



# **PHILIPPINE CLINICAL PRACTICE GUIDELINE ON PALLIATIVE AND END-OF-LIFE CARE FOR ADULTS WITH CANCER**

November 2023

## **Disclaimer and Contact Information**

This Clinical Practice Guideline (CPG) is intended to be used by physicians (palliative care specialists and providers, oncologists, and pain specialists, among others) and allied health professionals who are involved in the care of cancer patients, whether at home, in the community, or in a hospital, serving as a tool for implementing the Universal Health Care (UHC) Law and the National Integrated Cancer Control Act (NICCA). Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while taking care of individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

This clinical practice guideline is about palliative care and end-of-life care for adult cancer [all types] patients, encompassing referral, diagnosis, and management.

Key clinical issues covered in the CPG included pain management, dyspnea control, use of opioids, advance care planning, psychosocial and spiritual care, nutrition in palliative care, terminal extubation and palliative sedation, across all settings of care (facility-based, community-based and home care).

## **Contact Us**

Send us an email at agnesbausa@gmail.com for any questions or clarifications on the outputs and process of this CPG.

*Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: <https://ehospice.com/international-posts/integration-of-palliative-care-into-the-philippine-health-system/> along with this CPG.*

## Acknowledgments

*This CPG on Palliative and End-of-Life Care for adults with cancer was developed through the technical assistance of Jose B. Lingad Memorial General Hospital (JBLMGH) in collaboration with the Healthcare Practice and Policy Management (HPPM), Inc. and the University of the Philippines-National Institutes of Health. This project was made possible with the initiative and financial support from the DOH. The DOH neither imposed any condition nor exerted any influence on the operations and the final output formulation.*

*The Task Force members undertook extensive technical work in (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel discussion, and documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups, and committees, and facilitating the en banc meeting. The CPG Central Steering Committee and the Task Force Steering Committee were responsible for overall organization and management and were accountable for the quality of the CPG.*

*Lastly, this guideline was successfully accomplished through the extremely useful contribution and participation of panelists from different sectors who gave their time and vital inputs. Their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences were crucial in formulating the recommendations.*

*We thank you all for your contribution and support to this endeavor!*

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## Participating Societies, Organizations, Agencies and/or Institutions



Facilitating agency for guideline development: Jose B. Lingad Memorial General Hospital in collaboration with the Healthcare Practice and Policy Management (HPPM), Inc and the University of the Philippines-National Institutes of Health.

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## List of Abbreviations

<b>ACP</b>	Advance Care Planning
<b>AE</b>	Adverse Event
<b>AGREE</b>	Appraisal of Guidelines Research & Evaluation
<b>ASCO</b>	American Society of Clinical Oncology
<b>ASPEN</b>	American Society of Parenteral and Enteral Nutrition
<b>AWMF</b>	Association of the Scientific Medical Societies in Germany
<b>BPI</b>	Brief Pain Inventory
<b>CE</b>	Compassionate Extubation
<b>CI</b>	Confidence interval
<b>COI</b>	Conflict of interest
<b>COG</b>	Conference on Guideline Standardization
<b>CP</b>	Consensus Panel
<b>CPG</b>	Clinical Practice Guideline
<b>DCOI</b>	Declaration of Conflict of Interest
<b>DanPaCT</b>	Danish Palliative Care Trial
<b>DKG</b>	German Cancer Society
<b>DKH</b>	German Cancer Aid
<b>DNR</b>	Do Not Resuscitate
<b>DOH</b>	Department of Health
<b>EAPC</b>	European Association for Palliative Care
<b>ECOG</b>	Eastern Clinical Oncology Group
<b>EOL</b>	End-of-Life
<b>EORTC</b>	European Organization for Research and Treatment of
<b>QLQ-C</b>	Cancer Quality of Life Questionnaire
<b>ESAS</b>	Edmonton Symptom Assessment System
<b>ESMO</b>	European Society of Medical Oncology
<b>ESPEN</b>	European Society of Parenteral and Enteral Nutrition
<b>ERE</b>	Evidence Review Expert
<b>EtD</b>	Evidence-to-Decision
<b>FACT-Hep</b>	Functional Assessment of Cancer Therapy-Hepatobiliary
<b>FACT-L</b>	Functional Assessment of Cancer Therapy-Lung
<b>FAMCARE</b>	Family Satisfaction with the End-of-Life Care
<b>FPNS</b>	Fentanyl Pectin Nasal Spray
<b>GAD-7</b>	Generalized Anxiety Disorder – 7
<b>GGPO</b>	German Guideline Program in Oncology
<b>GIDA</b>	Geographically Isolated and Disadvantaged Areas
<b>GRADE</b>	Grading of Recommendations, Assessment,
	Development, and Evaluation
<b>HADS</b>	Hospital Anxiety Depression Scale
<b>HCS</b>	Hepatobiliary Cancer Subscale
<b>ICU</b>	Intensive Care Unit

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<b>JBLMGH</b>	Jose B. Lingad B. Memorial General Hospital
<b>LCS</b>	Lung-Cancer Subscale
<b>LST</b>	Life Sustaining Therapy
<b>MHPSS</b>	Mental Health and Psychosocial Support Network
<b>MOPS</b>	Manual of Operations, Procedures and Standards
<b>MV</b>	Mechanical Ventilator
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NIH</b>	National Institute of Health
<b>NRS</b>	Numerical Rating Scale
<b>OC</b>	Oversight Committee
<b>OS</b>	Overall survival
<b>PAPO</b>	Philippine Alliance of Patient Organization
<b>PEOL</b>	Palliative and End-of-Life
<b>PFS</b>	Progression-Free Survival
<b>PICO</b>	Population, Intervention, Comparator, Outcome
<b>PPOC</b>	Preferred Place of Care
<b>PPOD</b>	Preferred Place of Death
<b>QOL</b>	Quality of Life
<b>QUAL-E</b>	Quality of Life at the End-of-life symptom impact subscale
<b>RCT</b>	Randomized Controlled Trial
<b>RNAO</b>	Registered Nurses' Association of Ontario's
<b>SAE</b>	Severe Adverse Event
<b>SC</b>	Steering Committee
<b>SCL</b>	Symptom Checklist
<b>SDS</b>	Symptom Distress Scale
<b>SE</b>	Standard Error
<b>SMD</b>	Standardized Mean Difference
<b>SR</b>	Systematic Review
<b>TE</b>	Terminal Extubation
<b>TD</b>	Transdermal
<b>TF</b>	Task Force
<b>TWG</b>	Technical Working Group
<b>UHC</b>	Universal Health Care
<b>VAS</b>	Visual Analog Scale
<b>WHO</b>	World Health Organization

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# Executive Summary

**Table 1: Summary of Recommendations of Palliative and End Life of Care for Adults with Cancer**

<b>SUMMARY OF RECOMMENDATIONS</b> (Strength of recommendations, Certainty of evidence)	
<b>Question 1: Among adult cancer patients, does referral to palliative care improve quality of life and symptom control?</b>	
<b>RECOMMENDATION:</b> Among adult patients with advanced and metastatic cancer, <b>we suggest initiating palliative care and offering referral to relevant specialists.</b> (Weak, Very low)	
<b>Consensus Panel Considerations:</b> <ul style="list-style-type: none"><li>The consensus panel suggests integrating palliative care early in symptom management and addressing quality of life. This involves initiating the palliative care process and incorporating its principles in the discussion and management of cancer patients.</li><li>Palliative care can be initiated by healthcare providers in areas with limited specialists, with referrals to relevant specialists as needed.</li></ul>	
<b>Question 2: Among adult cancer patients with dyspnea, is the addition of opioids safe and more effective compared to the standard of care alone in the relief of dyspnea?</b>	
<b>RECOMMENDATIONS:</b> <ol style="list-style-type: none"><li>Among adult patients with advanced cancer, <b>we recommend the use of opioids for the relief of resting dyspnea.</b> (Strong, Moderate)</li><li>Among adult patients with advanced cancer, <b>we suggest the use of opioids for the relief of exertional dyspnea.</b> (Weak, Low)</li><li>Among adult patients with dyspnea caused by early-stage cancer, we do not suggest routine use of opioids for the relief of dyspnea. (Weak, Low)</li></ol>	

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**Consensus Panel Considerations:**

- The panel advises exploring other potential causes of dyspnea, aside from the cancer, for which curative treatments may be available.

**Question 3: Among actively dying hypotensive adult cancer patients, do opioids worsen hypotension or hasten death?****RECOMMENDATION:**

Among actively dying hypotensive adult cancer patients in need of comfort and pain relief, **we suggest including opioids in the treatment regimen.** (Weak, Very Low)

**Consensus Panel Considerations:**

- The panel clarified that opioids are used to control pain and distressing symptoms, providing comfort rather than hastening death. They suggest using opioids for actively dying patients due to inconclusive evidence regarding opioid-induced hypotension.

**Question 4: Among adults with cancer pain, is the 2-step ladder approach more effective than the WHO 3-step ladder approach in achieving pain control?****RECOMMENDATION:**

Among adult cancer patients with moderate to severe cancer pain, **we suggest the use of the 2-step ladder approach as initial therapy (use of low dose strong opioids).** (Weak, Low)

**Consensus Panel Considerations:**

- The consensus panel highlighted that pain is multifactorial and needs comprehensive evaluation and management. The panel suggests the 2-step analgesic ladder approach, emphasizing the initiation with low-dose strong opioids for moderate cancer pain (pain score of 4/10-6/10).

**Question 5: Among adult cancer patients without intravenous and enteral access, is transdermal opioid patch more effective than subcutaneous opioid administration in symptom (pain and dyspnea) control?**

**RECOMMENDATIONS:**

1. Among adult opioid-tolerant cancer patients without intravenous or enteral access, **we suggest transdermal fentanyl patch to control pain.** (Weak, Very Low)
2. Among adult cancer patients without intravenous or enteral access, **we suggest subcutaneous morphine to alleviate dyspnea.** (Weak, Very Low)

**Consensus Panel Considerations:**

- The panel suggests transdermal opioid patches for patients unable to tolerate oral medications or certain procedures (NGT, IV, SQ), as patch application can be easily done at home.
- The decision on home administration of subcutaneous opioids aimed at ensuring comfort, and its associated costs, should involve collaboration between the healthcare team, the patient, and their family.

**Question 6: Among adult cancer patients, will psychosocial and spiritual care improve symptom control, quality of life, and coping with permanency of outcome?**

**RECOMMENDATIONS:**

1. Among adult cancer patients, **we suggest giving psychosocial care in improving quality of life and reducing maladaptive coping response.** (Weak, Very Low)
2. Among adult cancer patients, **we suggest giving spiritual care in improving quality of life and quality of end-of-life care.** (Weak, Very Low)

**Consensus Panel Considerations:**

- The consensus panel highlighted that psychosocial and spiritual care should be tailored to the patient's needs, values, beliefs, culture and preferences, and done in a multidisciplinary approach.

- Some panel members shared positive experiences providing psychosocial and spiritual support to patients and their families.

**Question 7: Among adult cancer patients, will advance care planning increase patients' and families' satisfaction and perception of care?**

**RECOMMENDATION:**

**We suggest that advance care planning be offered early to adult cancer patients and their families.** (Weak, Very Low)

**Consensus Panel Considerations:**

- The panel highlighted that advance care planning (ACP) is done to enable any person to express their values and preferences for their end-of-life care.

**Question 8: Among adult cancer patients in the last six months of life, will parenteral or enteral nutrition improve quality of life and increase survival time?**

**RECOMMENDATION:**

**Among adult cancer patients with poor performance status and with life expectancy of a few months, or actively dying, we do not suggest routinely offering artificial nutrition and hydration.** (Weak, Low)

**Consensus Panel Considerations:**

- The panel discussed that not all patients with incurable advanced cancer are with poor performance status.

**Question 9: Among adult cancer patients at the end-of-life who are on ventilatory support, will terminal extubation improve quality of end-of-life care?**

**RECOMMENDATION:**

Among adult cancer patients at the end-of-life who are actively dying on ventilatory support, **we suggest multidisciplinary and individualized decision-making regarding the option of terminal extubation.** (Weak, Very Low)

**Consensus Panel Considerations:**

- Despite very low certainty of evidence, the panel unanimously agreed on a multidisciplinary and individualized approach to terminal extubation for actively dying patients, cognizant of the wishes of the patient and their family.

**Question 10: Among actively dying adult cancer patients with severe intractable pain/restlessness/agitation, is palliative sedation effective in the control of symptoms?****RECOMMENDATION:**

Among actively dying adult cancer patients with severe intractable pain/restlessness/agitation, **we suggest to consider palliative sedation to supplement ongoing symptom control (management).** (*Weak, Very Low*)

**Consensus Panel Considerations:**

- The panel suggested that palliative sedation, an adjunct to symptom control, be considered as an option for managing severe, intractable symptoms in dying patients.

**NOTE:***On weak strength of recommendation and very low to low certainty of evidence:*

In studying quality palliative and end-of-life care, conducting randomized controlled trials (RCTs) often experience methodological problems, including recruitment, patient attrition, and compliance. Effectiveness research in palliative care is complex and has many pitfalls. A substantial body of evidence exists to support clinical practice guidelines for quality palliative care, but the quality of evidence is limited. Ethical considerations arise due to the vulnerability of palliative care patients, adding complexity to conducting RCTs. Further studies, particularly prospective multi-center ones, are encouraged, especially those that take into consideration the specific needs, values, beliefs, and culture of Filipino patients and their families.

