions	Study Design & Method/Measures	Sampling, Recruitment and Sample	Refusal rate and reasons (where detailed)
Bellamy, Gott & Frey 2011	Three hospices in Auckland region New Zealand	To explore the views of hospice users regarding their motivations for taking part in a study	Qualitative In-depth, semi-structured interviews were undertaken.	Sampling: Purposive, to ensure heterogeneity. Recruited by: A third party (e.g. manager) responsible for each area and with knowledge of the patients' medical condition Sample: 21 hospice inpatients and outpatients; with cancer (n=16), COPD (n=1), MND (n=3) and AIDS (n=1).	Not detailed
Gysels, Shipman & Higginson 2008	Large London teaching hospital United Kingdom	To explore patients' and carers' preferences and expectations regarding their contributions to research	Qualitative Semi-structured open-ended interviews	Sampling: Purposive - patients were already enrolled in one of two other related studies. Recruited by: A clinician in the treating team/clinic. Sample: 64 palliative care outpatients with cancer (n=30), COPD (n=14), cardiac failure (n=10) or MND (n=10).	21 (25%) patients declined to participate for the following reasons: no reason given (n=6), too ill (n=4), denies breathlessness (n=4), did not want to be interviewed (n=2), wanted to put episode behind them (n=1), does not feel 'up to it' (n=1), went into hospice (n=1), thinks interview might hurt her (n=1), and did not want to take part (n=1) Others did not decline, but were not able to be included due to: death (n=1), gatekeeping by wife (n=2), not answering the phone (n=1), not home for the appointment (n=2), did not reply to the written information (n=4)
Head & Faul 2007	Hospice unit USA	1. What type of research activities would they willingly commit to complete? 2. What factors would discourage their participation? 3. What are their general attitudes towards research and the professionals who conduct it?	Quantitative Researcher administered descriptive survey with pre-experimental, one-groups, posttest-only design.	Sampling: Convenience - patients already admitted to a hospice program Recruited by: Surveys were distributed by social workers working in the hospice, not involved in the study. Sample: 21 hospice unit inpatients (n=12) and home patients (n=9) described as terminally ill.	Not detailed
Perkins, Barclay & Booth 2008	Specialist palliative care unit in Cambridge United Kingdom	To investigate the views of palliative care patients on what should be the key priorities for future research	Qualitative Six focus groups of 2-4 patients each	Sampling: Convenience – patients already receiving care from the Hospice service. Recruited by: A study investigator. Sample: 19 patients including 8 inpatients and 11 day therapy patients with cancer and a prognosis of 6 months or less.	Two (8%) patients declined to participate due to being too fatigued (n=1) and did not feel well enough (n=1)
Pessin, Galietta, Nelson, Brescia, Rosenfeld & Breitbart 2008	200-bed palliative care hospital in New York City United States of America	To assess the burden and benefit of participation in research that investigated attitudes toward hastening death, and other symptoms associated with end-of-life suffering among patients receiving palliative care	Quantitative Researcher administered survey containing the Burden and Benefit Scale questionnaire	Sampling: Purposive – via 1383 consecutive admissions to the hospital as part of a larger study Recruited by: Not detailed. Sample: From the initial cohort of inpatients with end stage cancer and a life expectancy of less than 2 months, three dropped out due to being upset by the questions, leaving 68 participants.	179 (65%) patients declined to participate for the following reasons: did not want to be involved in research, did not want to discuss death and dying, and believing they were too ill. There was no difference between those who participated and those who refused according to age, race or religion.

