How to conduct research in palliative care? A perspective from Italy

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Abstract

Background. In western countries, the increasing life expectancy and the growing number of individuals with advanced chronic conditions have resulted in a greater demand for palliative care. Specifically, Italy has witnessed substantial growth in the palliative care field, marked by the establishment of Palliative Care Networks and an academic fellowship program in 2022. To further enhance this field, it is crucial to conduct high-quality scientific research that produces results applicable in clinical practice.

Aim. This article explores challenges and potential solutions in conducting effective palliative care research, considering sample definition, research settings, outcomes, and ethical concerns. While focusing on the Italian context, the presented research framework can be applied to other contexts and regions.

Results. Palliative care research is complex and challenging due to its holistic approach, which encompasses various vital dimensions of patients and their families, including physical, emotional, and social needs. The Italian and worldwide experience provides insights into managing these challenges and enhancing the methodological rigor of studies and the practical application of research findings.

Conclusions. This article emphasizes the importance of developing protocols tailored to palliative care's unique characteristics, and the necessity of dedicated funding for palliative care research, calling for increased support and recognition. The article advocates for improvement of the quality and relevance of palliative care studies, promoting better patient outcomes and enhanced caregiving.

INTRODUCTION

Advancements in treatment of acute and chronic conditions have significantly contributed to increase life expectancy. However, this epidemiological change is associated with an increment in the number of people living with the consequences of serious chronic diseases towards the end of life, resulting in a greater need for palliative care. According to World Health Organization (WHO) data, every year 56.8 million people worldwide, including 25.7 million in the last year of life, require palliative care [1]. Despite this, only 14% of those in need actually receive a palliative and comprehensive approach [1].

Italy represents one of the countries with the oldest population in the world, with almost one-fourth of the 59 million citizens aged 65 years or older. It has been estimated that more than 500 thousands individuals in the country are in need of palliative care every year, but only 23% of them receive palliative approach [2]. To face this increasing need of palliative care, several organizational and educational measures were taken in the country. The delivery of palliative care is organized based on Palliative Care Networks (PCN), that guarantee access to services and continuity of care to patients with advanced stage chronic diseases, organ failure or cancer [3]. Integrated care pathways are ensured by a close collabora-
tion of the key nodes of the PCN which include home care, residential care/hospice, hospital and ambulatory care [4]. Furthermore, in order to improve education and training of medical doctors operating in the PNC, starting from 2022 a fellowship program in palliative care was established nationally [5]. The program aims to train a new generation of specialists with specific knowledge related to the clinical, diagnostic, and therapeutic issues that characterize the advanced stages of various chronic diseases. It also aims to develop advanced skills in the communication process, socio-familial, spiritual, and psychological assessment, care and treatment planning, and identifying patients’ preferences. Palliative care specialists should be capable of working in team with other specialists or with the general practitioner with the main aim of improving patients’ quality of life.

The establishment of PCN and the creation of fellowship programs paved the way to reorganize the care process for patients with palliative care needs and to improve the education and skill of healthcare personnel. To further advance the palliative care sector at a national level, it is crucial to bring in substantial research data that can guide clinical practice in this area. Indeed, palliative care research has been growing both internationally and in Italy. Figure 1 presents the number of the PubMed records selected based on the search term “Palliative care” (Panel A) and the term “Palliative care” and “Italy” (Panel B) between 1993 and 2022. Despite the increasing number of PubMed records over the past 30 years, research in palliative care is complex and challenging due to its holistic aim, which addresses multiple vital dimensions of patients and their families, includ-

![Figure 1](image.png)