**To ensure safety of the patients, a referral to Palliative and Hospice Care specialist is warranted for those in need of palliative sedation, opioid titration, palliative extubation/terminal extubation.** For further details on palliative and hospice care policies, standards, practices and referral system, **kindly read Department of Health Manual of Operations, Procedures and Standards (DOH-MOPS) for National Palliative and Hospice Care Program (2021).**

## 1. Introduction

Palliative care is an approach to care that improves the quality of life of patients and their families facing severe life-threatening conditions. Among the conditions which benefit most from palliative care is cancer. In June 2022 report by the Philippine Statistics Authority, neoplasms rank 3<sup>rd</sup> among the top causes of mortality in the country.

In 2015 the Philippines ranked 78<sup>th</sup> among 80 countries among the worst countries to die. In 2019, the National Integrated Cancer Control Act (NICCA) and Universal Health Care (UHC) Law mandated the inclusion of palliative care services in the care of cancer patients and patients with chronic, life-limiting illnesses, respectively. In 2021, The National Palliative and Hospice Care Program's Manual of Operations, Procedures, and Standards (MOPS) Basic and Intermediate Training modules for Palliative Care Providers were launched. As a result of these efforts, in 2021 the global ranking of the Philippines in the Cross Country Comparison of Expert Assessment of the Quality of Death and Dying rose to 38<sup>th</sup>. While there has been much progress in recent years in terms of its acceptance in the medical community and among patients and families alike, much work is still to be done. There is a need for capacity building among healthcare workers to augment the minimal number of practitioners and specialists in palliative care, thus making it possible to provide much-needed palliative care services in the country.

This will be the first local practice guideline on palliative and end-of-life care (PEOL) for adult patients with cancer in the Philippines. A CPG will help reduce practice variations, ensure standardization of professional practice, improve acceptability, and ensure access to quality care by formulating policies based on this CPG's recommendations. This is aligned with the DOH's vision of having comprehensive cancer care and optimized cancer survival by 2025.

**This CPG aims to improve adult cancer patients' management from diagnosis until the end-of-life.** The standard practice among palliative service providers for adult cancer care will help promote and preserve the quality of life among patients and their families. Specifically, it aims to improve the ethical, moral, culturally-sensitive, and acceptable management of cancer patients with primary consideration of improving quality of life (palliative care with curative intent) and quality of death (purely palliative and end-of-life care).

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This clinical practice guideline covers palliative care referral and management for adult cancer patients, covering all cancer types and stages, from diagnosis until end-of-life care. Key clinical issues covered in the CPG include pain management, dyspnea control, use of opioids, advance care planning, psychosocial and spiritual care, nutrition in palliative care, palliative extubation/terminal extubation and palliative sedation, across all settings of care (hospital/inpatient, outpatient, community or home-based).

The National Palliative and Hospice Care Program's Manual of Operations, Procedures, and Standards (MOPS) and this National Clinical Practice Guideline (CPG) aim to improve the quality of life for seriously-ill patients. By leveraging these resources, it is anticipated that the Philippines will do better in providing quality palliative and end-of-life care.

## **2. Objective, Scope, Target population and Target users**

The objective of this palliative and end-of-life care clinical practice guidelines is to create guideline recommendations in providing PEOL care among adult cancer patients, their families or caregivers, and healthcare providers.

This CPG was designed to serve as a tool for implementing the UHC Law and the NICCA. The intended users of this practice guideline are physicians (palliative care specialists and providers, oncologists, and pain specialists, among others) and allied health professionals who are involved in the care of cancer patients, whether at home, in the community, or in a hospital. Other target users of this guideline include national and local policymakers, planners, and managers of government and non-governmental organizations.

## **3. CPG Development Methodology**

### **3.1 Organization of the Process**

- Convening the Steering Committee, Technical Working Group, Consensus Panel and COI Committee
- Managing Conflicts of Interest
- Prioritizing the Clinical Questions

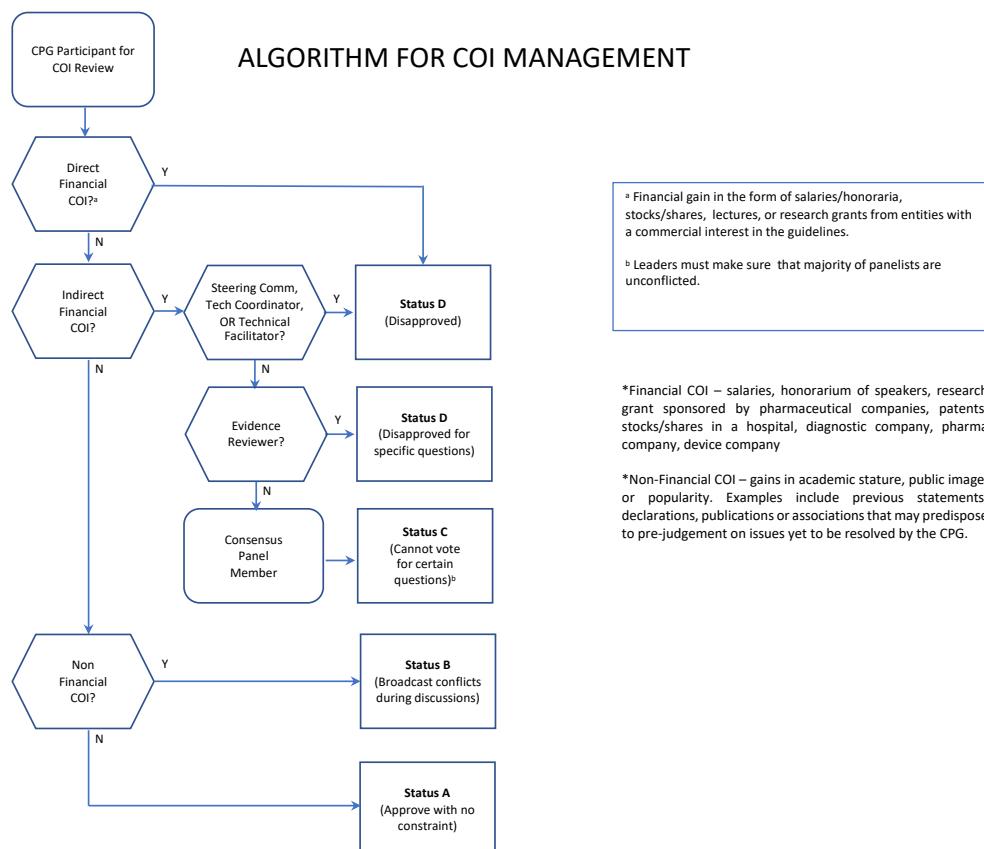
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All nominees of the PEOL relevant working groups declared conflicts of interest using the UP NIH eCOI forms and submitted a copy of their latest curriculum vitae. The independent three-person COI Review Committee assessed the COIs (financial and non-financial covering a 4-year period) of all the nominees based on the DOH Guideline for CPG Development in close coordination with the technical guidance from the UP NIH.

The COI review committee submitted an official report with their assessment and recommended action for each nominee to the Steering Committee (SC). The SC in turn, reviewed the information of the COI committee and shall discuss with the committee possible management measures for identified potential conflicts of interest.

Figure 1 shows how the results of the Conflict of Interest (COI) Review was managed. To minimize potential conflict of interest, the SC Chair was allowed to participate in discussions but was inhibited from voting on issues which could be influenced by her COI. Furthermore, a co-chair with minimal COI was designated to mitigate COI of the chair.

**Figure 1. Algorithm for COI Management**



Source: UP Manila-National Institutes of Health (2021)

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The mode of clinical practice guideline development of the palliative and end-of-life CPG followed the Department of Health and Philippine Health Insurance Corporation, Manual for Clinical Practice Guideline Development (2018) using the GRADE approach. Evidence reviewers systematically searched and retrieved existing CPGs. The eligibility of the CPGs was assessed by looking into the prespecified inclusion and exclusion criteria and evaluating the CPG's quality using the AGREE II tool. Once eligible, following the ADAPTE process, the guideline recommendation/s were adapted.

If no existing CPG was eligible to answer the clinical question, evidence reviewers conducted a search and retrieval of systematic review/s (SR). A 2-step review process was done to identify relevant SR/s. The first step was excluding unrelated topics based on the titles and abstracts obtained. The second step by examining the titles and abstracts for eligibility based on the prespecified inclusion and exclusion criteria. If found eligible, the SR was retrieved, and final screening was done by assessing the quality of the SR.

Search for published and unpublished primary studies was done from the last date of the literature search of the eligible systematic review. This was conducted to assess if eligible new primary study/s will affect the existing SR results and if revision and updating are needed.

If there are no eligible CPG and SR found, evidence reviewers conducted a new systematic review (*de novo*).

## 3.2 Evidence Summaries

- Search Methods and Strategies

The steering committee developed and finalized the guideline questions. Upon finalization of questions, members of the consensus panel were asked to rate outcomes as to their importance, using the following rating scale:

- a. 1 to 3 - low importance;
- b. 4 to 6 - important but not critical for decision-making; and,
- c. 7 to 9 - critical for decision-making.

For each question, a maximum of 7 critical and important outcomes were included.

Each clinical question was assigned to two evidence reviewers who independently searched for and retrieved CPGs, SRs, and primary studies.

Evidence reviewers employed a structured approach during the literature search, prioritizing the identified key concepts and issues in the PICO, and then applying methodology filters to focus on the study design. An online search was done using, but not limited to, the following databases (MEDLINE, CENTRAL, Google Scholar, HERDIN, and relevant oncology and palliative care journal sites), reference list of searched studies, study registries, and grey literature were searched. For CPGs, guideline clearinghouses and websites of organizations and relevant specialty societies developing guidelines. Evidence reviewers duly documented the search process, and ensured its replicability. They recorded the following details: sources searched, date when the search was conducted, period searched (from database inception until January 2023- July 2023), subject headings, keywords used, and results retrieved. The evidence reviewers then arranged the selection process and resulting yield in a diagram following the PRISMA format.

- Inclusion and Exclusion Criteria

Evidence reviewers initially screened existing practice guidelines by reviewing titles and abstracts. To be included, the guideline should have been updated or published within the last five years; the GRADE approach was used in the development of the guideline recommendations, guideline question correspond to the PEOL clinical questions (PICO), has benefits and harms assessment for the patient-important outcome, allows updating where it presents a full systematic review, comprehensive and repeatable search strategy, has existing and accessible evidence tables or summaries.

The final screening of the retrieved guidelines was through the assessment of the quality of the guideline using the AGREE II tool. The guidelines should have obtained an overall score of 75% and a score of 80% on the domain of Rigor and no other domain score of less than 75% and contains recommendations on palliative and end-of-life care for adult patients.

Inclusion and exclusion of SR and primary studies was based on a review PICO which is prespecified before searching articles. The prespecified outcomes that was considered are based on the identified critical and important outcomes in the preliminary outcome rating.

To be considered eligible, systematic reviews should have a rating of moderate to a high-quality using AMSTAR 2.

Studies were included for questions requiring a de novo process if they address the PICO components of the clinical question. Both randomized and non-randomized studies, as well as observational analytic cross-sectional studies, were included.

- Study Quality Assessment and Certainty of Evidence

Two evidence reviewers did data extraction for retrieved and appraised articles independently. Standard data extraction templates were used. Conflicts in data extraction between the two reviewers were resolved through discussion, or the inclusion of a 3<sup>rd</sup> person's inputs, if necessary.

Appraisal of studies included evaluating their directness, validity, results, and applicability. Two evidence reviewers did this independently. Conflicts in appraisal between the two reviewers was resolved through discussion, or the inclusion of a 3<sup>rd</sup> person's inputs, if necessary.

The Cochrane Risk of Bias tools was utilized for the quality assessment of primary studies for questions on therapy, the ROB 2 tool for randomized trials, and the ROBINS-I tool for non-randomized studies. The AGREE II instrument was used for clinical practice guidelines, and AMSTAR 2 for systematic reviews. The Newcastle-Ottawa scale was used to assess the quality of evidence for cohort and case-control studies.

Conflicts in quality assessment between the two reviewers was resolved through discussion, or the inclusion of a 3<sup>rd</sup> person's input, if necessary.

- Data Synthesis

Evidence reviewers did a systematic review for each guideline question. Where appropriate and possible, a meta-analysis was done using RevMan 5 software. When the results of studies cannot be combined, evidence reviewers conducted a qualitative synthesis and a narrative summary of individual studies. Results was assembled in an evidence profile or summary of findings table, whichever is appropriate.

- Quality assessment of the body of evidence

Evidence reviewers used the GRADE approach to rate the certainty of the evidence for each guideline question. The overall certainty of the evidence was based on the lowest certainty rating of the top seven critical and important outcomes.

Rating of the certainty of the evidence for each patient-important outcome across studies was conducted. Randomized controlled trials start with a high rating and observational studies (e.g., cohort, case-control, interrupted time series, or other quasi-experimental design, case series, and case reports) with a low rating. Randomized controlled trial rating was modified downward in the presence of any of the following:

- a. serious risk of bias due to study limitations,

- b. serious inconsistency between studies,
- c. serious indirectness,
- d. serious imprecision, and
- e. likely publication bias.

