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Should end-of-life patients be enrolled as participants in clinical research? A best-fit framework synthesis

ABSTRACT:

Aim: To identify and appraise evidence about ethical concerns regarding conducting medical research with end-of-life patients.

Design: A best-fit framework synthesis of the literature regarding ethical issues in research involving adult patients at the end of life was conducted.

Data sources: Five databases were searched (Cumulative Index to Nursing and Allied Health Literature, Web of Science, Embase, Medline, and PsychINFO) between January 2000 and August 2019.

Review methods: Data were synthesised and categorised according to the moral positions described by Foster.

Results: In all, 18 papers that met the inclusion criteria were included in this review. These papers provided rich knowledge not only about various ethical objections to researching the end of life, but also about the social, moral, and clinical requirements to perform rigorous studies on clinical interventions in this field.

Conclusions: Research on people at end of life is not an unsolvable ethical dilemma between providing the best possible care and enhancing new therapies. It is important to find a balance between the moral duties of providing care and achieving research outcomes that are rigorous and meaningful for service users.

Impact: Research ethics committees can be challenged by the evaluation of human research. This review provides up-to-date evidence on key challenges and ethical considerations about researching with end-of-life patients.

Keywords: Clinical research, palliative care, research ethics, nurse, nursing

INTRODUCTION

Research involving human participants can raise questions about researchers' behaviours and decision-making that are approached with different types of ethics frameworks (Hughes et al., 2010), which should underpin medical research (Seymour & Skilbeck, 2002) to protect the safety of study participants and to create high-quality research (Vollmer & Howard, 2010; World Medical Association, 2013). Therefore, clinical research involving human participants should be rigorously reviewed by a research ethics committee (World Medical Association, 2013).

Background:

Evaluating human research can be challenging, especially if it involves patients with advanced illness and those at end of life (Evans et al., 2013). This field of investigation has produced various ethical concerns (Seymour & Skilbeck, 2002) associated with both patient vulnerabilities and methodological complexities (Lee & Kristjanson, 2003). The Declaration of Helsinki developed by the World Medical Association (World Medical Association, 2013) has set ethical standards for medical and human research and stipulates that any research involving human subjects should be reviewed by a research ethics committee (Bruera et al., 2015). Patients can participate in a research once certain conditions have been met and a research ethics committee has determined that risks and benefits are appropriately balanced, the recruitment strategy is fair, and that patient consent is voluntary and informed (Bracken-Roche et al., 2017).

According to different ethics theories, various practical approaches have been developed for the evaluation of human research and can be used by ethics committees. Three broad areas of ethical concerns can be applied in any research study (Barrow & Khandhar, 2020; Bruera et al., 2015): (1) Respect for the person: Individuals should be treated as autonomous agents; (2) Beneficence: This involves not only respecting patients decisions and protecting them from harmful interventions, but also securing their well-being; and (3) Justice: Equals ought to be treated equally.

Additionally, the Foster framework (Foster, 2001; Seymour & Skilbeck, 2002) defines three broad areas of research evaluation: goal-based morality, duty-based morality, and right-based morality (Table 1). These three areas are derived from different but complementary philosophical approaches. The first emphasizes the actual outcome; the second acknowledges that there are rules of conduct that ought to be followed because the nature of those involved; and the third recognises the right of each person to autonomy. The Foster framework can be successfully used to review any specific research projects and to achieve an acceptable balance between different ethical demands (Bruera et al., 2015).

THE BEST-FIT FRAMEWORK SYNTHESIS

Aim

This synthesis aimed to identify and appraise the evidence about ethical concerns regarding conducting medical research with end-of-life patients. We used the Foster framework to organise the review in the belief that it would be a helpful tool to understand and report the potential risks and benefits of research in palliative care settings.

Design

To test this hypothesis, we performed a literature review of the existing evidence on the potential risks and benefits of research in this sensitive area. We used a best-fit framework synthesis to combine and organise the different components of our assessment (Carroll et al., 2011). The moral positions described by Foster were analysed (Foster, 2001; Seymour & Skilbeck, 2002). The approach was built on this existing model that provided a relevant pre-existing framework and themes against which data of the identified papers could be mapped (Carroll et al., 2011). The ENTREQ statement (Enhancing transparency in reporting the synthesis of qualitative research) was used to present this review (Tong et al., 2012).

