

# Palliative care research: trading ethics for an evidence base

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Good medical practice requires evidence of effectiveness to address deficits in care, strive for further improvements, and justly apportion finite resources. Nevertheless, the potential of palliative care is still held back by a paucity of good evidence. These circumstances are largely attributable to perceived ethical challenges that allegedly distinguish dying patients as a special client class. In addition, practical limitations compromise the quality of evidence that can be obtained from empirical research on terminally ill subjects.

This critique aims to appraise the need for focused research, in order to develop clinical and policy decisions that will guide health care professionals in their care of dying patients. Weighted against this need are tenets that value the practical and ethical challenges of palliative care research as unique and insurmountable. The review concludes that, provided investigators compassionately apply ethical principles to their work, there is no justification for not endeavouring to improve the quality of palliative care through research.

The World Health Organisation defines palliation as “the active total care of patients whose disease is not responsive to curative treatment”. This holistic approach aims to provide palliation by integrating symptomatic therapy with psychological and spiritual support for both the dying patient and their family.<sup>1</sup> To meet this objective, health care providers must apply the best available evidence to their clinical decisions, through a programme of continuing professional development.<sup>2</sup> In certain circumstances, however, the obligation to address unmet needs through research may conflict with a physician’s primary duty to the health of his or her patient.<sup>3</sup>

Five years on from the publication of the World Health Organisation report, a review of the literature reported that the potential of palliative care was still held back by a paucity of good evidence.<sup>4</sup> These circumstances are largely attributable to perceived ethical challenges that allegedly distinguish dying patients as a special client class.<sup>5</sup> In addition, practical limitations compromise the quality of evidence that can be obtained from empirical research on terminally ill subjects.<sup>6</sup> This has prompted McWhinney *et al* to contend that it is morally indefensible to conduct research in full knowledge that the impractical nature of the study seriously undermines the validity of the findings.<sup>7</sup>

This critique aims to appraise the need for focused research, in order to develop clinical and policy decisions that will guide general medical and palliative care professionals in their care of dying patients. Weighted against this need are tenets that value the practical and ethical challenges of palliative care research as unique and insurmountable. These two perspectives are argued from a null hypothesis that evidence based research need not violate the physician’s duty of care to his or her patient and may take place with the express intent of achieving symptomatic relief for both the present subject and future patients. The subjective nature of effective palliation<sup>6</sup> is at the crux of the discussion; to illustrate the debate, the text stresses recurrent themes in patients’ views on palliative care. For instance, many dying patients value autonomy, spiritual guidance, psychosocial support, and symptom relief, as well as the involvement of, and support for, their families.<sup>1 6 8</sup> Consideration of the wider body of research ethics is of limited usefulness to palliative care investigators, and is only detailed where the focus is pertinent to dying patients.

**Table 1** Symptom prevalence in patients with a terminal disease<sup>10</sup>

Symptom	Prevalence (%)
Anxiety	24–32
Confusion	5–38
Constipation	25–86
Depression	18–36
Dyspnoea	20–69
Fatigue	7–88
Incontinence	18–51
Loss of appetite	38–66
Nausea / vomiting	16–54
Pain	52–77
Sleep	19–88
Weakness	35–100

## THE NEED FOR AN EVIDENCE BASE

De Raeve commented: “We are going to have to think of some compelling justifications to permit research on dying people”.<sup>8</sup> In developing a reply, one is compelled to consider the high prevalence of inadequately managed symptoms and the adverse psychosocial impact of a terminal disease (table 1).<sup>10</sup> These findings are reflected by a survey, in which a quarter of nurses reported that they were unable to provide good care for dying patients in their present workplace.<sup>11</sup> Aside from the anticipated direct benefits of a trial, participation in research and access to the research milieu is often beneficial for patients.<sup>12</sup> Indeed, a pilot study found that the care of patients with cancer is jeopardised by oncologists’ reluctance to meet the challenges posed by research.<sup>13</sup> Accordingly, the author joins with Mout and colleagues<sup>14</sup> in striving for further improvements in the quality of palliative care and in asking whether unproven therapy truly helps the dying patient.