Observational studies rating was modified upward in the presence of any of the following:

- a. When a large magnitude of effect size exists,
- b. When there is a dose-response gradient and
- c. When all plausible residual confounders or other biases would reduce a demonstrated effect or suggest a spurious effect when results show no effect.

Rating the overall certainty of the evidence from very low to high.

#### Certainty of Evidence Definition and Implication

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely close to the effect's estimate, but it is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may differ substantially from the effect's estimate.
- Very Low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

### **3.3 Formulation of the Recommendations**

- Evidence to Decision Framework

The GRADE Evidence-to-Decision framework was followed for formulating recommendations. Using the GRADE approach, the certainty of the evidence for each clinical question was categorized into high, moderate, low, or very low quality. The technical working group prepared evidence summaries and draft recommendations for the consensus panel to review and reassess the relative importance of the outcomes to ensure that important outcomes identified that were not initially considered are included and to reconsider the relative importance of the outcomes considering the available evidence. Aside from the evidence presented, values, preferences and other considerations were taken into account. After this, the panel came up with a consensus on the direction and strength of the recommendations. The CP then developed the final recommendations.

The following primary considerations were the basis of the grading of the strength of recommendation:

- a. Certainty of the evidence;
- b. The balance between benefits and harms;
- c. Values, preferences, and burdens on patients;
- d. Cost and resource use; and,
- e. Other considerations include the level of priority of the problem, equity and human rights, and greater acceptability and feasibility of the options.

- **Consensus Process**

The technical working group sent the evidence summaries and draft recommendations (with their corresponding GRADE rating) to members of the identified multi-sectoral consensus panel for review. Virtual *en banc* consensus panel meetings were done in five sessions via Zoom. A technical/consensus facilitator facilitated each discussion. During each meeting, the assigned evidence reviewer presented the evidence summary and drafted a recommendation for each question. Panelists were able to clarify and discuss the evidence presented and other issues related to the question. The panelists were asked to vote on the direction (for or against), the strength of recommendation (strong or weak), and its final wording.

Initially, the nominal group technique was followed. Each panelist recorded their vote and presented it individually. A consensus is reached when there is equal to or greater than 75% agreement from the CP members both for the direction and strength of the recommendations. The voting was repeated at the most thrice until a consensus was reached.

The final statement of recommendations consisted of the evidence's certainty linked with the recommendation's strength. If there was a mismatch between the strength of the recommendation and the certainty of evidence, justifications/explanations for such were explicitly cited in the CPG. All recommendations were backed up by the summary of evidence.

The recommendations in the guideline are clear, identifiable, and actionable. The language is consistent and direct to avoid any ambiguity. The recommendations were written in an active voice and prescribe specific behavior required from the care provider to reduce variations in care. Brief but precise supporting text explained why the recommendation was made and how it will be carried out. The recommendation described who should do it, when or under what conditions it should be done, what the action is, and to whom it is directed.

The Conference on Guideline Standardization (COGS) checklist that incorporates all the elements in the CPG protocol and provides a template for reporting the recommendation statements was used for the standardized format of the completed CPG.

The lead CPG developers ensured that the CPG shall be following the elements of the AGREE checklist. The CPG was then be subjected to external review prior to submission to DOH.

Jose B. Lingad Memorial General Hospital (JBLMGH), along with the lead CPG developer, assigned a scientific writer for the CPG. He/she was involved throughout the duration of the CPG development process. Collation of all the evidence summaries and synthesis of the proceedings of the CP meetings was done.

### **3.4 Plan for Dissemination and Implementation**

Dissemination of the CPG will include activities that will raise awareness of the new CPG, such as:

1. Releasing of a DOH memo to notify all stakeholders of the publication,
2. Issuing a press release, releasing news articles, and utilizing social media accounts,
3. Organizing a dissemination forum,
4. Presenting the CPG in conferences, training, and implementation workshops,
5. Speaking engagements by experts in appropriate forums for the benefit of stakeholders, and the general public,
6. Creating information, education, and communication materials for laypeople and patients, among others.

The assessment of the DOH-endorsed or National CPG's effectiveness will entail collecting and synthesizing data reflecting its impact. The lead CPG Developers shall recommend a set of quality indicators to guide in monitoring and evaluation of the CPG's impact, which can be conducted 1-2 years after initial implementation.

### **3.5 External Review**

Two external reviewers who are experts in supportive oncology, palliative, and hospice care were asked to review the draft CPG to comment on the content, acceptability, and appropriateness of recommendations.

Comments from the external review were collated and submitted to the steering committee for resolution. The CPG was then submitted to the Secretary of Health for final approval as a DOH-endorsed CPG or “National CPG.”

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## 4. Recommendation and Evidence Summaries

### 4.1 Palliative Care and improvement of quality of life and symptom control

**Question 1: Among adult cancer patients, does referral to palliative care improve quality of life and symptom control?**

#### RECOMMENDATION

Among adult patients with advanced and metastatic cancer, **we suggest initiating palliative care and offering referral to relevant specialists.** (*Weak recommendation, very low certainty of evidence*)

#### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The consensus panel discussed that advanced cancer could be stage III cancer and beyond and may have/have not metastasized. Most of the evidence appraised is on advanced cancer.
- The primary concern during the consensus panel discussion is the reality that not all places in the Philippines have a certified palliative care specialist. Palliative care can be initiated and given by healthcare providers who are not necessarily specialists but have knowledge and skills in primary palliative care.
  - *Read Section VII, pages 110-112, on Palliative Care Education And Certification, DOH-MOPS for National Palliative and Hospice Care Program.*
- Although the certainty of evidence is very low and strength of recommendation is weak, the consensus panel still suggests initiating palliative care which means starting the palliative care process, incorporating palliative care and its principles in the discussion and management of patients diagnosed with cancer. A hospice and palliative care specialist further suggested to initiate palliative care to manage symptoms and address quality of life.
- The panel further emphasized that palliative care should be available not only at the advanced stage of cancer but at any point of the disease continuum.

- The consensus panel also further suggests offering referral to relevant specialists as needed in the care of the patient.
  - *Read Sections III and IV, pages 32-78, on Palliative And Hospice Care Policies, Standards, Practices And Referral System, DOH-MOPS for National Palliative and Hospice Care Program.*

## **Key Findings**

- Much of the evidence related to the effects of palliative care is concerned with the care of patients with advanced malignancies.
- A total of 49 unique randomized controlled trials (RCTs) were included.
- For quality of life, pooled results of 22 RCTs at “1-3-month follow-up” and 14 RCTs at “4-7month follow-up” both demonstrated a significant positive impact of palliative care on quality of life. However, pooled results of 2 RCTs showed no significant difference in quality of life at “ $\geq$  10- month follow-up.”
- For pain control, a meta-analysis of 18 RCTs focused on Chinese cancer patients showed palliative care to be effective in relieving pain; however, substantial heterogeneity was observed in both the overall ( $I^2 = 90.8\%$ ) and subgroup analyses ( $I^2 > 75\%$ ) (certainty of evidence: very low). In an RCT involving Korean patients with advanced pancreaticobiliary cancer, while the proportion of patients with  $\geq 50\%$  reductions in pain between the palliative care and control groups did not differ significantly at four weeks (certainty of evidence: low), the proportion of patients with Brief Pain Inventory (BPI)  $\leq 3$  was significantly higher in the palliative care group at the same time point (certainty of evidence: moderate)
- For symptom control, pooled results of 7 RCTs showed that at 3 months, the symptom intensity of the patients receiving palliative care was not significantly different from the usual care arm and that a moderate heterogeneity was observed across trials ( $I^2 = 58\%$ ) (certainty of evidence: very low).
- For quality of end-of-life care, one RCT determined that FAMCARE-2 scores were significantly higher in the palliative care group compared to the standard care group at 12 (certainty of evidence: low) and 24 weeks (certainty of evidence: very low).
- There were no studies available that investigated, or were relevant to peaceful death or dignified death, healthcare provider’s stress or distress, and well-coordinated care or better interdisciplinary care.

## **Background**

One of the primary considerations for referral to palliative and hospice care is metastatic or locally advanced incurable cancer. In the Philippines, it is estimated that out of the 80,000 new patients diagnosed with cancer yearly, over 75% are in advanced stages and will require palliative care and pain relief.<sup>1</sup> However, palliative care in the country is still in its formative years. Though efforts have been made to increase awareness and provision of the service, many are misinformed or have misperceptions that referral to palliative care is equivalent to giving up on life or accepting a death sentence and that patients will only be referred to palliative care when actively dying.

Several challenges or barriers have been identified that impact the referral to and effective delivery of palliative care services, with factors related to resources (especially in geographically isolated and disadvantaged areas or GIDA), limited knowledge or understanding about palliative and hospice care among healthcare professionals, poor health literacy among patients, cost considerations, and societal/cultural concerns, among others.<sup>2,3</sup>

This summary aims to provide the available evidence and recommendations about the effect of palliative care among select clinical (patient) and psychosocial (patient, family/caregiver, and healthcare provider) outcomes in adult cancer patients.

## **Definition of Terms**

- a. **Palliative care.** Refers to a systematic, organized, multidisciplinary care approach to patients, across all ages, with any chronic life-limiting or life-threatening illness. It aims to improve patients and their family's quality of life through a holistic, age-appropriate, gender-responsive, culturally sensitive, and rights-based approach. It is care directed to the anticipation, prevention, and relief of suffering through early identification, impeccable assessment, treatment, and management of pain and other problems involving the patient's physical, emotional, social, and spiritual needs. It starts as soon as the patient is diagnosed with a life-threatening disease. Using the best available evidence, it promotes dignity, quality of life, and adjustment to progressive illnesses.<sup>2</sup>
- b. **Quality of life.** An assessment of an individual's overall well-being and life satisfaction encompasses cognitive, emotional, physical, preparatory, social, and spiritual domains, and personal autonomy and health care provision.

- c. **Pain control.** Relief from cancer-related pain to a level that allows for an acceptable quality of life.
- d. **Symptom control.** The improvement or resolution of distressing symptoms (encompasses any or all symptoms reported from all body systems, including pain); and the prevention of additional symptoms which can cause discomfort and suffering.
- e. **Peaceful death or dignified death.** Dying accompanied by respectful and skillful caregiving is a death free from dependency on psychological affronts that are not usually perceived as dignified (allowing the patient to die free of suffering and according to their decisions/will).
- f. **Quality of end-of-life care.** The degree to which health services for cancer patients and their families increase the likelihood of achieving comfort and peaceful death at the end-of-life.
- g. **Healthcare provider's stress or distress.** Psychological distress among healthcare providers covers depression, anxiety, stress, burnout, and low resilience symptoms.
- h. **Well-coordinated care or better interdisciplinary care.** It is a patient-centered approach that strives to meet the needs and preferences of patients while strengthening the caregiving capabilities of families and service providers. It includes collaboration between all members of a care team, no matter their specialty, role, or location; has clear communication between all parties involved in a patient's care, including the patient/patient's caregiver; strives to avoid unnecessary and redundant tests and procedures, which can both improve the care experience and reduce the cost of care; requires assessing all of a patient's needs – not just their immediate clinical needs.
- i. **Advanced cancer/malignancy.** Cancer that is unlikely to be cured or controlled with treatment; end- stage cancer or terminal cancer; late-stage cancer, metastatic cancer; cancer that cannot be cured though sometimes can be controlled.

## Review Methods

Existing clinical practice guidelines (CPG) that could answer the clinical question were searched and subsequently assessed for eligibility and quality using the AGREE II tool. In parallel, literature searches were conducted as detailed below.

## Literature Search

A systematic literature search was conducted on 15 Feb 2023 using the following electronic databases through the Ovid platform, from the earliest publication date available in each database until 15 Feb 2023:

- Medline (1946 to 14 Feb 2023)
- EMBASE (1974 to 14 Feb 2023)
- Cochrane Central Register of Controlled Trials (Jan 2023)
- EBM Reviews - Cochrane Database of Systematic Reviews (2005 to 15 Feb 2023)

The literature search was designed using relevant indexing terms (i.e., subject headings) that correspond to the PICO approach: population (adult cancer patients), intervention (palliative care [referral]), and outcome (quality of life, pain control, symptom control, quality of end-of-life care [patient and family experience], healthcare provider's stress or distress, peaceful death or dignified death, well-coordinated care or better interdisciplinary care). To enhance the focus of the search, free text searches and variable truncations of the keywords were searched in the abstract and title fields. There were no language restrictions applied. The full literature search strategy executed in Ovid is outlined in the Appendix.

The final literature search outputs were initially screened for systematic reviews/meta-analyses published in the past six years, followed by a search for recently published primary studies (in the form of clinical trials). The included studies in the retrieved systematic reviews and additional primary studies identified were assessed for eligibility based on the inclusion and exclusion criteria.