*Figure 1*
Number of the Pubmed records selected based on the search term “Palliative care” (Panel A) and the term “Palliative care” and “Italy” (Panel B) between 1993 and 2022.
<table>
<thead>
<tr>
<th>Problem</th>
<th>Consequences</th>
<th>Possible solutions</th>
<th>Barriers to implementation of possible solutions</th>
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<tr>
<td><strong>Sample</strong></td>
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<tr>
<td>Heterogeneity of patients receiving palliative care</td>
<td>Specific needs of particular patients’ populations can be not appropriately evaluated</td>
<td>Focus on symptoms (i.e., pain, dyspnoea) rather than diseases (oncological and non-oncological) Include heterogeneous samples in sufficient numbers to measure benefits and harms of interventions. Develop and implement risk-stratification models and report harms and benefits according to risk strata</td>
<td>Solutions adoptable in observational studies, but difficult to implement in Randomized Clinical Trials (RCT) due to the need of enrolling a large and heterogeneous sample Need of relevant research funds to enrol large samples</td>
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<tr>
<td>Attrition due to particular characteristics of patients receiving palliative care</td>
<td>High rate of loss to follow Study underpowered and limited validity of study results</td>
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<tr>
<td>Most studies conducted in a single setting of care and with limited sample</td>
<td>Sample not representative of population suffering from the examined condition Results not generalizable to non-oncological patients Limited applicability and results generalizability of study results in clinical practices</td>
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<tr>
<td>Most research performed in cancer</td>
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<td><strong>Setting</strong></td>
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<tr>
<td>Palliative care covers different settings</td>
<td>Research often performed in a single setting Limited generalizability of study results</td>
<td>Enrol samples from or replicate study findings in different PC settings to confirm the consistency of results (hospital, home care, hospice, nursing home)</td>
<td>Organization and resources may limit the possibility of performing research in settings Organization of research protocols may vary depending on setting (i.e., residential vs. home care)</td>
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<td><strong>Outcomes</strong></td>
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<td>Definition of outcomes that are relevant in palliative care patients</td>
<td>Traditional single disease-oriented outcomes cannot adequately capture multidimensional and patient centered concepts of palliative care Reduced relevance of research findings</td>
<td>Adoption of multidimensional and patient centred outcomes (symptoms control, quality of life, patient reported outcomes) Combine patient centred outcomes with more objective measures (i.e., hospitalizations, ER admissions, procedures performed)</td>
<td>Patient centred outcomes are difficult to assess at the end of life due to lack of collaboration and can be affected by several factors and present with large fluctuations in these measures Patients receiving palliative care are at risk for rapid clinical deterioration and are likely to drop out at follow-up assessment</td>
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<td><strong>Ethical issues</strong></td>
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<td>Patients research burden</td>
<td>Need to reduce redundant or unnecessary activities in patients with limited life expectancy Reduced participation to research activities</td>
<td>Simplify study protocols Explain to patients personal and societal benefit of research</td>
<td>Not always applicable because not sufficiently regulated Models not standardized and codified</td>
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<td>Informed consent</td>
<td>Patients unable to understand research aims and/or accurately interpreting their conditions Impossibility to released informed consent</td>
<td>Consent waivers or alternative consent models Consent released by a proxy</td>
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<tr>
<td>IRB evaluation</td>
<td>IRB members not familiar with PC research Inadequate evaluation of IRB protocols</td>
<td>Education of IRB members about palliative care populations and research Creation of a lexicon of key terms in palliative care research Creation of a taxonomy of key potential IRB concerns as related to palliative care</td>
<td>Resistance of deviating from standard rules of traditional research</td>
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IRB: institutional review boards.
ing physical, emotional, and social needs. Research in this field substantially differs from traditional clinical research in terms of the population involved, objectives, and methods. In this paper we will define a framework to develop research activities in palliative care in Italy, by assessing problems, consequences and possible solutions related to different aspects of research studies, including sample definition, settings, outcomes and ethical issues (Table 1).

DEFINITION OF STUDY SAMPLE

The definition of an appropriate study sample is the first key step in conducting research. The sample must be representative of the examined condition or disease, and the generalizability of study results largely depends on how study participants are selected. Palliative care patients inherently exhibit a high level of heterogeneity [6]. Patients often present with multiple symptoms simultaneously, variable by nature and by response to treatments, regardless of the underlying pathology. Furthermore, the same condition can be observed in patients with different baseline disease and health characteristics. For this reason, samples selected in palliative care research tend to be characterized by a high level of heterogeneity. While this approach improves generalizability of study findings, making its results applicable to a larger population, it may leave specific needs of particular patient populations unmet.