## Utility

In September of 2000, the Nuffield Trust published a declaration on care for the dying. The document articulated a need for national standards to provide adequate professional training,

an authoritative document on best practice, and longitudinal audit of the quality of the services available.<sup>11</sup> To achieve these ends, physicians must integrate clinical expertise with the best available external evidence, the central tenet of evidence based medicine. Neither evidence base alone is sufficient; clinical expertise is essential to guide the interpretation of research findings, for even excellent research may be inapplicable to or inappropriate for an individual patient. Likewise, reviewing the current best evidence is crucial if clinicians are to prevent their practice from becoming outmoded to the detriment of their patients.<sup>15</sup> While providers do not always make the best use of the available evidence,<sup>5</sup> there are also significant gaps in the literature,<sup>4</sup> which inherently compromise the ability of a clinician to offer the best level of care available.

The Royal College of Physicians' guidelines on the practice of research ethics committees states that vulnerable patients should never be subjected to research that might be carried out with equal efficacy in autonomous, competent adults.<sup>16</sup> The goals of patients receiving palliative care differ substantially, however, from those in other clinical settings (see below)<sup>5</sup> and the clinical endpoints are rarely transferable.<sup>17</sup> Thus, it is seldom possible to extrapolate palliative guidelines from therapeutic research conducted on patients receiving curative therapy.<sup>17</sup> For clinical research to be valid, the variables measured must represent causally related biological entities, legitimised by established science.<sup>18</sup> Investigators can gain an insight into the pathology of the dying process by conducting non-therapeutic research on patients with chronic diseases, but the end stages can only be adequately scrutinised in terminal patients.<sup>17</sup> In conclusion, while clinicians' care of the terminally ill may be informed by research conducted on patients with curative disease, certain aspects of the dying process are distinct from potentially curative medicine, necessitating focused research on dying patients themselves.

### Making amends

In hospitalising the dying and isolating them from society, physicians have fostered cultural taboos about death.<sup>19</sup> Viewing death merely as a negative clinical outcome also trivialises the event, stripping it of significance for patients and their families.<sup>20</sup> As a consequence, the medical profession has instituted emotional barriers to the public endorsement of research in this group.<sup>19</sup> Ultimately, a vicious circle is established, in which cultural attitudes towards death influence clinicians to further shield society.<sup>20</sup> Palliative care specialists have an important role in overturning this misguided philosophy, by affirming death as a natural process.<sup>4,20</sup> It may be argued that quantifying palliative care research risks treating individuals as statistics and is in direct opposition to this goal. Nonetheless, to contest entrenched beliefs one must ground a challenge in irrefutable evidence, which can only come from germane research.

### Market forces

Regardless of their moral stance, health care providers must work in an environment where cultural preoccupations and economic policies dictate that the allocation of health care resources remains value-laden.<sup>6</sup> In the United States, end of life expenditure through Medicare already consumes 10–12% of the total health budget.<sup>21</sup> This economic burden is predicted to rise as the proportion of patients dying from chronic or progressive illnesses increases.<sup>22</sup> Accordingly, the current disparity between provision and need is set to widen,<sup>23</sup> necessitating the use of morally defensible selection criteria to maximise the utility of finite resources.

There has been a longstanding bias towards the provision of palliative care for cancer patients; up to 70% of patients with cancer are cared for by a palliative care team, yet only a few patients without malignant disease receive specialist palliative

care.<sup>24</sup> Patients may be allocated resources on the basis of need, the differential likelihood of benefit, opportunity costs, and prior commitment. To be just, these criteria must be continually reappraised on the basis of the best available evidence.<sup>6</sup> Therefore, research and audit are essential if palliative care is to defend its ever-increasing share of the National Health Service (NHS) budget and charitable provision, and is to allocate that share justly.

The current climate of patient driven consumerism has placed increasing demands on the palliative services to deliver on the World Health Organisation aims. Moreover, questioning the quality of care offered and striving to improve it are key elements of a physician's statutory duty to his/her patients. In short, a terminal diagnosis does not excuse complacency or futility in the mindset of health care providers charged with imparting effective palliation.