In addition, a search for ongoing trials was performed via the U.S. National Library of Medicine's ClinicalTrials.gov website using the following query parameters:

- Condition or disease: cancer OR neoplasm OR malignancy OR malignancies OR metastases OR metastatic OR tumor OR tumor
- Intervention/treatment: palliative care OR palliative medicine OR palliative therapy OR cancer palliative therapy OR palliative program OR palliative procedure
- Age group: 'Adult (18-64)' and 'Older Adult (65+)'
- Recruitment status: 'Not yet recruiting', 'Recruiting', 'Enrolling by invitation'; and 'Active, not recruiting'

## **Study Eligibility**

### *Inclusion Criteria*

- Studies that included adult patients with cancer receiving palliative care offered via an “inter- or multi-disciplinary team” of healthcare professionals. Studies that used multi-faceted interventions and patients only utilized some of its components.
- Randomized controlled trials (standard, fast-track, and adaptive study designs that use individual patient or cluster randomization were considered)
- No restrictions on the type of delivery (inpatient, outpatient) or place of consultation (clinic, hospital, patient’s home). The active comparator was treatment as usual or standard oncological care.

### *Exclusion Criteria*

- Studies evaluating the impact of only one domain of palliative care
- Studies on stand-alone palliative therapies
- Studies combining cancer with non-cancer patients
- Studies where clinical outcomes were not clearly stated
- Studies that did not target patients (e.g., caregivers as the targeted population in the study)
- Duplicate reporting of patient cohorts
- Conference or meeting abstracts, editorials or commentaries

## **Results**

### **Characteristics of Included Studies**

Much of the evidence related to the effects of palliative care is concerned with the care of patients with advanced malignancies. Overall, two systematic reviews/meta-analyses (SR) and 12 RCTs were considered for the review. The SR by Hoomani Maidabidi et al. focused on the evaluation of the quality of life, where the study sample encompassed 25 RCTs published between 2001 and 2021 and consisted of 5,160 adult patients (mean age: 60.21 years) with advanced cancer in 11 countries. In the other SR, Zhao et al. reviewed the effects of palliative care on pain among Chinese cancer patients, where 18 RCTs published from 2006 to 2019 were identified from four Chinese academic databases and consisted of 1,370 adult patients (median age: 61.31; range: 43 to 76.26 years). The remaining individual RCTs considered for review also involved adult patients ( $\geq 18$  years) in which cancer types across trials varied. At least three individual studies investigated caregivers along with the patients.

## **Quality of Life (Patient)**

In recent years, the evidence base for palliative care has continued to grow. In 2022, Hoomani Majdabadi et al. focused on the impact of palliative care on the quality of life, where they synthesized the most recent evidence of the effects of early palliative care on patients with incurable cancer ( $n = 25$  RCTs).<sup>4</sup> Eligible palliative care interventions were offered via an interdisciplinary team early on or at the end-of-life stages in the form of inpatient, outpatient, integration care, or even combined with other models.

A significant positive impact of palliative care on quality of life was observed both in the “1 to 3-month follow-up” ( $SMD = 0.1$ ; 95% CI: 0.019 to 0.18, which translates to an effect size of Hedges’  $g^1[g] = 0.096$  with an SE of 0.044) and in the “4 to 7-month follow-up” ( $SMD = 0.25$ ; 95% CI: 0.1 to 0.41, which translates to an effect size of  $g = 0.257$  with an SE of 0.084) period. Review of two studies in the “ $\geq 10$ -month follow-up” period, however, was not significant ( $SMD = 0.19$ ; 95% CI: -0.03 to 0.42, which translates to an effect size of  $g = 0.234$  with an SE of 0.138;  $Q = 1.3$ ;  $df = 3$ ;  $I^2 = 0\%$ ).

<sup>1</sup> Hedges’  $g$  is an effect size measure that represents the standardized difference between means (has less bias compared to Cohen’s  $d$ )

## **Pain control (Patient)**

A 2019 systematic review and meta-analysis on the effects of palliative care on pain among Chinese cancer patients was available.<sup>5</sup> In this study, 18 RCTs published from 2006 to 2019 were identified from four Chinese academic databases and consisted of 1,370 adult patients (median age: 61.31; range: 43 to 76.26 years). More than half of the included studies (67%) adopted a combination of pharmacological (e.g., WHO three-step analgesic ladder and analgesic pumps) and non-pharmacological (e.g., musicotherapy, acupuncture) strategies. Visual analog scales (VAS) and numerical rating scales (NRS) were used to assess cancer pain. Based on the overall pooled results using a random-effects model, palliative care was shown to be effective in relieving pain ( $SMD = 1.47$ , 95% CI: 1.07 to 1.88), but substantial heterogeneity was observed in both the overall ( $Q = 184.81$ ,  $p < 0.001$ ;  $I^2 = 90.8\%$ ) and subgroup analyses ( $I^2 > 75\%$ ).

In a recently published RCT involving 288 Korean patients with advanced pancreaticobiliary cancer, the role of early palliative care (integrated with usual oncologic care with automated symptom screening and monitoring)

was also evaluated for pain (and depression) improvement.<sup>6</sup> In this study, the proportion of patients with ≥50% pain reduction between the palliative care and control groups did not differ significantly at four weeks (29.5% vs. 25.2%; P = 0.4194). However, the proportion of patients with Brief Pain Inventory (BPI) ≤ 3 (51.1% vs. 38.9%, P = 0.0404) was significantly higher in the palliative care group at four weeks.

There were two RCTs involving the European population wherein pain scores were reported using a specific subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Both studies, the Danish Palliative Care Trial (DanPaCT) and the PALINT trial compared the early integration of (specialist) palliative care with standard care compared to standard care alone among patients with advanced cancer.<sup>7,8</sup> In the DanPaCT trial, there was no significant difference in pain between the palliative care (n = 145) and the control (n = 152) groups over eight weeks (mean weighted change = -3.4, 95% CI: -9.5 to 2.6; P = 0.27).<sup>7</sup> Similarly, in the PALINT trial, no significant difference in pain was detected among the palliative care and control groups at three months (P = 0.551) and six months (P = 0.894).<sup>8</sup>

### **Symptom control (Patient)**

Symptom intensity data was reported in eight studies.<sup>9-16</sup> Six different measuring scales or tools, such as the Edmonton Symptom Assessment System (ESAS)<sup>9-11</sup>; Symptom Distress Scale, (SDS)<sup>12</sup>; Hepatobiliary Cancer Subscale (HCS) of the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)<sup>13</sup>; Rotterdam Symptom Checklist: Physical Symptoms<sup>14</sup>; Lung-Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L)<sup>15</sup>; and the Quality of Life at the end-of-life symptom impact subscale (QUAL-E)<sup>16</sup> were used by the trials for measuring symptom intensity.

The pooled results showed that at three months, the symptom intensity of the patients receiving palliative care was not significantly different from the usual care arm (SMD = 0.06, 95% CI: -0.15 to 0.26) and that a moderate heterogeneity was observed across trials ( $I^2 = 58\%$ , P = .03). (See Appendix D, Forest Plot no. 1).

### **Peaceful Death or Dignified Death (Patient Psychosocial)**

There were no studies available that investigated peaceful or dignified death.

## **Quality of End-of-Life Care (Patient Psychosocial; Family and Caregiver Psychosocial)**

There were three RCTs where family/caregiver satisfaction with care was evaluated using the Family Satisfaction with the End-of-Life Care (FAMCARE) questionnaire.<sup>13,17-18</sup> In two out of three studies, while it was stated that there were no differences in terms of family satisfaction between arms in the studies by Maltoni et al. and Scarpi et al., data was not shown/available in their respective publications.<sup>13,17</sup>

In the remaining study, Brims et al. investigated the effect of regular (early) specialist palliative care in combination with standard care soon after the diagnosis of malignant pleural mesothelioma, compared to standard care alone.<sup>18</sup> It was determined that FAMCARE-2 scores were significantly higher in the palliative care group at 12 (mean difference adjusted for baseline: 4.1, 95% CI: 0.7 to 7.4, P = 0.02) and 24 (mean difference adjusted for baseline: 6.1, 95% CI: 2.1 to 10.1, P = 0.003) weeks.

## **Healthcare Provider's Stress or Distress (Healthcare Provider Psychosocial)**

There were no studies available that are relevant to healthcare providers' stress or distress.

## **Well-coordinated Care or Better Interdisciplinary Care (Healthcare Provider Psychosocial)**

There were no studies available that are relevant to well-coordinated care or better interdisciplinary care.

### **GRADE Summary of Findings Table**

**Table 2. (Early) Palliative care versus standard oncological care among adult cancer patients**

CRITICAL OUTCOMES	BASIS (No. and type of studies, total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Quality of life (Ff up: 1 to 3 months)	22 RCTs (n = 5,508)	SMD 0.1	0.019, 0.18	Benefit	Very low

Quality of life (Ff up: 4 to 7 months)	14 RCTs (n = 2,757)	SMD 0.25	0.1, 0.41	Benefit	Low
Quality of life (Ff up: ≥ 10 months)	2 RCTs (n = 297)	SMD 0.19	-0.03, 0.42	Inconclusive	Low
Pain control (VAS or NRS)	18 RCTs (n = 1,370)	SMD 1.475	1.071, 1.878	Benefit	Very low
Pain control, ≥ 50% reduction (Ff up: 4 weeks, BPI)	1 RCT (n = 278)	RR 1.1710	0.7972, 1.7210	Inconclusive	Low
Pain control, ≤ 3 score (Ff up: 4 weeks, BPI)	1 RCT (n = 278)	RR 0.8000	0.6450, 0.9923	Benefit	Moderate
Pain control (ffup: 8 weeks, EORTC QLQ-C30)	1 RCT (n = 297)	MD 3.4	-9.5, 2.6	Inconclusive	Moderate
Symptom control (ffup: 3 months)	7 RCTs (n = 989)	SMD 0.06	-0.15, 0.26	Equivalent	Very low
Quality of End-of-Life Care (Family and Caregiver; ff up: 12 weeks; assessed with FAMCARE-2)	1 RCT (n = 114)	MD 4.1	0.7, 7.4	Benefit	Low
Quality of End-of-Life Care (Family and Caregiver; ff up: 24 weeks; assessed with FAMCARE-2)	1 RCT (n = 88)	MD 6.1	2.1, 10.1	Benefit	Very low

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## Certainty of evidence

In both systematic reviews and meta-analyses included (Hoomani Maidabidi et al. and Zhao et al.), the risk of bias varied across trials included in their respective analyses. In the SR by Hoomani Maidabidi et al., at least 16 studies had a high risk for selection bias ( $n = 2$ ), performance bias ( $n = 8$ ), detection bias ( $n = 2$ ), attrition bias ( $n = 5$ ), reporting bias ( $n = 4$ ), and other bias ( $n = 3$ ). Further, in the studies included in the “1 to 3-month follow-up” category ( $n = 22$ ), interventions including those that may not be explicitly stated as palliative care were included; it also included interventions from interdisciplinary palliative care to those in which the palliative care domains were delivered by a non-palliative care specialist (indirectness). In the “4 to 7-month follow-up” category ( $n = 14$ ), moderate heterogeneity ( $I^2 > 50\%$ ) was observed (inconsistency). Lastly, in the “ $\geq 10$ -month follow-up” category ( $n = 2$ ) the SMD straddled the no-effect value of 0 (imprecision). Whereas in the SR by Zhao et al, out of the 18 studies included, the method of randomization and the method of statistical analyses were not adequately described in 7 and 3 studies, respectively. There was a lack of description about withdrawals and dropouts in all 18 studies. Further, some of the point estimates were widely different, and some interval estimates were overlapping across the 18 studies; high heterogeneity ( $I^2 = 90.8\%$ ) was also observed (inconsistency). In at least 8 out of the 18 studies, the eligibility criteria were not clearly described; there were also differences in the pharmacological and non-pharmacological strategies for addressing pain (indirectness).

In the individual studies included under pain control, symptom control, and quality of end-of-life care, seven studies had high risk for selection ( $n = 3$ ), performance ( $n = 6$ ), detection ( $n = 1$ ), attrition ( $n = 1$ ), and reporting bias ( $n = 1$ ). For the pooled studies under symptom control, moderate heterogeneity ( $I^2 = 58\%$ ) was observed across trials (inconsistency). The interval estimates for the outcomes measured for pain control (at 8 weeks) and symptom control straddled the no-effect value of 0, whereas wide confidence intervals were noted for studies included in the 24-week follow-up period under quality of end-of-life care (imprecision). The study for quality of end-of-life care (applies to both 12- and 24-week follow-up period), it was specific to patients with malignant pleural mesothelioma, and the uniformity of the intervention provided across sites was a concern (indirectness).

Publication bias was detected in the SR by Hoomani Maidabidi et al., where the p-value in Egger's test was 0.01.

The overall certainty of evidence is very low due to the mentioned considerations.

## RECOMMENDATIONS FROM OTHER GROUPS

Based on numerous randomized trials showing that palliative care significantly enhances physical well-being, patient satisfaction, and goal-concordant care, the American Society of Clinical Oncology (ASCO) advises integrating palliative care into standard oncological care.<sup>19</sup> Similarly, the Registered Nurses' Association of Ontario's (RNAO) best practice guidelines recommends the integration of palliative care.<sup>20</sup>

Note: The evidence and recommendations formed in the guideline from ASCO were centered around patients with advanced-stage malignancies, while the best practice guidelines from RNAO focused on end-of-life care for adult patients experiencing the last 12 months of a progressive life-limiting illness (i.e., not restricted to malignancies).