Another concern related to samples selection arises from the fact that the majority of palliative care studies are monocentric, performed in a single setting of care and with a limited sample size, which can have an impact on the power to detect differences between treatment strategies and on the generalizability of results [6]. Additionally, scientific research on palliative care has traditionally focused on oncological diseases. However, pain and other physical, psychosocial, and spiritual problems, which represent the main focus of palliative care, can be observed across a multitude of oncological and non-oncological diseases. Although there has been an increasing number of studies focusing on patients with non-oncological diseases in recent years, the generalizability of findings obtained from an oncological sample to patients suffering from other conditions remains a concern. A final concern related to sample selection in palliative care studies is due to participants drop out and attrition. The rate of survival is difficult to define in this population, especially for non-oncological patients. Short- and mid-term prognosis of these patients is variable, and the risk of loss to follow-up, due to difficulties to attend follow-up visits, is elevated.

All the above-mentioned factors represent important issue to be considered in the identification of an appropriate sample to perform research, since they may influence the generalizability of research results and increase the risk of underpowered studies that lack a sufficiently large sample size to answer the research question. This complexity argues for adapting sample selection by including large, diverse populations, that are representative of the condition cared for in clinical practice. Being the focus of palliative care “(...) the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”, the research sample should be enrolled based on the presence of these conditions rather than specific diseases. Given the heterogeneity due to variability in patients’ initial condition and level of risk, responsiveness to specific treatments, and vulnerability, effects can be compared within homogeneous risk strata defined according to their characteristics. Observational research can likely better accommodate the large, heterogeneous populations needed to achieve this goal.

PALLIATIVE CARE SETTINGS

Palliative care spans across various settings, based on different degrees of disease severity and patients’ preferences, with the possibility of transition from one setting to another based on specific needs. More specifically, in Italy, the PCN includes the following settings:

• hospital, where an expert medical-nursing team offers palliative care consultations. Hospitals can both activate early palliative care pathways and help carers in the management of terminally ill patients;
• ambulatory services, caring for self-sufficient patients, which are granted multi-dimensional and specialist medical services aimed at controlling symptoms and assisting their families;
• hospice, providing temporary hospitalization for patients in the last stages of their life;
• home care, providing care to patients in their own homes, aiming not only to enhance their quality of life and functional health status but also to replace hospital care with home-based care for societal reasons [4]. In addition to these settings, despite not being formally included in the PCN, palliative care should cover also nursing homes, that traditionally admit individuals with a high level of complexity, multimorbidity, functional and cognitive impairments, and with a high mortality rate [7].

These settings are interconnected to ensure continuity in the care process, but the development of palliative care shows uneven progress. Currently, 90% of Local Health Authorities (Azienda Sanitaria Locale – ASL) have implemented local PCN; however, only 79% of these have established dedicated care pathways. Despite this, palliative care remains inadequately integrated into hospital settings and dedicated palliative care professionals are absent in over 40% of teams providing home care services [8].

There is also a notable disparity between the northern and southern regions in providing palliative care. Southern regions exhibit a lower number of services, particularly hospice facilities [8]. It is anticipated that efforts will be made to bridge or at least narrow this gap in the coming years. The most recent 2023 Budget Law mandates that by 2028, palliative care should be accessible to 90% of those in need [9].

In terms of research, different settings can vary in terms of care organizations and available resources, and these factors can influence research findings. For this reason, to make research results generalizable to all patients suffering from a certain condition, they should be
found to be consistent across settings. Studies should enroll participants from different settings or replicate their findings across settings, especially those often neglected by clinical research (i.e., nursing homes). This might require the development of setting-specific study protocols that take into account organizational factors and resources.