### THE DYING PATIENT: A SPECIAL CASE?

To be valid, an argument against research in a palliative setting must demonstrate that dying patients constitute a special client class, for whom research raises distinct ethical challenges. From this stance, one may argue that special restrictions, protection, and guidelines are necessary to direct research. In contrast, if patients near the end of life are not subject to unique ethical constraints, then research may be acceptable within the context of strategies devised to protect subjects who pose similar challenges.<sup>5</sup> This debate is structured around five lines of reasoning proffered in support of this unique status.<sup>5,7</sup>

#### Vulnerability

Palliative care patients are frequently regarded as a vulnerable group, who are incapable of protecting their own interests because they lack decision making capacity or because their choices are not voluntary.<sup>5</sup> It has been contended that these limitations demand a greater degree of stewardship from the provider, to defend the patient against exploitative research.<sup>8</sup> Mount *et al* maintain that this stance devalues an individual's personhood, implying that they are not able to contribute to society, are incapable of questioning their suffering, and cannot truly express or realise any altruistic motives.<sup>14</sup> Given that "quest" is a recurrent motif in the outlook of terminally ill patients,<sup>25</sup> one can reason that researchers should not treat study participants merely as a "means", but rather join with them in seeking meaning in death. Accordingly, research honours the subject as a teacher and, by their motives, investigators demonstrate compassionate concern for the patient's plight.<sup>14</sup>

Jonas argued that consent is only valid if the subject articulates a willingness to participate and can identify with the research goals.<sup>8</sup> If, however, a patient's suffering creates a sense of desperation, the patient may be willing to participate in any research because of the expectation, whether justified or not, of adventitious benefits.<sup>26</sup> Moreover, patients experiencing the dependency of a terminal condition may feel overwhelming gratitude on referral to a palliative care specialist, which could manifest as a compulsion to consent to research.<sup>5,8,26</sup> Often, patients do not appreciate that they can decline to participate without jeopardising their care<sup>8</sup>; it is the responsibility of the physician to address these concerns.

Such concerns are brought into acute relief in dying patients, but are relevant to all clinical research (albeit to varying degrees) and do not constitute a specific argument against palliative care trials.<sup>5,14</sup> Cassell alleges that all illness confers a state of "diminished autonomy", which is restored through good management.<sup>26</sup> Thus, every clinical research proposal warrants specific consideration and, where appropriate, safeguards may be implemented to surmount the ethical challenges: To assure the validity of informed consent, each subject recruited for a study that presents a "demarcated

risk"—that is, greater than the risks encountered in routine care, should undertake a formal capacity assessment. One can underscore the distinction between the clinician and the researcher by delegating the recruitment to an independent party. Thirdly, implementing a "lead in period" can mitigate feelings of desperation by optimising symptom management prior to recruitment.<sup>5</sup> In practice, though, dying is a dynamic process, in which symptom control is under perpetual review<sup>26</sup>; an optimal baseline has not been set. Further, given the short time window available for research on dying patients,<sup>7</sup> symptom management above this ill defined threshold may never be achieved, let alone sustained.

Over the course of a longitudinal study, these complications may invalidate earlier consent, and it may be necessary to repetition for consent at regular intervals.<sup>6</sup> This approach can, however, apply unwarranted duress to remain in the study and most dying patients will progress to a phase where, through incapacity, they are not competent to consent. Undoubtedly, though, research could yield information about interventions that could be used at this stage.<sup>5</sup> It could be argued that, if the very process of death entails losing control, one may respect autonomy by understanding its compromised nature, and not require it to be constantly exercised.<sup>27</sup> For example, the qualitative investigator may benefit the participants by granting them attention and time to reflect.<sup>8</sup> Adopting Grogono's role of an *amicus mortis*,<sup>27</sup> however, not only compromises objectivity (especially when scrutinising the clinician-patient relationship), but reflection can also be distressing and may be viewed as coercion.<sup>8</sup>

(The dilemma surrounding the acceptability of surrogate consent is not confined to palliative care and has been well debated elsewhere.<sup>28</sup> For these reasons, the topic is not detailed here.)

### Double agents

In all fields of clinical research, investigators are also health care providers who must balance their competing responsibilities to patient care and scientific rigour.<sup>5</sup> Researchers must decide whether or not to disclose confidential information if it has clinical significance, or whether to intervene to relieve the symptoms that they discover.<sup>26</sup> These problems may be particularly troubling to palliative care investigators, because the general standard of care for the dying is poor.<sup>29</sup> Investigators are almost certain to discover problems that are unrecognised and symptoms that are inadequately controlled.<sup>26</sup> Psychological research poses significant problems; patients change their behaviour if they know that they are being studied.<sup>30</sup> This necessitates deception/concealment that is both intrusive and violates the ethical principles of informed consent.<sup>30</sup> However, the protocols in place for other areas of research, which usually involve delegating the decision to independent review by an informed body, are sufficient to overcome this hurdle.<sup>5</sup>

### The family

Care practices need to be informed by an awareness of how familial support and cultural background determine the caregiver's needs,<sup>5</sup> and the extent to which meeting those needs can mitigate "anticipatory grief" and facilitate a good bereavement.<sup>31</sup> The distinct agendas of caregivers and patients imply that it may be misleading to use either one as a proxy measure for the other.<sup>26</sup> Thus, a family-centred management strategy needs to consider the findings of focused research, conducted with the express aim of meeting the needs of the patient and their family.