GROUP OR AGENCY	RECOMMENDATION	STRENGTH OF RECOMMENDATION/CERTAINTY/QUALITY OF EVIDENCE
American Society of Clinical Oncology or ASCO <sup>19</sup> (guideline publication: 2017; published online 28 Oct 2016) <sup>a</sup>	Patients with advanced cancer should be referred to interdisciplinary palliative care teams (consultation) that provide inpatient and outpatient care early in the course of disease, alongside active treatment of their cancer	Strong recommendation
	Palliative care for patients with advanced cancer should be delivered through interdisciplinary palliative care teams with consultation available in both outpatient and inpatient settings.	Moderate recommendation
	Patients with advanced cancer should receive palliative care services, which may include referral to a palliative care provider. Essential components of palliative care may include: <ul style="list-style-type: none"><li>• Rapport and relationship building with patients and family caregivers</li><li>• Symptom, distress, and functional status</li></ul>	Moderate recommendation

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	<p>management (e.g., pain, dyspnea, fatigue, sleep disturbance, mood, nausea, or constipation)</p> <ul style="list-style-type: none"> <li>● Exploration of understanding and education about illness and prognosis</li> <li>● Clarification of treatment goals</li> <li>● Assessment and support of coping needs (eg, provision of dignity therapy)</li> <li>● Assistance with medical decision-making</li> <li>● Coordination with other care providers</li> <li>● Provision of referrals to other care providers as indicated.</li> </ul> <p>For newly diagnosed patients with advanced cancer, the Expert Panel suggests early palliative care involvement within 8 weeks of diagnosis.</p>	
	<p>Among patients with cancer with high symptom burden and/or unmet physical or psychosocial needs, outpatient programs of cancer care should provide and use dedicated resources (palliative care clinicians) to deliver palliative care services to complement existing program tools.</p>	Moderate recommendation
	<p>For patients with early or advanced cancer for whom family caregivers will provide care in the outpatient, home, or community setting, nurses, social workers, or other providers may initiate caregiver-tailored palliative care support, which could include telephone coaching, education, referrals, and face-to-face meetings. For family caregivers who may live in rural areas and/or are unable to travel to clinic and/or longer distances, telephone support may be offered.</p>	Weak recommendation

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Registered Nurses' Association of Ontario or RNAO <sup>20</sup> (Mar 2020)	The Expert Panel recommends that health-service organizations implement an interprofessional model of care for the provision of palliative care and end-of-life care to persons and families.	Strong recommendation
	The Expert Panel recommends that the interprofessional health team, in collaboration with the person and family, develop an individualized, person-centred plan of care and re-evaluate the plan of care based on the changing status, needs and preferences of the person.	Strong recommendation

<sup>a</sup> Guidelines into Decision Support (GLIDES) methodology and the accompanying BRIDGE-Wiz software were used to craft the ASCO guidelines

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

It has been suggested that providing palliative care earlier in the management process can lead to indirect cost savings and in turn enhance the overall value of cancer care by shortening hospital stays and reducing intensive care unit admissions towards the end-of-life.<sup>21</sup>

A literature review of 46 international publications from 2002 to 2011 evaluating the cost and/or utilization implications on palliative care interventions among cancer and non-cancer patients affirmed that palliative care is generally less expensive relative to comparator groups, and the cost difference is often statistically significant.<sup>22</sup> A more recent narrative analysis of 43 systematic reviews from 2000 to 2019 on the cost-effectiveness of palliative and end-of-life care interventions, intervention costs, and/or impact on healthcare use found that the most cost-effectiveness evidence pertain to home-based interventions through reduced healthcare costs and resource use, while palliative care consultations for in-patients were consistently associated with fewer hospitalizations, readmissions, and reduced costs.<sup>23</sup> Majority of the studies included in the latter research involved cancer patient groups. It should be noted however, that both reviews had a broad range of interventions and settings in scope, study types and inherent limitations, and diverse

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approaches to costings and outcome measurements which have an impact to generalizability.

In the Philippines, there are a few small-scale local cost-analysis studies available for palliative and hospice care.<sup>2</sup> At present, research in the form of costing reviews and analyses are currently ongoing to determine the cost of medicines, services, and programs at different levels, as well as collect data from existing programs and institutions, and conduct epidemiologic/actuarial studies on the financial sustainability and development of benefits (PhilHealth).<sup>2</sup>

## **PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY**

A 2022 narrative synthesis by Patra et al. focused on the patients' and family caregivers' perspectives on palliative care referral for patients with cancer and determined that their predisposition to palliative care engagement was influenced by timely referral, comprehensive communication, perception, and stigma about palliative care.<sup>24</sup> In particular, four themes were generated from 14 studies (eleven studies from North America and three studies from Asia (Korea (n = 1 study) and Japan (n = 2 studies), published between 01 Jan 1990 and 31 May 2022) in scope of their evaluation, and in general, their review emphasizes the need for a patient and family- centered, integrated, collaborative model of care in oncology, and highlights the positive impact of a palliative care team on patient and family experience.

### *a. Theme 1: Timing and reasons for making a palliative care referral*

Patients and families believe that timely palliative care referral correlates with the patient's length of stay in hospice for 3 weeks or above and results in better end-of-life care. Delayed referrals contribute to lack of preparedness and frequent visits to emergency departments, while early referrals at cancer diagnosis or first chemotherapy dose are perceived too early. Communication and a holistic approach are valued.

### *b. Theme 2: Meaning of palliative care referral*

Negative perceptions of palliative care were due to media representation, physicians' views, and fear of loss of hope and death. Some families avoided discussing hospice as it could hinder hope for a cure, while

others viewed hospice as crucial support for their loved ones and relief for the family. Recommendations include rebranding palliative care as symptom control and pain/symptom management.

c. *Theme 3: Process of palliative care referral*

Families often experience intense emotions and fear during the transition to palliative care but find comfort and support from the hospice team.

d. *Theme 4: Experience in palliative care referral*

Families in the USA, Canada, and Japan perceived positive end-of-life experiences differently, with access to holistic care and personalized options contributing to positivity.

In the Philippines, despite the establishment of palliative care services and fellowship training, many advanced disease patients in the country still lack access to palliative care and are referred too late.<sup>3</sup> However, some private hospitals have more developed supportive and palliative care services and other institutions have had or are planning to start similar programs.

Lack of physician referrals is the main reason for the lack of access to palliative care in the Philippines, due to a lack of education, awareness, and institutional standards for end-of-life care; whereas, late referrals to palliative care often result from the desire to minimize emotional damage and maintain hope, difficulty in making accurate prognoses, and reluctance to admit defeat.<sup>3</sup> Ongoing but ineffective treatments may also be fueled by these factors.

Some attending physicians' reluctance to refer cancer patients to supportive and palliative care could stem from the perception of losing control and the belief that it is their job to provide psychological support and manage symptoms.<sup>3</sup> This leads to a disinclination to refer people who could potentially benefit from supportive and palliative care services and misunderstandings about when cancer-directed therapy and palliative care can be offered at the same time.<sup>3</sup>

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## 4.2 Adding opioids to the standard of care in the relief of dyspnea

**Question 2: Among adult cancer patients with dyspnea, is the addition of opioids safe and more effective compared to the standard of care alone in the relief of dyspnea?**

### RECOMMENDATIONS

1. Among adult patients with advanced cancer, **we recommend the use of opioids for the relief of resting dyspnea.** (*Strong recommendation, moderate certainty of evidence*)
2. Among adult patients with advanced cancer, **we suggest the use of opioids for the relief of exertional dyspnea.** (*Weak recommendation, low certainty of evidence*)
3. Among patients with dyspnea caused by early-stage cancer, we do not suggest routine use of opioids for the relief of dyspnea. (*Weak recommendation, low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The consensus panel discussed that there are other disease entities that can cause dyspnea apart from lung cancer that are potentially curative with appropriate treatment (i.e. infection).

### Key Findings

- There were seven RCTs identified that evaluated the use of opioids for the relief of dyspnea among patients with cancer.
- The use of opioids was associated with similar or lower severity of breathlessness compared to placebo. The evidence for benefit was limited to patients with resting dyspnea, while the findings for patients with exertional dyspnea were inconclusive. There was no significant difference between opioids and placebo in respiratory rate, oxygen saturation, and walking distance. On the other hand, findings regarding the incidence of adverse events such as dizziness, drowsiness, nausea, and pruritus were inconclusive.
- The overall certainty of evidence was judged to be very low due to

- indirectness as the patients' studies were mostly those with advanced cancer already on a stable dose of opioid, as well as issues in inconsistency or imprecision.
- There was no evidence obtained for quality of life and psychosocial outcomes such as anxiety/distress, peaceful death, confidence, coping, and reassurance.

## Background

Dyspnea, defined as difficulty of breathing or shortness of breath is a common symptom among patients with cancer, especially those with advanced disease. Patients may experience dyspnea while at rest or with exertion. It can significantly limit their ability to take part in daily activities, diminish their quality of life, and cause distress to the patient and their loved ones.

In situations where treatment of the primary cause and contributing factors to dyspnea do not fully relieve symptoms, adjunct interventions may offer some benefit. The use of opioids for the relief of refractory cancer-related dyspnea has been investigated in several clinical trials but with conflicting results.

## Review Methods

A systematic search was performed using MEDLINE, CENTRAL, and Google Scholar for studies published until January 25, 2023, using MESH and free text search for opioids, dyspnea, and cancer. A search for ongoing trials was performed using the NIH *clinicaltrials.gov* website.

We sought clinical practice guidelines, meta-analyses, systematic reviews, and randomized controlled trials that evaluated the use of opioids compared to usual care among patients with cancer experiencing breathlessness. Outcomes of interest included clinical outcomes (relief of dyspnea, quality of life, oxygen saturation), psychosocial outcomes (anxiety/distress, peaceful death, confidence, coping, reassurance), and safety. No limits were placed on cancer stage, etiology of breathlessness, and opioid type or route of administration. Risk of bias was assessed using the Cochrane Risk of Bias tool. Meta-analysis was performed using Review Manager 5.4 with pooling of results done using the random effects model.

## Results

We identified one clinical practice guideline<sup>1</sup> published in the last five years, and five meta-analyses<sup>2-6</sup> that evaluated the efficacy of opioids compared to

usual care for the relief of cancer-related dyspnea. These, however, either focused only on patients with advanced cancer<sup>1-4,6</sup> or had methodological issues in their analysis<sup>5</sup>. Hence, we proceeded to search for relevant RCTs that involved patients with cancer with no restriction based on disease extent.

### **Characteristics of included studies**

We identified seven relevant RCTs (n=164) that evaluated opioids against placebo for cancer-related dyspnea. Six of these have already been included in the latest published meta-analysis<sup>7-12</sup>. The remaining study<sup>13</sup> was previously excluded due to small sample size but was included in this analysis because it still provided evidence relevant to the clinical question. No new RCTs and no RCTs on patients with early-stage cancer were identified.

All are small studies with sample sizes ranging from 18-40. Four studies<sup>7,8,12,13</sup> only recruited patients with advanced cancer, while the remainder<sup>9-11</sup> included a minority of patients with non-metastatic disease. In five studies<sup>7-11</sup>, all patients were already on a stable dose of opioid for cancer pain, while the remaining two studies<sup>12-13</sup> included some opioid-naïve patients. Two studies<sup>7,13</sup> evaluated patients with resting dyspnea, while the rest<sup>8-12</sup> were among patients with dyspnea on exertion.

Interventions evaluated include morphine (subcutaneous)<sup>7-13</sup>, hydromorphone (nebulized, oral, and subcutaneous)<sup>8</sup>, and fentanyl (nebulized, sublingual, and subcutaneous)<sup>9-12</sup>. In all the studies, only a single dose of intervention / placebo was administered. Outcomes assessed include dyspnea, respiratory rate, oxygen saturation, walking distance, heart rate, blood pressure, and adverse events.

### **Efficacy outcomes**

Based on seven RCTs, the administration of opioids resulted in a similar or lower severity of breathlessness compared to placebo (SMD: -0.35; 95% CI: -0.72, 0.03; I<sup>2</sup>=28%). Subgroup analysis by type of dyspnea showed that opioids were as good as or better than placebo for exertional dyspnea (SMD: -0.14; 95% CI: -0.49, 0.21; 5 RCTs], and beneficial for the relief of resting dyspnea (SMD: -1.05; 95% CI: -1.83, -0.26; 2 RCTs) (Table 1). Subgroup analysis by disease stage was not performed because this data was not reported in any of the included studies.

Administration of opioids was associated with a similar or lower respiratory rate (MD: -0.41 breaths per minute; 95% CI: -2.32, 1.50; 5 RCTs) compared to placebo among patients with cancer-related dyspnea. On the other hand, its effect on 6-minute walking distance was inconclusive (MD: 2.30 meters;

95% CI: -12.31, 16.92; 3 RCTs) among patients with exertional dyspnea.

None of the studies evaluated quality of life or psychosocial outcomes such as anxiety/distress, peaceful death, confidence, coping, and reassurance.