OUTCOMES

The main goal of palliative care is to improve the quality of life of patients facing life-threatening illness and their caregivers through a multidisciplinary approach. Traditional research tends to focus on disease-specific outcomes, for example, stroke prevention or exacerbation of chronic obstructive pulmonary disease. Such outcomes make little sense in palliative care where the focus should be on “universal” outcomes. Universal health outcomes—outcomes on which all diseases exert an effect—represent the consequences that matter most to patients. Focusing on them would ensure that both harms and benefits of treatments are compared. Examples of universal outcomes include symptom burden (e.g., dyspnea, pain, fatigue), function (physical, cognitive, psychological, social), and health-related quality of life. These factors can be assessed by means of patient-reported outcomes or by standardized professional evaluations. In this context, a review showed that efficacy of treatments and symptom control and quality of life are used as primary outcomes in 75% of palliative care research [6]. This finding underlines the patient-oriented nature of palliative care research which is focused on the individual patient’s experiences.

In addition to symptoms and quality of life, Patient-Reported Outcomes (PROs) are also considered relevant outcomes in palliative care research. PROs are directly reported by the patient without interpretation by a clinician or anyone else. They pertain to the patient’s health status, quality of life, functional status, symptom burden, personal experience of care. The importance of PROs is also emphasized by the Italian Plan for Care of Chronic Diseases (Piano Nazionale Cronicità) released by the Italian Ministry of Health, which underlines the relevance of these measures as research outcomes and for monitoring the quality of care provided. Despite being extremely useful in assessing the impact of specific symptoms and outcome measures that really matter to patients at an individual level, PROs are difficult to standardize and often do not allow direct comparisons among patients [10]. Additionally, outcomes in palliative care research should also focus on caregivers’ evaluation. The burden of caring for patients at the end of life may adversely affect caregivers’ health, which, in turn, can have negative effects on the quality of life of both patients and caregivers.

The above-mentioned outcomes can adequately capture multidimensional (clinical, psychological, spiritual, functional) and patient centered nuances that differ from those usually assessed in traditional research, which are disease specific and often focused solely on the clinical dimension. However, assessing outcomes in palliative care poses several challenges. First, quality of life, symptoms severity, and PROs are subjective outcomes that require patient collaboration for their evaluation. Patients with cognitive impairment, very severe diseases or in the last days of life may not be adequately assessed by these measures. To address this issue, the use of proxy-reported quality of life assessments has been proposed, but several studies have suggested that evaluations of quality of life by proxies may be inaccurate [11]. Second, quality of life, symptoms severity and PROs can be affected by internal factors, such as mood, expectations, time, sentiments, and knowledge of prognosis, as well as by external factors, such as treatment context, interactions with the healthcare providers, and patients’ socioeconomic situation, leading to fluctuations in these measures. Given this variability, it has been proposed to collect measurements longitudinally and at multiple time points to assess the trajectories of symptoms progression and recovery. Finally, patients receiving palliative care are at risk of rapid clinical deterioration and are likely to drop out at follow-up assessment. For this reason, it seems relevant to select outcomes that may be sufficiently sensitive to change and for which a meaningful change can be easily reached in the short timeframe. Given these issues, it seems reasonable, in performing palliative care research, to combine subjective outcomes (i.e., quality of life, symptoms severity and PRO) with more objective measures (i.e., hospitalizations, ER admissions, procedures performed) in order to have a more comprehensive assessment of patient health trajectories.

ETHICAL ISSUES: PATIENTS’ BURDEN AND ETHICS COMMITTEES

Ethical concerns may arise regarding the involvement of complex and sick patients and their families in palliative care research. Some of these concerns can be classified in two main categories: 1) Patient level and 2) Ethics Committees level concerns.

Considering the issue from a patient level, it may be felt within the scientific community that participation of patients receiving palliative care in research can increase their burden, potential distress, and even harm [12]. These concerns are based on the perception that palliative care patients are particularly frail and vulnerable, with very limited life expectancy, therefore warranting extra protection from redundant or unnecessary activities. However, available research data suggests that views expressed by palliative care patients towards research are similar to those of other patient populations. Their participation in research is driven by the potential for personal gain, altruism, and a desire to retain autonomy, despite the wish to avoid complex studies [12]. The acquisition of informed consent relies on the patients’ capacity to understand research objectives, their own condition, and the potential risks and benefits associated with study participation. These elements may be lacking in palliative care patients due to the severity of their condition, cognitive impairment, psychiatric illnesses, or pharmacological sedation. Furthermore, obtaining formal written consent can be time-consuming,
cognitively challenging, and burdensome for some participants, especially those with sensory or physical impairments, or other serious illnesses.