Ross & Cornbleet 2003	Specialist palliative care units, United Kingdom	To determine the willingness of patients receiving specialist palliative care to take part in clinical trials	Qualitative Structured interview of five questions, with answers recorded by the interviewer	Sampling: Convenience – patients admitted to the palliative care unit at least 48 hours prior. Recruited by: A study investigator Sample: 40 palliative care inpatients with advanced malignancy Evidence of refusal to participate: One (2.5%) patient declined to participate.	
Siu, Leung, Liu & Leung 2013	Department of Clinical Oncology, Queen Mary Hospital, Hong Kong Special Administrative Region & Clinical Oncology Department China	To understand patients' views on failing to gain expected beneficial outcomes from palliative medicine clinical trials by asking their reasons of being willing to participate in clinical trials, experiences during the process of clinical trials, and whether they feel they have gained anything out of the experience	Qualitative Semi-structured interviews using a discussion approach rather than a question and answer format.	Sampling: Purposive – patients with metastatic and progressive disease, who had previously participated in a palliative medicine clinical trial but unable to gain expected beneficial outcomes from interventions. Recruited by: not detailed. Sample: 7 patients with metastatic cancer already participating in palliative chemotherapy trial or trialling drug for symptom control	No patients declined to participate.
Terry, Olson, Ravenscroft, Wilss & Boulton-Lewis 2006	20-bed hospice, part of the public hospital system but administered by the Sisters of Mercy, Singleton Australia	To see whether terminally ill patients were indeed desperate for cure, whether cure was the only outcome of research they values and whether they did have difficulty distinguishing research from treatment	Qualitative Semi-structured interviews were conducted using open-ended predetermined questions, structured beforehand to cover broad areas	Sampling: Convenience - current hospice inpatients Recruited by: A member of the palliative care team, other than the researchers or treating physician. Sample: 22 hospice inpatients described as dying. 18 had advanced malignant disease. The diagnoses of the remaining 4 patients has been withheld to protect their identity.	No patients declined to participate.
White, Hardy, Gilshenan, Charles & Ross Pinkerton 2008	Palliative Care service integrated within the oncology service at the Mater Misericordiae Hospital, Brisbane Australia	To determine if patients with advanced cancer are interested in participation in research that does not involve anti-cancer therapy, particularly in the context of a RCT, and if so, what factors are important in their decisions	Quantitative Self-report questionnaire	Sampling: Convenience - patients known to the Palliative Care service. Recruited by: Not detailed. Sample: 101 patients 'with an active, progressive, far-advanced disease for whom prognosis is limited and the focus of care is quality of life'.	No patients declined to participate.
Williams, Shuster, Clay & Burgio 2006	Hospice services located across four south-eastern states (Alabama, Florida, Louisiana and Mississippi) United States of America	To examine hypothetical interest in research studies of hospice patients and caregivers as compared to ambulatory senior citizens	Quantitative Self-report questionnaire	Sampling: Convenience – recruited from existing hospice patient group Recruited by: Via a project coordinator at each site. Sample: 142 hospice patients enrolled in the hospice service for at least one week. Response rate: 396 surveys were initially distributed, indicating a response rate of 36%.	N/A

Figure 1. PRISMA



Referee: 1 Comments to the Author	
according to the Whittemore and Knafl method of undertaking an integrative review there is a requirement for an overall classification system for managing the data from diverse methodologies. It is not clear (to me) what classification system has been used to attend to the different methodologies. My thoughts were that – by using the Caldwell et al research critique framework and allocating a score for these to facilitate analysis – that this was a means of classifying the research – but this is not clearly articulated as such.	Further detail has been added to the 'Quality Appraisal' section (page 5) to aid clarity and address this concern.
Referee: 2 Comments to the Author	
Title: Adequately described the integrative review; method used was explicit after the colon. I would suggest adding 'on' after "perspectives" to enhance clarity.	Thank you. This change has been made on page 4.
Abstract: Provided a reasonable summary of the review. In an appropriate structured format. Mostly sufficiently detailed except a start date for literature searched under "Data Sources" would have been helpful and rewording of the first 2 sentences under "Results" should result in a more succinct statement and a sharper focus.	This change has been made (page 1-2).
What is already known about the topic?: Second bullet needs reworded to improve clarity – to whom does "their" refer?	The word 'their' has been removed and the bullet point has been re-worded to aid clarity (page 2).
Methods: It would have been helpful for the reader to see an explanation about how an integrative review is an approach that falls between a simple literature/evidence review and a complex systematic review.	Further detail has been provided in the 'Design' section to explain this (Page 4).
Though the subheadings following the "Design" subheading are appropriate for this method, it would have been much clearer for the reader if a few more details about the approach had been shared (could use the subsequent subheadings to focus the reader in the "Design" section). For example, the structure should stress narrative analysis to explain the compilation of literature and synthesis of varied studies, detailed and systematic search strategies should be identified, rigorous appraisal methods should be used, and synthesis typically combines diverse research methodologies and other types of evidence (though only empirical reports were included in this integrative review).	Further detail was added to the 'Data abstraction and synthesis section (page 5) to explain how and why the review findings are presented narratively. The systematic search strategies are detailed in the 'Search methods' and 'Search outcome' sections as well as in Table 1. The ability to synthesise research evidence from diverse methodologies has been further detailed in 'Design' section (page 4).
I believe that "integrative review" is a less	This has been further detailed in the 'Design'