### Safety outcomes

Based on evidence from the included RCTs, administration of opioids was not found to have a significant effect compared to placebo on oxygen saturation (MD: 0.06%; 95% CI: -0.77, 0.89; 5 RCTs), heart rate (MD: -2.62 beats per minute; 95% CI: -10.19, 4.94; 2 RCTs), systolic blood pressure (MD: 6.35 mmHg; 95% CI: -6.07, 18.77; 2 RCTs), and diastolic blood pressure (MD: 1.60 mmHg; 95% CI: -4.27, 7.46; 2 RCTs) (Table 2). In addition, the current evidence also did not demonstrate a significant effect of opioids compared to placebo on the incidence of dizziness (RR: 0.68; 95% CI: 0.15, 3.11; 2 RCTs), drowsiness (RR: 0.64; 95% CI: 0.14, 3.00; 3 RCTs), nausea (RR: 1.94; 95% CI: 0.41, 9.20; 3 RCTs), and pruritus (RR: 0.52; 95% CI: 0.07, 3.73; 2 RCTs). One study that evaluated subcutaneous fentanyl showed more injection site pain compared to placebo (median: 2 vs 0 on Numerical Rating Scale; p=0.01).

**Table 3. Opioids vs. Usual Care for Cancer-related Dyspnea**

OUTCOMES	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Resting dyspnea	2 RCTs (n=38)	SMD: -1.05	-1.83, -0.26	Benefit	Moderate
Exertional dyspnea	5 RCTs (n=126)	SMD: -0.14	-0.49, 0.21	As good as or better	Low
Breathlessness	7 RCTs (n=164)	SMD: -0.35	-0.72, 0.03	As good as or better	Low
Respiratory rate (/min)	5 RCTs (n=102)	MD: -0.41	-2.32, 1.50	Equivalent	Low
Oxygen saturation (%)	5 RCTs (n=102)	MD: 0.06	-0.77, 0.89	Equivalent	Moderate
Walking distance (m)	3 RCTs (n=64)	MD: 2.30	-12.31, 16.92	Inconclusive	Low

Minimum clinically important difference thresholds: respiratory rate 4 breaths/min, oxygen saturation 4%, walking distance 10m.

**Table 4. Opioids vs. Usual Care for Cancer-related Dyspnea**

OUTCOMES	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Heart rate (/min)	2 RCTs (n=44)	MD: -2.62	-10.19, 4.94	Inconclusive	Very Low
Systolic blood pressure (mmHg)	2 RCTs (n=44)	MD: 6.35	-6.07, 18.77	Inconclusive	Very Low
Diastolic blood pressure (mmHg)	2 RCTs (n=44)	MD: 1.60	-4.27, 7.46	Inconclusive	Very Low
Dizziness	2 RCTs (n=44)	RR: 0.68	0.15, 3.11	Inconclusive	Low
Drowsiness	3 RCTs (n=62)	RR: 0.64	0.14, 3.00	Inconclusive	Low
Nausea	3 RCTs (n=62)	RR: 1.94	0.41, 9.20	Inconclusive	Low
Pruritus	2 RCTs (n=44)	RR: 0.52	0.07, 3.73	Inconclusive	Low

Minimum clinically important difference thresholds: heart rate 5bpm, systolic/diastolic blood pressure 5 mmHg

### Certainty of evidence

Of the seven studies, three studies<sup>7,12,13</sup> had unclear risk of bias due to unclear method of random sequence generation and allocation concealment, while the remaining four studies<sup>8-11</sup> were deemed to have low risk of bias.

The certainty of evidence for all outcomes was downgraded once due to indirectness because the population recruited in the RCTs were mostly limited to patients with advanced cancer who are already on a stable dose of opioid. Additionally, the certainty of evidence for respiratory rate was downgraded for inconsistency, while walking distance, breathlessness, dizziness, drowsiness, nausea, and pruritus were also downgraded due to imprecision. For heart rate, systolic and diastolic blood pressure, the certainty of evidence was also downgraded for inconsistency and imprecision. The overall certainty of evidence was judged to be very low.

## RECOMMENDATIONS FROM OTHER GROUPS

The American Society of Clinical Oncology (ASCO) published a guideline (2021) for the management of dyspnea among patients with advanced cancer. Their recommendation was to offer opioids for those in whom dyspnea is not adequately relieved by non-pharmacologic interventions. The strength of recommendation was moderate despite the lack of high-quality evidence because “dyspnea is extremely distressing, and many patients continue to experience dyspnea despite optimal nonpharmacologic therapies”<sup>1</sup>.

The European Society of Medical Oncology (ESMO) (2020) also recommends the use of regular, oral, low-dose morphine as the first-line pharmacologic treatment for severe chronic breathlessness which persists despite non-pharmacological measures. Their guideline includes recommendations on dosing for opioid-naïve and opioid-tolerant patients, as well as prophylactic dosing<sup>14</sup>.

The National Comprehensive Cancer Network (NCCN) recommends first considering non-pharmacologic interventions for cancer-related dyspnea such as fan therapy, cooler temperatures, stress management, relaxation therapy, and physical comfort measures. For dyspnea that persists despite these measures, pharmacologic options include opioids started in low doses and titrated accordingly. Opioid-tolerance should be taken into consideration with dosing. Benzodiazepines may be considered if coexisting anxiety is present, but caution should be exercised when used in combination with opioids outside of end-of-life care because of the risk of respiratory depression<sup>15</sup>.

GROUP OR AGENCY	RECOMMENDATION	STRENGTH OF RECOMMENDATION/CERTAINTY/QUALITY OF EVIDENCE
Management of Dyspnea in Advanced Cancer: ASCO Guideline (2021) <sup>1</sup>	Systemic opioids should be offered to patients with dyspnea when nonpharmacologic interventions are insufficient to provide dyspnea relief	Evidence quality: low Strength of recommendation: moderate

Management of breathlessness in patients with cancer: ESMO Clinical Practice Guidelines (2020) <sup>14</sup>	Regular, oral, low-dose morphine is the first-line pharmacological treatment for severe chronic breathlessness, which persists despite non-pharmacological measures.	IIB. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
NCCN Clinical Practice Guidelines in Oncology – Palliative Care (2023) <sup>15</sup>	Opioids in low doses, with titration as appropriate, can be used to treat dyspnea that is resistant to other therapies. Opioid tolerance should be taken into consideration with dosing. Consider alternatives to morphine in patients with known renal compromise	2A. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

There are no published local or international economic evaluation studies on the use of opioids for breathlessness among patients with cancer. In the Philippines, the cost of morphine sulfate is Php 44.00 per tablet for the immediate-release form, while the slow-release preparation is Php 14.25. On the other hand, fentanyl costs Php 116.00 per 100mcg tablet.

### PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

A cohort study in Taiwan involving patients with dyspnea from terminal cancer found that 59% of patients and 89% of families report satisfaction with opioid use regarding its effect on controlling dyspnea. Additionally, 100% of medical staff and 96% of families found the use of opioids for dyspnea to be ethically acceptable<sup>17</sup>.

The prescription of opioids in the Philippines is restricted to physicians who possess a narcotics license and requires a special prescription form. Cited barriers to the use of opioids in the Philippines include fear of possible legal, regulatory, or licensing sanctions, as well as perceived danger of opioid use due to stigmatizing language in the country. Another barrier identified was that opioid use was associated by patients with the end-of-life<sup>18</sup>.

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## 4.3 Use of Opioids among actively dying hypotensive adult cancer patients

**Question 3: Among actively dying hypotensive adult cancer patients, do opioids worsen hypotension or hasten death?**

### RECOMMENDATION

Among actively dying hypotensive adult cancer patients in need of comfort and pain relief, **we suggest including opioids in the treatment regimen.**  
*(Weak recommendation, very low certainty of evidence)*

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The panel discussed that on critical outcomes, blood pressure was not included but it is a clinical sign and an important parameter in an actively dying patient. Clinicians worry that when they give opioids it can lead to hypotension. The use of opioids for comfort and pain among actively dying patients is still being suggested because there is still inconclusive evidence that opioids cause hypotension.
- The panel highlighted that opioids are used as part of pain relief and comfort care and not to hasten death. It is appropriate to spend time with the family members to explain this and with the goal of giving what is appropriate and acceptable.

### Key Findings

- Three RCTs investigated the effect of opioids on whether it caused lowering of systolic and diastolic blood pressures among patients with advanced cancer while a systematic review of 28 cohort studies reviewed the link between opioids and cancer survival.
- 2 RCTs compared fentanyl to placebo in patients with advanced cancer and reported effects on blood pressure. 1 RCT compared different doses of sublingual fentanyl spray on blood pressure among opioid-tolerant patients after completing a shuttle walk test.
- Based on the pooled results of the 2 trials that compared fentanyl with placebo, there was no statistical difference between the

intervention and control in their effect on both the diastolic and systolic blood pressures. Likewise, the RCT that compared 2 different doses of fentanyl sublingual spray on blood pressure reported no significant change in blood pressure among patients in either arm of the trial.

- Regarding whether opioid use can hasten death, 17 retrospective cohort studies suggest that opioid use or high dose opioid use for cancer-related pain may be associated with shorter survival. However, no studies were found on the effects of opioid use specifically among actively dying hypotensive adult cancer patients.
- The overall certainty of evidence was assessed to be very low due to indirectness, inconsistency, and imprecision. The patients in the included studies, although classified as having advanced cancer, were not explicitly stated to be actively dying & hypotensive at the time of assessment. The RCTs that looked at hypotension were also specifically powered to detect exertional dyspnea as its primary outcome and not changes in blood pressure (secondary outcome). There was significant heterogeneity when meta-analyses were performed for the studies that compared fentanyl with placebo on blood pressure as well as on the studies that compared the effect of opioids on cancer survival.
- There was no evidence obtained for patient comfort, quality of end-of-life care, patient's autonomy for end-of-life decisions, and confidence and full trust in the medical team.

## Background

The use of opioid medications is considered an important part of palliative care especially when dealing with advanced symptoms such as intractable cancer pain. Their use, however, has been associated with adverse effects that can limit their use. Aside from the commonly known side effects such as constipation, nausea, and drowsiness, opioids have been hypothesized to affect the cardiovascular system<sup>1</sup>. Opioids are posited to cause histamine release, which leads to vasodilation and hypotension. Because mu opioid receptors have been documented to be located throughout the central and peripheral nervous system including the brain, spine, gut, lung, and heart, a common clinical concern is that opioids may cause or worsen hypotension<sup>1,2</sup>. This association may be of particular concern to palliative care providers who are frequently consulted about the care of patients with tenuous hemodynamics who have an active medical problem that can cause hypotension.

Presently, there is little guidance regarding the use of opioid therapy to

palliate symptoms for patients with advanced cancer with or without hemodynamic instability, and the impact of opioids on blood pressure has not been thoroughly studied.

Aside from hypotension, the use of opioids can also cause some adverse effects such as respiratory depression, constipation, nausea, and dizziness, in cancer pain patients which may contribute to increasing mortality. Several retrospective studies have also suggested that opioid use may promote tumor progression by activating the mu-opioid receptor, by increasing angiogenesis or by inducing immunosuppression, thus negatively impacting the survival of patients with advanced cancer<sup>11</sup>. It seems that current evidence regarding the effect of opioids on the patient's survival is still conflicting.

### **Definition of Terms:**

- a. **Actively dying** - actively dying means that the patient is in the final phase of the dying process when the patient is very close to death and exhibits many signs & symptoms of near-death. In a systematic review, actively dying was defined as "The hours or days preceding imminent death during which time the patient's physiologic functions wane".<sup>3,4</sup>
- b. **Hasten death** - make death happen faster or sooner or shorten survival. According to the Annals of Palliative Medicine, hastened death includes, but is not exclusive of, lawful assisted dying where an individual who meets a specific criterion can be prescribed or administered medications to end their life.<sup>8</sup>
- c. **Overall Survival (OS)** - refers to the time which begins at diagnosis or at the start of randomization to treatment and up to the time of death. It is usually used as an indication of how well a treatment works and is often considered the gold standard endpoint in oncologic clinical trials.<sup>12</sup>

### **Review Methods**

A systematic search was performed from January 3, 2023, until March 19, 2023, using MEDLINE, Cochrane Library, HERDIN, Google Scholar, and clinicaltrials.gov as databases. Combined MeSH and free text search was done using the following keywords: cancer, end-of-life care, palliative care, actively dying patient, opioids, hypotension, blood pressure, hastened death, cancer-specific survival, overall survival, patient comfort, peaceful death, dignified death, quality of end-of-life care, end-of-life decisions, patient safety, confidence and trust on medical team, and their synonyms. The references in identified articles were also reviewed manually for possible

inclusions.

The evidence reviewers searched for clinical practice guidelines, systematic reviews, randomized controlled trials and cohort studies that evaluated the effect of opioids on the blood pressure of cancer patients whether compared to placebo, other opioids, or other pain relievers. Outcomes of interest included changes in blood pressure, particularly hypotension, patient comfort, peaceful or dignified death, quality of end-of-life care, patient autonomy for end-of-life decision, patient safety and patient's confidence and trust on the medical team. No limits were placed on the type of cancer, cancer stage, type of opioid used or route of administration. Studies that did not include patients with cancer were excluded.