Search methods

Five databases (Cumulative Index to Nursing and Allied Health Literature, Web of Science, Embase, Medline, and PsychINFO) were searched between January 2000 and August 2019 (Figure 1). Moreover, we manually screened papers identified in four systematic reviews (Duke & Bennett, 2010; Gysels et al., 2012; Kars et al., 2016; Wohleber et al., 2012) regarding ethical concerns at the end of life.

The investigation was pre-planned to search for all available papers, for which key search terms included ‘research ethics’, ‘clinical ethics’, ‘palliative care’, and ‘end-of-life care’. The search terms are reported in Appendix 1. Papers enquiring about ethical issues in research involving end-of-life patients (those who were in their last days, weeks, or months of life) because of a chronic disease (Higginson et al., 2013) were included. Non-English language papers and exploratory studies regarding patients’ or relatives’ points of view about clinical research enrolment were excluded.

A framework synthesis can include both empirical and non-empirical papers to understand the issue of concerns and develop a theoretical framework (Carroll et al., 2011). Thus, we included not only research papers but also expert consultation and opinion papers. Moreover, although not all the included papers used a recognised method of data collection and analysis, they might provide qualitative data to further inform research governance (Duke & Bennett, 2010).

Search outcomes

Of the 1800 titles and abstracts screened, 208 full-text papers were assessed for eligibility. A total of 18 papers were included in the final analysis (Figure 1). All the 18 papers included in this review, were published in peer-reviewed journals and were informative, well-developed, well-reasoned, logical, and persuasive according to the assessment of two

reviewers (AO and TFS) (Table 2). This review did not exclude papers on the basis of quality assessment. Two reviewers (AO, TFS) extracted data from the included papers and each of them checked the extraction and coding performed by the other and then discussed the resulting themes according to the pre-existing framework. If no agreement could be reached about inclusion and data extraction, the third reviewer (PG) was consulted.

The papers were excluded based on the appropriateness and relevance of their titles and abstracts. Full-text papers that were irrelevant to the review based on the aims and focus were also excluded. Clinical, practical examples have been provided.

Quality appraisal

Given the type of synthesis and the diverse nature of the included evidence, no formal appraisal was undertaken. No existing tool was suitable to appraise the quality of papers with such diverse designs and types as those included in our review. Papers were deemed appropriate and were included if they were informative, well-reasoned, logical, and persuasive (Duke & Bennett, 2010). The papers that met the inclusion criteria were reviewed considering the contribution made towards understanding the ethical challenges of clinical studies involving adult end-of-life patients. The rigour of this analysis could be influenced by the synthesis difficulty and data interpretation from different types of papers.

Data abstraction

The descriptive characteristics of the 18 papers are shown in Table 2. These include eight opinion papers, two debates, two summaries, one expert consultation, one critique, as well as two surveys and two qualitative studies. The author's countries of origin of include the United States of America (n=10), the United Kingdom (n=5), Australia (n=2), and Canada (n=1). Two papers focused on research involving vulnerable adults, six on the rigor of research methods in palliative care clinical research, one on the moral choices and ethical dilemmas in researching the end of life, and one on the ethics committees' competences about elements of standard in palliative care treatments.

Synthesis

The Foster framework (Foster, 2001; Seymour & Skilbeck, 2002) was used as a priori means of coding and organising our results. The findings reported by the included papers were synthesised and analysed using a deductive process.

FINDINGS

Goal-based morality (Figure 2)

From a social justice perspective, there is an interest in providing good health care for all patients (Lee & Kristjanson, 2003); however, researchers claim that there are few well-conducted clinical trials aimed at improving the care of end-of-life patients (Henry & Scales, 2012). Hence, not performing studies in an area where practice has not been

evaluated is unacceptable and limits the ability to provide the best treatments (Currow et al., 2011). Although the process is distinct from curative medicine (Henry & Scales, 2012; Jubb, 2002), most of the available evidence regarding the end of life has been derived from attempting to modify causes of death and is not focused on dying (Currow et al., 2011). For these reasons, the value, validity, generalisability, and dissemination of studies on this matter have ethical implications (Casarett, 2005).