In undertaking research of this type, the investigator is obliged to obtain informed consent from all family members concerned, as well as from the patients.<sup>3</sup> This in itself is not a barrier to research, but creates a logistical burden that may compound caregivers' reluctance to participate and imposes

practical limitations on the size of the trial.<sup>5</sup> One can, however, lessen the burden of research that poses a minimal risk, by negotiating with research ethics committees to accept verbal consent from the relatives if the patient has granted full, informed consent.

### Changing perspectives

The Declaration of Helsinki (II:2) recommends that: "The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods".<sup>3</sup> Although this holds true in a palliative setting, patients whose disease is not responsive to curative therapy often have very different goals for care.<sup>5</sup> Put simply, there may be a decreased emphasis on survival and a new focus on symptom relief, dignity and meaning, social relationships, and control.<sup>5</sup> Alternatively, some patients strive for as much time as possible, regardless of their quality of life.<sup>32</sup> Patients receiving palliative care may perceive that periods spent answering questions detracts from valuable time that may be spent strengthening relationships and concluding business with relatives and others.<sup>5</sup> The same protocol may not prove so onerous to patients with curative disease.

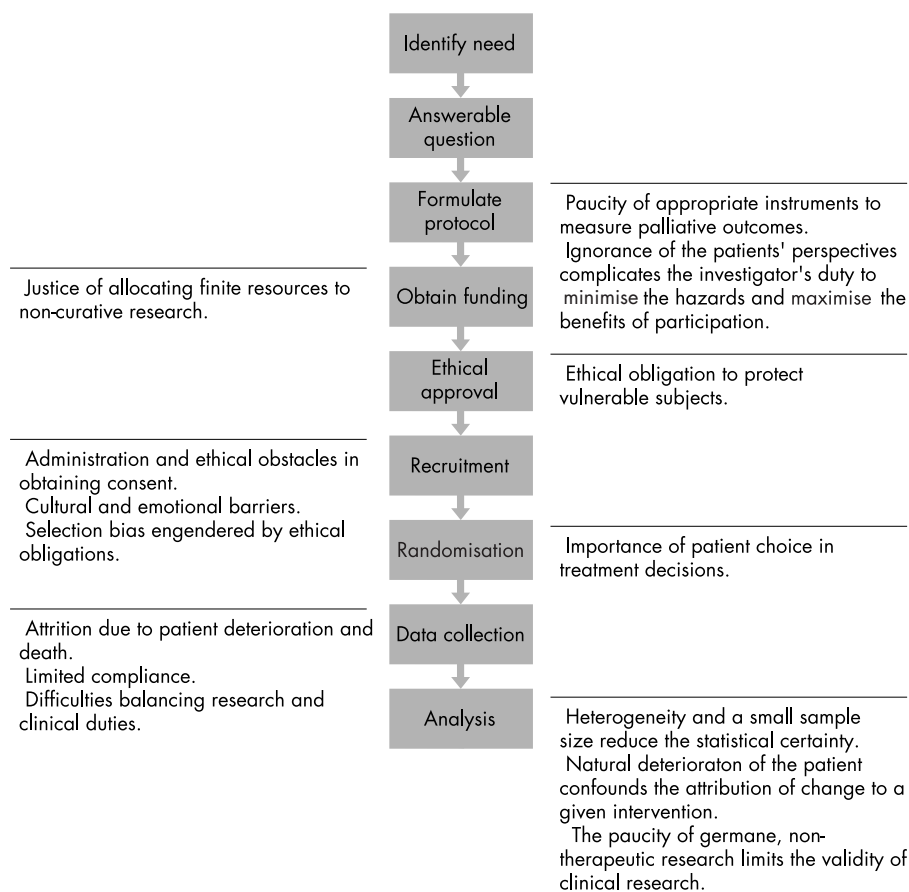
Unlike the previous three concerns, this ethical challenge is unique to palliative care and deserving of individual attention, but it is not unassailable.<sup>5</sup> Studies evaluating the experiences of the dying account for only one per cent of the total body of literature on palliative care.<sup>4</sup> Thus, there is an urgent need to commission research into how palliative patients perceive these risks and benefits. Only with this knowledge base can research ethics committees define an acceptable risk threshold.