As a result, consent waivers or alternative consent models have been proposed in palliative care research, including broadcast notification (general notification, usually by flyers or brochures in clinical areas or via mail), integrated consent (combines clinical and research consent within the same encounter), or consent released by a proxy (or legally authorized representative). These strategies are not addressed in Italian law n. 219/2017, which focuses mainly on clinical consent. An amendment to this law in this direction could lead to a more modern approach to informed consent, facilitating the inclusion of frail patients in clinical studies without compromising their right to self-determination, providing them the chance to get access to trials and treatments from which they would be otherwise excluded [13, 14].

A second level of concern relates to Ethics Committees, which are independent bodies responsible for the ethical clearance of studies. Palliative care is a relatively new discipline and Ethics Committees members may not have sufficient skills in palliative care nor be familiar with the specific research features of palliative care research. As mentioned, palliative care research differs significantly in terms of sample, setting, and outcomes from traditional research, which may lead to inadequate evaluation of research protocols. Possible solutions proposed to solve this issue include better education of Ethics Committees members about palliative care populations and research, the creation of a lexicon of key terms in palliative care research and the development of a taxonomy of key potential Ethics Committees concerns as related to palliative care research [15]. These aspects are particularly relevant to standardize the approach of Ethics Committees, particularly in Italy where a reorganization of Ethics Committees system has been recently realized, with the establishment of 3 National and 40 local Ethics Committees [16].

STUDY DESIGN SELECTION

Quantitative studies have traditionally been considered the gold standard for studying the effects of an intervention and its effectiveness, as they allow for the measurement of a variable and establish clear cause-effect correlation. In clinical trials it is possible to verify hypothesis through a systematic and predefined analysis, whose results can be generalized to the entire population. In the palliative care field, the main study topics are the effects of a non-pharmacological (i.e., acupuncture, music therapy, aromatherapy, relaxation techniques) or pharmacological intervention, or the effectiveness of these measures, intended as their applicability in the real world. The research’s main objectives guide the study design choice. Case-control studies can hardly be applicable in this area, unless they investigate the symptom burden in units that routinely document the intensity and prevalence of different symptoms. Prospective studies, either parallel or crossover, are more suitable when a therapeutic intervention is to be studied [17]. Although double-blind randomized clinical trials provide the highest-level evidence data, they are challenging to perform in palliative care due to both organizational and ethical issues, as previously mentioned.

Qualitative studies are also well-suited for investigating end-of-life issues. These studies, having been born in sociological, psychological, and anthropological fields, allow to understand a phenomenon in its complexity rather than just measure it. This approach applies well to research in the palliative field, whose main themes (e.g., symptom burden) present a significant subjective component, also expressed in terms of perceived benefit. Qualitative studies employ individual interviews, focus groups and observational groups to gather data. The main objective of those studies is to understand and discover new elements by posing open-ended questions to study participants. This allows the examinators to have a “bottom-up” understanding of the study main topic, which is particularly useful when you want to understand how a treatment intervention is perceived by the patient or family members. The use of open questions allows researchers to obtain a large number of data even from small populations, partially overcoming the problem of small population samples in palliative care research. Qualitative studies are characterized by an iterative process where the data is collected and analyzed simultaneously, providing great flexibility to the whole research process [18]. However, qualitative studies still present uncertainties about the validity of the collected data, mainly linked to the complex assessment of methodological rigor [19]. This can be limited by using descriptive checklists to improve methodological accuracy [19].