In contrast, some authors argue that these patients are too ill and vulnerable to allow for valid and generalisable research (Fine, 2003; Jubb, 2002; Stevens et al., 2003). Because of life-threatening diseases and limited prognoses, they have high attrition that can impact the quality of the results (Jubb, 2002). Moreover, end-of-life patients have high heterogeneity due to various diseases with different trajectories and uncertain prognostication, duration, and characteristics of the phase of illness (Henry & Scales, 2012). Variability can be due to either the biological response to treatments (Fine, 2003) or how different services can deliver various levels of care (Currow et al., 2011). Additionally, anticipated ethical concerns may decrease study participation and potentially its generalisability (Abernethy et al., 2014). Because of these methodological issues, ethical concerns have been raised about the justice of allocating finite resources to non-curative research (Jubb, 2002).

Despite the described perspectives, all reviewed papers concluded that barriers to end-of-life research are surmountable (LeBlanc et al., 2010). Research ethics committees should balance the feasibility of a clinical trial to ensure that all the potential difficulties are methodologically addressed (Currow et al., 2011), and that adequately generated and disseminated knowledge can directly influence clinical practice or policy (Currow et al., 2011). Excluding these patients from clinical research could compromise the development of end-of-life care as an evidence-based speciality, which can be seen as a form of discrimination (Henry & Scales, 2012). Because research ethics committees may be unfamiliar with the unique features of such research (Abernethy et al., 2014), standard guidelines for trial design and reporting are available. A study that is not adequately designed is not ethically defensible (Currow et al., 2011).

Goal-based morality can justify non-therapeutic research according to the importance of the knowledge it can produce (Duke & Bennett, 2010; Fine, 2003). Terminally ill cancer patients could be asked to undergo procedures such as biopsies to learn more about cancer histology and to develop new target therapies. This non-therapeutic research is ethically justified because of the benefits to society (Kleiderman et al., 2012).

Placebo-controlled trials are considered as non-therapeutic research, and according to the Declaration of Helsinki, are acceptable if no proven interventions exist (World Medical Association, 2013). These trials require careful consideration of the study design to ensure that the placebo group does not receive substandard care (Wohleber et al., 2012). This can help clinicians to understand the gaps between their perceptions of benefit from an unproven but commonly used drug or service. For instance, ketamine was administered as

a coadjutant in chronic pain management, however, a placebo-controlled trial demonstrated no net clinical benefit compared to placebo (Sanderson et al., 2013). The introduction of fast-track trials, either for pharmacological or service evaluation, is a successful example of overcoming the concerns of substandard care, as described by Higginson et al.'s evaluation of a new service for neurological patients, or Dolan et al.'s study on methadone treatment (Higginson & Booth, 2011). All these trials were aimed at generating and disseminating knowledge that could improve the quality of care for future patients.

Duty-based morality (Figure 3)

Participation in studies may be upsetting for end-of-life patients or may worsen their clinical conditions (LeBlanc et al., 2010; Phipps, 2002). They can experience physical symptoms and psychological discomfort that may cause them to misunderstand the goal of the proposed research (therapeutic misconception) (Henry & Scales, 2012; Phipps, 2002). Moreover, because of their limited prognoses, they have a narrow opportunity to benefit from the results of the research (Daly & Rosenfeld, 2003; Stevens et al., 2003).

On the other hand, not undertaking studies in this population is more disadvantageous because research is key to establishing evidence-based treatments for the management of end-of-life patients, which is currently lacking (Jubb, 2002; O'Mara et al., 2009). In some cases, a research could offer a potential direct clinical benefit to its participants (Casarett, 2005). For instance, descriptive studies can potentially discover important clinical information about unrecognised and untreated symptoms and unmet needs that can be finally addressed (Casarett, 2005; Phipps, 2002). Moreover, patients often express their willingness to participate in clinical research to help future patients and clinicians (Phipps, 2002). In this way, they can feel a sense of purpose and usefulness despite their prognosis (Abernethy et al., 2014; Currow et al., 2011).