Risk of bias of included RCTs was assessed using the Cochrane Risk of Bias tool for randomized trials while risk of bias assessment for the systematic review was done using the CASP SR. A meta-analysis was performed on the 2 RCTs that compared fentanyl with placebo using Review Manager 5.4 with pooling of results done using random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of evidence and to rate the certainty of evidence in the included studies for each specific outcome measure.

## **Results**

Three (3) randomized controlled trials that examined the effect of opioids on blood pressure were included in this evidence review (n=96). Seventeen retrospective cohort studies (n=17,374) that examined the link between opioids and hastened death were also included.

### **Characteristics of included studies**

We were able to retrieve two relevant RCTs (n=46) which primarily evaluated the effect of opioids against placebo on exertional dyspnea<sup>5,6</sup>. The first RCT included 24 cancer patients who were randomized to receive either a fentanyl pectin nasal spray (FPNS) or a placebo<sup>5</sup>. The second RCT included 22 cancer patients who were randomized to receive either a fentanyl buccal tablet (FBT) or placebo<sup>6</sup>.

The third RCT (n=30) recruited cancer patients with active disease complaining of exertional dyspnea and who had previously been on opioid therapy. The study examined two dosage preparations of sublingual fentanyl spray, low dose (15-25% morphine equivalent daily dose or MEDD) & high dose (35-45% MEDD) and their effects on exertional breathlessness, blood pressure, and other vital signs<sup>7</sup>.

For the three randomized controlled trials, the outcome measures included change in dyspnea using Dyspnea Numeric Rating Scale<sup>5,6</sup>, walk distance at six minutes<sup>5,6</sup>, Dyspnea Borg Scale<sup>5,6</sup>, Modified Dyspnea Borg Scale<sup>7</sup>, and Fatigue Borg Scale<sup>5,6,7</sup>. Other outcomes which are considered secondary outcomes included respiratory rate, oxygen saturation, heart rate, systolic & diastolic blood pressure, and the occurrence of adverse events<sup>5,6,7</sup>.

The seventeen retrospective cohort studies explored the association between opioid use and hastened death. The population of the included studies were composed of cancer patients regardless of cause who have had treatment with any type of opioids for cancer-related pain. Outcome measures included progression-free survival (PFS) and overall survival (OS). We considered overall survival as a surrogate outcome for hastened death, so we focused on this as the primary outcome<sup>8</sup>.

## Outcomes

### Effect on Blood Pressure

For the 2 placebo-controlled trials<sup>5,6</sup>, a meta-analysis was performed using random effects model. Based on the overall pooled results, we found no significant difference between opioids and placebo on their effect on blood pressure. For diastolic blood pressure, the calculated mean difference was 1.60 mmHg (95% CI, -4.27 to 7.46,  $I^2=31.6\%$ ) and for the systolic blood pressure, the calculated mean difference was 6.35 mmHg (95% CI, -6.07 to 18.77,  $I^2=59\%$ ). There was also significant heterogeneity in the systolic blood pressure findings.

The third RCT which compared two dosage preparations of sublingual fentanyl spray, low dose vs high dose<sup>7</sup>, reported no significant change in blood pressure among patients in either arm of the trial. For diastolic blood pressure, the difference between beginning and end of walk had a calculated mean difference of -2.60 mmHg (95% CI, -9.25 to 4.05). For systolic blood pressure, the difference between beginning and end of walk, the mean difference was 2.40 mmHg (95% CI, -7.55 to 4.35).

### Effect on Hastening Death

For the outcome of hastened death, we performed a quantitative synthesis on studies that compared the association of opioid required vs. no opioid required and another quantitative synthesis for studies that compared high-dose opioids vs. low-dose opioids on overall survival. The meta-analysis revealed that compared to those patients who were not given opioids, patients who required opioids had poorer overall survival (HR=1.532, 95%CI 1.253–1.873). For the meta-analysis that compared high-dose opioid use vs. low- opioid use, high-dose opioid use was associated with poorer overall

survival (HR=1.053, 95%CI 1.019–1.088). However, it should be noted that the heterogeneity between studies was considerably substantial with an I-squared of 74.9% for the opioid required vs. no opioid required and 90.1% for the low-dose opioid vs. high-dose opioid use (See Forest Plot no. 3, Fig. C).

None of the studies evaluated quality of end-of-life care, patient's autonomy for end-of-life decisions, peaceful or dignified death, and confidence and full trust in the medical team.

### **GRADE Summary of Findings Table**

**Table 5. Opioid vs. No Opioid on Systolic and Diastolic Blood Pressure for Advanced Cancer Patients**

CRITICAL OUTCOMES	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Diastolic Blood Pressure	2 RCTs (n=46)	MD: 1.60	-4.27 - 7.46	Inconclusive	Low
Systolic Blood Pressure	2 RCTs (n=46)	MD: 6.35	-6.07 – 18.77	Inconclusive	Low

**Table 6. High-Dose Opioid vs. Low-Dose Opioid on Systolic and Diastolic Blood Pressure for Advanced Cancer Patients**

CRITICAL OUTCOMES	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Diastolic Blood Pressure	1 RCT (n=30)	MD: -2.60	-9.25 – 4.05	Inconclusive	Low
Systolic Blood Pressure	1 RCT (n=30)	MD: 2.40	-7.55 – 4.35	Inconclusive	Low

**Table 7. Opioid required vs. No opioid required on the Overall Survival of Patients with Cancer**

CRITICAL OUTCOMES	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Overall Survival	7 cohort (n=3,523)	HR = 1.53	1.25 - 1.87	Harmful	Very Low

**Table 8. High-Dose Opioid vs. Low-Dose Opioid on the Overall Survival of Patients with Cancer**

CRITICAL OUTCOMES	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Overall Survival	10 cohort (n=13,851)	HR = 1.05	1.02 - 1.09	Harmful	Very Low

### Certainty of evidence

The three included RCTs that measure blood pressure had an overall low risk of bias. Over-all certainty of evidence was downgraded to low because of indirectness and imprecision. The patients in the included studies, although classified as having advanced cancer, were not explicitly stated to be actively dying & hypotensive at the time of assessment. The included studies were also specifically powered to detect exertional dyspnea as its primary outcome and not changes in blood pressure (secondary outcome). There was also significant heterogeneity in the systolic blood pressure findings in the systematic review performed for the studies that compared fentanyl with placebo ( $I^2$ -squared of 59%).

The meta-analyses on the prospective cohort studies that looked at the association between opioid use and overall survival had low risk of bias; however, the over-all certainty of evidence was downgraded to very low due to issues of inconsistency, indirectness, and imprecision. The subjects of the included studies were composed of patients with different types and stages of cancer from early diagnosis to far- advanced cancer. The interventions also varied (different types of opioids used, different routes of administration) and were introduced at different points in cancer care (from

early stage at time of diagnosis to relatively late stage at time of referral to hospice care units). Some were exposed to prolonged opioid use (~3 years), while others were given opioids only upon their last hospitalization. These likely may have contributed to the substantial heterogeneity in the quantitative synthesis of the evidence.

Based on the three trials that looked into the effect of opioids on blood pressure among advanced cancer patients, there was inconclusive evidence to show that giving opioids to treat cancer-related pain and dyspnea resulted in further reductions in blood pressure. In all three trials, there was no statistical difference between the intervention and control in their effect on both the diastolic and systolic blood pressures.

The studies that explored the effect of opioids on overall survival suggest that opioid use or high dose opioid use for cancer-related pain may be associated with shorter survival. It must be noted, however, that the type of studies included in the meta-analysis were all observational retrospective studies and not randomized controlled studies. This means that the overall result can only suggest an association and not establish a cause-and-effect relationship. There is a high potential for residual confounding variables which may have been a factor in the relatively poor overall survival among those cancer patients who received opioids. The authors of these studies have also pointed out that patients who required higher doses of opioids had higher pain scores to begin with, which means they were probably worse off at the beginning of the observation.

Increased pain and increased opioid demand were mostly due to disease severity and progression (e.g., bone metastases, extensive pleural invasion, and vital organs compression), which would be associated with a higher likelihood of shortened survival.

## **RECOMMENDATIONS FROM OTHER GROUPS**

The National Comprehensive Cancer Network (NCCN) recommends to maintain analgesic therapy and titrate to achieve optimal comfort for dying patients. The ESMO CPG recommends that decisions regarding opioid therapy should not be influenced by the concern about hastening death.

GROUP OR AGENCY	RECOMMENDATION	STRENGTH OF RECOMMENDATION/ CERTAINTY/QUALITY OF EVIDENCE
National Comprehensive Cancer Network 2023 (accessed February 23, 2023)	For dying patients (life expectancy weeks to days), maintain analgesic therapy and titrate to optimal comfort. Avoid opioid dose reduction solely for decreased blood pressure or respiratory rate.	Category 2A - Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
ESMO Clinical Practice Guidelines 2021	Concern about hastening death should not influence decisions regarding opioid therapy. The medical use of opioids may be associated with a shortened survival in advanced cancer patients, but cause and effect relationship remains uncertain and decisions should be guided by goals of care, patient prognosis and risk-benefit assessment of the treating physician.	Level IV, B - generally recommended based on retrospective cohort or case-control studies, with strong or moderate evidence for efficacy but with little clinical benefit.

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

There are no local or international published cost-effectiveness studies on the use of opioids in actively dying patients for the treatment of cancer pain.

In the Philippines, the cost of a modified release tablet of 10mg of morphine sulfate is Php 13.00 while the 30 mg tablet costs Php 32.25 and the 60mg tablet costs Php 76.64. The fentanyl 12.5 mcg/hr transdermal patch, on the other hand, costs Php 550.00 whereas the 25 mcg/hr transdermal patch costs Php 1,030.00. The different forms of oxycodone HCl are priced as follows: 10mg controlled-release tablet - Php 127.26; 20mg controlled-release tablet - Php 316.01; 40mg controlled-release tablet - Php 487.24.

### PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

A qualitative study investigated the attitudes and perceptions of morphine use in cancer pain among patients with advanced cancer. Although the

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respondents voiced concerns about morphine being associated with dependence and end-stage illness, most participants were still open to using morphine for cancer pain as they prioritized adequate pain control and reduction in suffering<sup>9</sup>.

A cross-sectional survey on attitudes and perceptions among cancer patients in Australia revealed that majority of the respondents (72.7%) were either neutral or strongly disagreed that morphine can shorten life. Seventy four percent were also either neutral or strongly agreed that morphine has no effect on life expectancy<sup>10</sup>.

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## **4.4 Effectiveness of the 2-step ladder approach versus WHO 3-step ladder approach in achieving pain control**

**Question 4: Among adults with cancer pain, is the 2-step ladder approach more effective than the WHO 3-step ladder approach in achieving pain control?**

### **RECOMMENDATION**

Among adult cancer patients with moderate to severe cancer pain, **we suggest the use of the 2-step ladder approach as initial therapy (use of low dose strong opioids)**. (*Weak recommendation, low certainty of evidence*)

### **Consensus Panel Considerations:**

The consensus panel considered the following when formulating the recommendations:

- The panel highlighted that pain is multifactorial and needs comprehensive evaluation and management. Mechanism-based pain management is important.
- Consensus among panel members was not reached after the first round of voting for the direction of the recommendation. Some of the issues raised were (1) having past experiences where tramadol (one of the drugs in the Step 2 of the 3-step ladder approach) worked, and (2) it may not be easy to step-up immediately from step 1 to step 3 considering existing issues on cost and equity. The recommendation was revised to include the statement “use of low dose strong opioids” specifically for cases of moderate pain, defined as pain score of 4/10-6/10. Consensus was finally reached thereafter.

### **Key Findings**

- Two RCTS evaluated the efficacy and safety of the two-step approach compared to the conventional three-step ladder approach of WHO. One study reported pain control, while the other reported days of pain with intensity  $\geq 5$  and  $\geq 7$  (worst, average, least, now).

- The two-step approach had a statistically lower percentage of days with worst pain  $\geq 5$  and days with worst pain  $\geq 7$  compared to the WHO-3 step ladder approach.
- Patients in the 2-step ladder approach had statistically lower global distress scores than the 3-step ladder approach on day 20.
- There was no statistically significant difference in time to stable pain control and pain relief after 20 days, mean daily average pain, mean daily worst pain, percentage of days with average pain  $>6$ , percentage of days with worst pain  $>6$ , and pain interference score after 20 days between the two- step approach, the WHO-3-step ladder approach.
- The number of patients who experienced serious adverse events or adverse events (combined) was not statistically different between the two arms.
- The certainty of the evidence was low due to the risk of bias and imprecision. Both studies were open-label trials, and one study had unclear allocation concealment. Both studies have low statistical power.
- We did not find evidence that reported the patient's compliance with the regimen, the healthcare provider's distress or anxiety, or the risk of opioid addiction.

## **Background**

In 1986, the World Health Organization (WHO) introduced the WHO analgesic ladder to provide adequate pain relief for cancer patients<sup>1,2</sup>. The WHO recommends using non-steroidal anti-inflammatory drugs and paracetamol (acetaminophen) for mild pain as step 1. The second step of the ladder is to add a weak opioid for mild-to-moderate pain, such as codeine and tramadol. Lastly, the third step of the ladder was to give a strong opioid for moderate-to-severe pain, such as morphine which is titrated for pain relief or for the occurrence of dose-limiting adverse events<sup>2</sup>.