common term in some countries and so I would suggest that a few more details are needed to help an international audience better understand if this method is credible and also if the authors followed the method.	section (page 4).
I would prefer to see a beginning and an end date for the literature that was searched, e.g., "published between January 1, 1990 and February 28, 2017" (the latter date is in the abstract). The databases searched cover different dates, e.g., CINAHL is 'younger' than Medline, and so it would be helpful to have a clearer sense of the dates.	Given that the intention was to include all published literature available via each of the databases, a beginning date was not selected for the databases searches. Rather, only an end date was selected, being the date the search was run. Each database has a different year of commencement.
Table 2 indicated that participants in studies reviewed were over 18 years of age, but typically 18 years of age is considered adult. Should it be ">18 years of age"? The last exclusion criterion is simply the converse of the last inclusion criterion, so redundant to include as it was not a specific exclusion criterion.	Thank you. These changes have been made to Table 2.
Findings/results: As appropriate for the method, results were reported in a narrative format. It would, however, have been useful as noted above for the authors to have previously explained how results from an integrative review are typically reported. Otherwise, the reader might expect a lot more statistical results than are provided.	Thank you. This detail has now been added in the 'Data abstraction and synthesis' section (page 5).
The strengths of the review were not explicitly discussed when limitations were noted – would be useful to counterpoint the limitations.	Information on the strengths of this review has now been added (page 12).
Though not in the adult arena, it might be useful to discuss how these findings are similar to (or different from) how parents of seriously ill children view research participation: Steele, R.; Cadell, S., Siden, H., Andrews, G., Smit Quosai, T., & Feichtinger, L. (July, 2014). Impact of research participation on parents of seriously ill children. Journal of Palliative Medicine, 17(7), 788-796. doi:10.1089/jpm.2013.0529	Thank you for this suggestion. However the research team made a very deliberate decision to not make comparisons with similar literature in paediatric populations. This is because the role of parents, the child's lack of capacity to consent, and the difference in acceptance related to dying mean that the phenomena of 'the dying persons' perspective on, or experience of participating in research, between paediatric and adult populations is too different, and hence useful comparisons cannot be drawn.
such as being careful to use an article ('a', 'the') at times, e.g., on p. 7, line 12-13 where "the end of life" would improve readability.	This has been addressed throughout the manuscript.
I would suggest that commas are used incorrectly at times.	The use of commas has been reviewed throughout.
Using parallel formats for verbs also needs some attention, e.g., p. 7, lines 31-35 where "contributing" rather than "contribute" would	The manuscript has been reviewed and changes made in accordance with this suggestion.

be a better fit.	
On p. 9, lines 40-42, the word “either” is used but then 3 options are noted.	The word ‘either’ has been removed.
It is customary to write “the end of life” when a noun, but “end-of-life” when an adjective. Using the hyphenated vs. non-hyphenated versions in this way would help the reader.	Thank you. This has been addressed throughout the manuscript.
Editor(s)' Comments to Author:	
Could you perhaps consider combining the information about included paper the latter two tables.	Duplicate detail from the ‘results’ section has been deleted, where it is also detailed in Table 4.
Can we ask that you much more clearly articulate what is novel about this review - it may be that this is the focus on the VERY end of life- although then you need to be more specific and critical please about how this was operationalised in included papers and your inclusion criteria.	Further detail has been provided in the conclusion to more clearly demonstrate what is novel about this review (page 13).