In duty-based morality, research ethics committees are challenged with the anticipation of risks and benefits of a clinical trial and respecting the principles of beneficence and non-maleficence. Risks and benefits that are relevant to end-of-life patients may be harder to define because patients' goals and preferences change substantially with the progression of the disease (Casarett & Karlawish, 2000; Currow et al., 2011; Henry & Scales, 2012).

Therapeutic research can be judged as morally appropriate if it investigates the equipoise of intervention and results in an outcome about how best to manage a therapeutic need (Currow et al., 2011). Examples are phase III randomised controlled trials conducted in advanced tumours, where standard treatments are compared to new therapies. In such cases, research can be carried out because data on the risks and benefits of the new drug have been previously known from the laboratory, based on phase I and II studies (World Medical Association, 2015). Phase I trials have been designed to test toxicity rather than the efficacy of treatment (Cassel et al., 2016). These non-therapeutic trials can be morally justified only if they give particular attention to the protection of patients' vulnerabilities and avoidance of therapeutic misconception (Dubov, 2014).

Although it is a non-therapeutic research, the concept of equipoise can be applied to qualitative research because of the uncertainty of its outcomes (Phipps, 2002). Considering the methodologies of qualitative research and the sensitive topics of end of life, multiple recommendations should be taken into account to minimise the burdens and harms of participants and researchers (Koenig et al., 2003; Sivell et al., 2019).

Right-based morality (Figure 4)

An ethically appropriate study should be presented to patients to allow them to make informed decisions about their participation (Currow et al., 2011). One of the essential requirements of ethical research is informed consent (Agrawal, 2003; Daly & Rosenfeld, 2003). Valid consent depends on the patient's ability to understand the risks and benefits of study participation and to avoid coercion (Phipps, 2002). It has been argued that end-of-life patients are vulnerable and relatively or absolutely incapable of protecting their interests due to their medical condition (Henry & Scales, 2012; Jubb, 2002). The capacity to consent can be influenced by the presence of cognitive impairment or can vary over time, either due to experimental or therapeutic medications, or the deterioration of clinical conditions (Agrawal, 2003; Casarett, 2005; Gysels et al., 2013). Additionally, end-of-life patients may choose to participate out of desperation rather than an informed choice (White et al., 2008). The investigator is often also the clinician and patients may feel the pressure to participate in research to please their doctor (Currow et al., 2011). Moreover, a deep level of engagement between researchers and patients can make an eventual withdrawal from the study difficult (Agrawal, 2003; Jubb, 2002; Stevens et al., 2003).

Other authors state that patients should be assessed in the context of their actual clinical situation to decide whether or not they have the capacity to consent (Henry & Scales, 2012). Vulnerability should not be equated with involuntariness, and dying should not be equated with coercion (Agrawal, 2003; Keeley, 2008). Not all patients with cognitive impairment lack decision-making ability (Casarett & Karlawish, 2000), and research can be conducted when they are unable to provide consent, if the knowledge cannot be gained otherwise (Hickman et al., 2012). In these cases, research ethics committees should be consulted to evaluate whether researchers can forgo the informed consent process (Hickman et al., 2012). The most important purpose of informed consent is to explain the study's methods, potential risks and benefits, and the rights of research participants, especially the opportunities to withdraw (Casarett, 2005; Phipps, 2002). Therefore, it should be delivered in a concise, simple, and straightforward manner, and it should be a continuous process to ensure sensitivity to changes in personal capacity to participation as well as signs of distress (Gysels et al., 2013). In cases of physical distress and cognitive impairment, some studies use flexible approaches to data collection to enable patients to participate (Hickman et al., 2012).

In conclusion, research ethics committees should avoid gatekeeping from research, which is caused more by the desire to protect people from harm, from overburdening them (Agrawal, 2003; Stevens et al., 2003; White et al., 2008), or from a societal taboo against

speaking about death, rather than by valid ethical concerns (Keeley, 2008). Gatekeeping restricts individual autonomy and negatively influences the quality and generalisability of the research (Keeley, 2008). Gatekeeping could also prevent silent users or underrepresented groups from being involved in clinical studies (Abernethy et al., 2014). Hence, clinicians, ethics committee members, and researchers must be better trained in the moral and practical issues of end-of-life research (Abernethy et al., 2014; Gysels et al., 2013).