### Palliative care research: impractical?

The hierarchy of evidence based medicine places great emphasis on the quantification of data, in pursuit of statistical significance from a sufficiently large sample to allow generalisations to be made.<sup>33</sup> Palliative care research is, however, especially taxing (see figure 1). In a quality assessment of palliative cancer care studies, Rinck *et al* reported one or more methodological problems with all 11 randomised controlled trials examined.<sup>34</sup> Having reviewed over 800 papers, Salisbury and colleagues described a dearth of good quality evidence on which to base any conclusions.<sup>35</sup> Indeed, their own experiences led McWhinney *et al* to conclude that randomised controlled trials are impractical for palliative care services.<sup>7</sup>

Double blind randomised controlled trials are held up as the gold standard of clinical research; they allegedly match for all potentially confounding variables and offer the best protection against selection and observation bias.<sup>37</sup> Even so, the unpredictability of randomisation deprives patients of choice and control, which are key aspects of palliative therapy.<sup>32</sup> Therefore, the very act of randomisation could produce a biased underestimate of effect.<sup>38</sup> Fulfilling Freedman's clinical equipoise requirement for ethical randomisation may reduce this,<sup>39</sup> but the problem is only avoided by patient self selection into the various arms of the trial, which biases the findings beyond any practical use.<sup>37</sup> These fears may be allayed by considering that patients exercise control over research participation itself, but this raises the possibility that the study group may not be representative if the more autonomous patients opt out of randomisation.<sup>37</sup>

Qualitative evidence is dismissed by some as anecdotal<sup>37</sup> and the ethical fallout from needlessly instituting a harmful therapy, or dismissing an intervention of potential benefit, is reprehensible. Nonetheless, the aspects of palliation that are most subjective must first be appraised by qualitative research, to define the objectives for more focused, empirical studies. Where it is not possible to avert the significant ethical and practical obstacles to empirical research, qualitative studies



**Figure 1** Practical and ethical challenges to palliative care research, applied to a model randomised controlled trial.

may substitute, provided the researcher judges the evidence with conscientious regard to its relative merits and flaws. Indeed, a dual approach combining qualitative and quantitative research may enrich the findings and better inform the practice of palliative care.

Importantly, investigators are not excused from addressing critical questions on practical grounds. To do so risks compounding the current preoccupation with describing activities and problems in palliation, rather than evaluating new and existing approaches to care.<sup>41</sup> The scientific, clinical, and funding communities must not tolerate underpowered, badly designed trials on the pretext that the ethical and practical obstacles absolve shoddily conducted research. Indeed, it is ethically deplorable to carry out a trial on a vulnerable population, in full knowledge that its design seriously compromises the validity of the findings. To avoid this, it may be necessary to restrict palliative research to investigators who are experienced in conducting research on vulnerable groups and are familiar with the ethical and practical challenges posed by dying patients; new researchers must be closely supervised by experienced professionals until they acquire the requisite skills.

### CONCLUDING REMARKS

This discussion can be conceptualised as a conflict between needs and values. On the one hand, both political and professional agendas require evidence of effectiveness to address deficits in care, to strive for further improvements, and justly to apportion finite resources.<sup>6-9</sup> Conversely, whilst no research can be said to be benign, dying patients represent a special client class for whom research raises both heightened and distinct ethical objections.<sup>3</sup> This strictly dichotomous view does not, however, give due regard to patient heterogeneity,

the dynamic nature of dying, and the relative risks and benefits of different modes of investigation.<sup>14</sup>

The review concludes that the beneficence and maleficence of each proposal deserve individual consideration. In some instances, investigations are not justifiable and others warrant stringent guidelines to safeguard the research subject. Meeting these obligations and overcoming any practical obstacles demands robust protocols to permit the collection and interpretation of significant data. Nevertheless, medical oncologists have cited rigid protocol design as the primary deterrent to the accrual of patients into clinical trials, in addition to an excessive time commitment.<sup>42</sup> Therefore, to encourage recruitment and cultivate the success of a trial, studies that do not pose significant ethical dilemmas should be unfettered from time consuming, precautionary administrative duties imposed by research ethics committees.

In conclusion, provided palliative care investigators compassionately apply ethical principles to their research, there is no justification for not endeavouring to improve the standards of palliation.

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