A new approach that is gaining ground is mixed-methods research, where qualitative research and randomized clinical trials are combined. Indeed, in the field of palliative care, the effectiveness of interventions and the benefits perceived by patients are both crucial pieces of information [20]. Qualitative research can act as a precursor to quantitative research, bringing to light new study topics based on patient preferences. It can also help clarify why an effective intervention in trials has not been applied to everyday clinical practice, or identify issues related to participant enrollment. Similarly, randomized clinical trials provide methodological rigor to the study. Mixed methods research is a valid approach to study end-of-life issues, since with its holistic vision enriches the quantitative data through the analysis of the context in which those data are collected. However, it should not be forgotten that this approach is relatively new and has limitations. Researchers need ample experience and specialized training, such as in framing questions, honing listening skills, building rapport, and collecting data. Otherwise, there is a risk of diminishing the overall quality of the research. A recent methodological review demonstrated that there is still room for integration in terms of a formal definition of how these two methods are integrated with each other [21]. Finding the right balance between the two methods, in terms of planning and finance management, is also crucial.
FROM RESEARCH TO GUIDELINES

Clinical practice today is guided by evidence-based medicine, a difficult model to apply to the palliative care model. The palliative care field produces fewer studies and of reduced quality compared to those of traditional research [22]. This is probably due to factors described in this article, that make research in palliative care a difficult task: small and heterogeneous samples, difficulties in having an adequate follow-up period, ethical issues, scarce funds allocated to this line of research and a low number of PhD/academic projects focusing on palliative care [22].

Patients features, outcomes, and methods of investigation make this branch of medicine unsuitable for evidence-based methodology. In managing these patients, the priority is the subjective perception of well-being of the individual and the caregiver, and therefore the guidelines which are based on clinical trials that typically assess average effects of a given treatment, might not be applicable to the palliative care population and are not always followed in clinical practice. This deviation from evidence-based methodology can be observed in the example of anticholinergic drugs used to treat excessive respiratory secretion at the end of life. Despite a Cochrane systematic review demonstrating the substantial absence of benefit in this practice [23], a focus group with staff members in inpatient palliative care services showed that they were still used to reduce the psychological stress of staff, patients and family members [24].

A possible solution could be to improve the quality of palliative research by increasing multi-center international studies, with short assessment periods, and adopting a combination of individual and objective outcomes. Similarly, evidence-based medicine must become more flexible, and able to balance quantitative and qualitative elements, to develop a methodologically rigorous clinical practice that does not set aside the subjective well-being of the individual patient. The concept of evidence-based medicine should be reconstructed, not to lose completely the individual-oriented perspective.

CONCLUSIONS

In this article we presented relevant considerations for conducting palliative care research, in order to make results applicable in clinical practice. Aspects related to the Italian palliative care context are presented, but the general research framework described can be adapted to other contexts and regions.

It is crucial to enhance research in palliative care to support all patients (oncologic and non-oncologic), especially given their vulnerability. High-quality research enables more informed clinical practice, bringing benefits to both patients and caregivers. Achieving this goal requires careful selection of study design, including mixed-methods approaches, thoughtful choice of sample and outcomes, and increased collaboration among different centers and internationally.

Artificial intelligence and machine learning techniques have become prominent resources for researchers and can represent valuable instruments to this aim [25-27]. These tools can be employed to predict patient need for palliative care services, support decision-making, streamline data collection and analysis, and guide the selection of the most suitable study design. This holds true for various types of studies, but it can have particularly intriguing implications in the field of palliative care. For instance, the integration of wearable devices (such as smartwatches) with AI could facilitate the acquisition of data (e.g., vital signs), real-time monitoring, and more precise analysis, simultaneously reducing the burden on the patient. On the other hand, given that these technologies are still relatively new and fast-changing, and a comprehensive understanding of their full potential and possible consequences is yet to be achieved, there is a lack of regulations governing their use. This is crucial when considering their utilization as a resource in a sensitive research field like palliative care.

In conclusion, palliative care research is complex and challenging due to its holistic approach, which encompasses various vital dimensions of patients and their families, including physical, emotional, and social needs. The Italian and worldwide experience provides insights into managing these challenges and enhancing the methodological rigor of studies and the practical application of research findings. The definition of appropriate palliative care research protocols requires a clear recognition of the specific characteristics and peculiarities of this field, and calls for specific funds to be allocated to this research area.

Author’s contributions

GO, CC and MBZ designed the study. CC and MBZ contributed to the literature search, and the writing of the manuscript. GO, RL, RA, SD, GG, EM, IP, and MAR critically revised the manuscript. All the co-authors reviewed the manuscript and approved the final version.

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