Patients affected by dementia are an example of how the progression of a disease can affect a person's ability to understand and appreciate the consequences of clinical trials (Casarett & Karlawish, 2000). It is necessary to conduct regular capacity screenings to assess the capability to consent as it changes over time (Monroe et al., 2013). Regarding studies on pain among cognitively impaired patients, it is argued that these concerns are particularly relevant in therapeutic research, where patients can have direct benefits or harm from the development of a new treatment. People with dementia may be included in the research only if their involvement is essential to the goals of research and if additional and multiple safeguards are applied (Monroe et al., 2013). The same ethical concerns have been highlighted in other studies on therapeutic research in patients with delirium. In this case, advanced or proxy consent has been suggested as a practical solution (Sweet et al., 2014).

Regarding the nature of qualitative research, there are issues concerning the fact that it is not always possible to anticipate the outcomes and not attain a complete informed consent (Duke & Bennett, 2010; Koenig et al., 2003). Moreover, participants should be aware that qualitative research does not have a therapeutic intent and it is not an adjunction to their medical care. Therefore, in the informed consent process, it should be clear that an eventual withdrawal will not impact health care (Richards & Schwartz, 2002).

One paper reported the difficulties in a qualitative study conducted to explore the palliative care needs of patients affected by chronic obstructive pulmonary disease (COPD). The high standards of informed consent were compromised in the context of the wish of non-maleficence (Gardiner et al., 2010). The terms COPD and palliative care were removed from the information sheet because the ethics committee was worried that they could cause distress to patients. This change has led to inadequate information providing (Gardiner et al., 2010). The same practical difficulties have been found in studies of patients with end-stage heart failure (Fitzsimons & Strachan, 2012).

DISCUSSION

Limitations of the review

This study has a few limitations. First, only papers published in English were included. As such, the included papers were based on ideas of Western morality and did not look at any other cultural influence in the way clinical research can be ethically evaluated. Second, a more comprehensive understanding can be obtained from the inclusion of studies about

the experiences of and views towards the participation of clinical research from researchers', patients', and relatives' perspectives. This will be further explored in another review. In addition, the methods used in the review were underpinned by an existing model and were predicated on the review's team beliefs regarding the appropriateness of the Foster framework. Furthermore, the types of all the included papers were diverse; therefore, no quality assessment was undertaken.

Strength of the review

Using the Foster framework, we were able to determine both the barriers and benefits of researching end-of-life patients. This framework has been shown to be useful in the analysis of ethical committees' concerns to protect the safety of study participants and to create high-quality research. Moreover, the Foster framework was developed according to the World Medical Association's Declaration of Helsinki. The description of clinically practical examples showed that this framework could be applicable and generalisable in everyday clinical work.

The use of a priori developed themes is a pragmatic approach for data synthesis, enabling rapid coding and analysis of papers. The taken approach does not require an extensive literature review, consultations, or topic expertise to develop a priori framework to apply to the analysis.

Implications

The use of ethical models, such as the Foster Framework, may help researchers, ethics committees and practitioners in better evaluating research protocols to foster a rigorous tradition of research in palliative and end-of-life care. In fact, a more systematic evaluation of ethical issues is needed in end-of- life research, clinical practice and institutional review boards.

According to the moral position described by Foster, in the evaluation and application of a study protocol, researchers, ethics committees, and practitioners should reflect not only the risks and benefits of clinical research but also the feasibility of the studies, creation of evidence-based knowledge that can be disseminated to influence daily practice. In this way, concerns about the ethics of researching the end of life can be addressed and barriers to the advancement of science in this area may be overcome.

CONCLUSION

In clinical research, guidelines have been developed to ensure that the rights of patients are protected, and that research is developed and delivered in an ethical way using evidence-based standards. This review provides up-to-date evidence on various challenges and ethical considerations about researching with end-of-life people. Combining a better understanding of the ethical issues in end-of-life care with appropriate scientific methods not only outlines the potential risks and benefits of research in this sensitive area, but also informs about good clinical practice, development, and conduct of clinical research with wider vulnerable groups.

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