WHO analgesic ladder has been widely used for several decades. Based on validation studies, it has been reported that the WHO analgesic ladder can provide pain relief for 70 to 80% of patients<sup>1</sup>. However, there were some concerns regarding the use of second-step drugs in the WHO ladder<sup>2,3</sup>.

Some questioned the use of second-step drugs in the WHO ladder and would want to omit step 2 with strong opioids<sup>4</sup>. Some of the concerns reported regarding the second step of the WHO ladder are: the use of weak opioids may cause an unjustified delay in initiating step-3 drugs, low-dose strong opioids have a better therapeutic index as compared to high-dose weak opioids, and based on some studies, the step 2 drugs were reported to have no major advantage between the step 1 and 3 drugs<sup>4</sup>. Despite these concerns, it is still unknown if removing step 2 in the WHO analgesic ladder will be more effective, safe, and effective in controlling pain in cancer patients<sup>2</sup>.

## Review Methods

A systematic search was done from database inception until March 1, 2023, through MEDLINE, and until March 02, 2023, for Cochrane CENTRAL, HERDIN, Google Scholar, and clinicaltrials.gov using the combined MeSH and keywords search on cancer pain, WHO analgesic ladder, weak opioids, and strong opioids and its synonyms. The full search strategy is presented in Search Strategy no. 4.

The review included randomized controlled trials that compared the two-step approach and the WHO-3-step ladder approach for cancer pain in adult patients  $\geq 18$  years of age. The outcome of interest included pain control, quality of life, symptom control, compliance to the regimen, healthcare provider's distress or anxiety, patient safety, and risk of opioid addiction.

Two direct pieces of evidence were found, and the risk of bias was assessed using Cochrane risk of bias assessment criteria<sup>2,4</sup>. However, the study cannot be pooled due to different definitions of the outcomes. We also did not find any evidence that reported the patient's compliance with a regimen, the healthcare provider's distress or anxiety, and the risk of opioid addiction.

## Results

### Characteristics of included studies

We found two (2) RCTs that included 199 cancer patients on step 1 of the WHO analgesic ladder with an indication for weak opioid therapy according to WHO ladder guidelines<sup>2,4</sup>. One study was a multi- country study that included patients from the United Kingdom, Mexico, and Uganda<sup>4</sup>, and the other was conducted in Italy<sup>4</sup>.

Both studies randomized patients to the two-step or WHO-3-step ladder approaches. In the WHO- 3-step approach, patients received weak opioids and were maintained for as long as it was considered effective and well

tolerated. When it becomes insufficient, step III drug treatment will be used. For the two-step approach arm, patients received a strong opioid. In one study, no restrictions were placed on using a specific drug within each drug step<sup>4</sup>. Meanwhile, in the other study, for weak opioids, either tramadol (maximum dose 100 mg four times a day) or codeine (maximum dose 60 mg four times a day) could be used. For strong opioids, only morphine and oxycodone could be used<sup>2</sup>.

Outcomes measured in the Fallon et al., (2022) study were stable pain control ("the first day of 3 consecutive days with average pain score  $\leq 3$  on an NRS 0-10; 0 being no pain to 10 worst pain ever imagined"), mean of daily average pain scores; mean of daily worst pain; percentage of days with average pain score  $\geq 6$  and with worst pain score  $\geq 6$ ; pain intensity, pain relief (0% no relief to 100% complete relief), pain interference with daily function, pain distress in scores at day 10 and 20 and side effects. The Brief Pain Inventory (BPI) tool was used to assess pain. Based on the BPI tool. Pain interference is how much pain interferes with various daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. Determined as the average of the scores in each domain, 0 being does not interfere to ten completely interfere<sup>5</sup>. The study also measured the global distress score at day 10 and 20 using the NCCN distress thermometer: 1-no distress, 10- extreme distress<sup>2</sup>.

In the study of Maltoni et al., the outcomes reported were days of pain with intensity  $\geq 5$  and  $\geq 7$  (worst, average, least, now), degree of satisfaction of patient to the antalgic effect of drugs, use of co-analgesics, adjuvants, and other treatments and side effects of the drugs<sup>4</sup>.

### Efficacy outcomes

In the study of Maltoni et al. (2005), it was reported that patients in the two-step approach have a statistically lower percentage of days with worst pain  $\geq 5$  (28.6% of 1400 days vs. 22.8% of 1249 days,  $p<0.001$ ) and in days with worst pain  $\geq 7$  (11.2% and 8.6%,  $p=0.023$ ) as compared to the WHO-3-step approach<sup>4</sup>. There were no other statistically significant differences reported between the two treatments in the pain control outcomes<sup>4</sup>.

In the study of Fallon et al. (2022), patients in the 2-step ladder approach had statistically lower global distress scores than the 3-step ladder approach only on day 20 but not on day 10. There were no statistically significant differences reported between the two-step approach and the WHO-3 step ladder approach either on day 10 or day 20 for the following outcomes: time to stable pain control (average pain score of 3 on NRS for first three days), pain relief, mean daily average pain, mean daily worst pain, percentage of days

with average pain >6, percentage of days with worst pain >6, and in pain interference with daily function score between the two treatments<sup>9</sup>. (See Table 9).

## SUMMARY OF FINDINGS FOR EFFICACY OUTCOMES

**Table 9. Two-Step Approach vs. WHO Three-step Approach for Cancer Pain**

CRITICAL OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>For Pain Control</b>					
Average pain	1 RCT N=153	MD 0.09	-0.43 to 0.61	Inconclusive	Low
Worst pain	1 RCT N=153	MD 0.39	-0.22 to 1.00	Inconclusive	Low
Days of pain with intensity $\geq 5$	1 RCT N=54	2- step: 22.8% of 1249 days 3- step: 28.6% of 1400 days $p < 0.001$		Benefit	Low
Days of Pain with Intensity $\geq 7$	1 RCT N=54	2- step: 8.6% of 1249 days 3- step: 11.2% of 1400 days $p = 0.023$		Benefit	Low
Percentage of days with average pain $> 6$	1 RCT N=153	MD 0.2	-6.3 to 6.7	Inconclusive	Low
Percentage of days with worst pain $> 6$	1 RCT N=153	MD 6.0	-3.84 to 15.84	Inconclusive	Low

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Pain intensity Day 10	1 RCT N=153	MD -0.11	-0.63 to 0.41	Inconclusive	Low
Pain relief Day 10	1 RCT N=153	MD 1.30	-6.56 to 9.16	Inconclusive	Low
Pain intensity Day 20	1 RCT N=153	MD 0.00	-0.42 to 0.42	Equivalent	Low
Pain relief Day 20	1 RCT N=153	MD -3.00	-9.37 to 3.37	Inconclusive	Low
Stable pain control 3 consecutive days with pain ≤3	1 RCT N=153	HR 1.03	0.72 to 1.49	Inconclusive	Low
<b>Quality of Life</b>					
Pain interference Day 10	1 RCT N=153	0.13	-0.63 to 0.89	Inconclusive	Low
Pain interference Day 20	1 RCT N=153	0.05	-0.58 to 0.68	Inconclusive	Low
<b>Patients' distress</b>					
Global distress score Day 10	1 RCT N=153	0.26	-0.55 to 1.07	Inconclusive	Low
Global distress score Day 20	1 RCT N=153	0.99	0.2 to 1.78	Benefit	Low

Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: [https://ehospice.com/international\\_posts/integration-of-palliative-care-into-the-philippine-health-system/](https://ehospice.com/international_posts/integration-of-palliative-care-into-the-philippine-health-system/) along with this CPG.

## Safety outcomes

In the study of Fallon et al 2022, 93 adverse events were reported, 51 in 19 patients in the WHO-3 step ladder approach and 42 in 17 patients in the two-step approach. The study also reported 8 serious adverse events (SAEs), 5 in the two-step approach group and 3 in the WHO-3-step approach ladder group. All 5 reported SAEs (chest pain, death, nausea, hypercalcemia, and epistaxis) in 5 patients in the two-step approach arm were reported to be unrelated to the treatment arm. Meanwhile, the 3 SAE reports of constipation in 3 patients were reported to be possibly related to the WHO-3 step ladder arm. Results showed that there was no significant difference between the two treatment groups in the number of patients who had SAE/AE ( $OR=0.99$ , 95% CI: 0.50 to 1.94) (See Table 10)<sup>2</sup>. For specific adverse events reported, no statistically significant difference was also found, except for nausea, wherein the patients in the WHO-3 step ladder approach had higher odds of experiencing nausea as compared to patients in the WHO-2 step ladder approach ( $OR=2.93$ , 95% CI 1.31-6.58;  $P=0.009$ )<sup>2</sup>.

## Opioid Dependence or Abuse

We could not find any evidence that compared the dependence or abuse of weak opioids and strong opioids used for pain relief directly. However, a systematic review reported that the incidence of opioid dependence among adults who were treated with any opioids for chronic non-cancer pain relief ranged from 0 to 24% and the prevalence ranged from 0% to 31%<sup>7</sup>. The study reported that it is not possible to estimate the incidence of dependence or abuse of opioids used for cancer pain<sup>7</sup>. An overview of Cochrane reviews was conducted to determine the adverse events associated with medium and long-term use of opioids for chronic non-cancer pain. The study reported that in the Cochrane reviews included, there were no reports of opioid abuse and dependence, overdoses (fatal or non-fatal), or endocrinological harms. The authors mentioned that the lack of data on dependence or abuse might be due to the strict inclusion criteria used in the reviews or due to the short duration of the studies conducted<sup>8</sup>.

## Summary of Findings for Safety Outcomes

**Table 10. AEs and SAEs- Two-Step Approach vs. WHO 3-step Approach for Cancer Pain**

CRITICAL OUTCOMES	BASIS (No and type of studies, total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>Safety Outcomes</b>					
Adverse Events and Serious Adverse Events*	1 RCT N=153	0.99	0.50 to 1.94	Inconclusive	Low

\*Nausea, Vomiting, Constipation, Drowsiness, Confusion, Disorientation, Hallucinations, Shadows, Dreams, Jerks, Hypercalcemia, Epistaxis, Death, and Chest pain

### Certainty of evidence

The certainty of the evidence is low due to the presence of risk of bias and imprecision. For risk of bias, both studies were open-label. Thus, outcome assessment may introduce reporting bias. Moreover, in one study, the allocation concealment was not reported. For imprecision, both studies did not reach statistical power, and 95% CIs of some results are wide.

## RECOMMENDATIONS FROM OTHER GROUPS

GROUP OR AGENCY	RECOMMENDATION	STRENGTH OF RECOMMENDATION/CERTAINTY/QUALITY OF EVIDENCE
European Society for Medical Oncology, 2018 [3]	<ul style="list-style-type: none"> <li>a. For mild to moderate pain, weak opioids such as tramadol, dihydrocodeine and codeine can be given in combination with non-opioid analgesics</li> <li>b. As an alternative to weak opioids, low doses of strong opioids could be an option, although this recommendation is not currently part of WHO guidance [II, C].</li> <li>c. There is no evidence of an increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids [II, C]</li> </ul>	<ul style="list-style-type: none"> <li>a. III, C</li> <li>b. II, C</li> <li>c. II, C</li> </ul>
American Society of Clinical Oncology, 2023 [6]	<ul style="list-style-type: none"> <li>a. Opioids should be offered to patients with moderate-to-severe pain related to cancer or active cancer treatment unless contraindicated</li> <li>b. For patients who are candidates to begin opioid treatment, clinicians may offer any of the opioids approved by the US Food and Drug Administration or other regulatory agencies for pain treatment (Type: Evidence-based, benefits outweigh harms)</li> </ul> <p>Qualifying statement: The decision of which opioid is most appropriate should be based on factors such as pharmacokinetic properties, including bioavailability, route of administration, half-life, neurotoxicity, and cost of the differing drugs</p>	<p>Evidence quality: Moderate Strength: Strong</p> <p>Evidence quality: Moderate to low Strength: Weak</p>

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## **ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE**

### **COST**

We did not find any cost-effectiveness study regarding the two-step approach and 3-step approach in the Philippine setting. Here we present the estimated price of some of the available analgesics in the Philippines.

#### **Cost in the Philippines**

**Table 11. Prices of some Non-Opioid Analgesics, Weak and Strong Opioids**

<b>DRUG</b>	<b>ESTIMATED PRICE</b>
<b>Non-opioid Analgesic</b>	
Acetaminophen 500 mg tablet	Php 2.00 to 4.50
Ibuprofen 200 mg tablet	Php 6.75 to 12.25
Diclofenac 50 mg tablet	Php 16 to 37.50
Celecoxib 200 mg capsule	Php 17.75 to 73.50
<b>Weak Opioids</b>	
Tramadol 50 mg capsule	Php 27.75 to 55.00
Tramadol HCl paracetamol 37.5mg/325mg 1 Tablet	Php 26.50 to 54.50
<b>Strong Opioids</b>	
Oxycodone 10 mg controlled-release tablet	Php 175.39
Oxycodone 10 mg/mL, 1 mL vial	Php 775.23
Oxycodone 10 mg/mL, 2 mL vial	Php 1,284.96
Morphine 10 mg modified-release tablet	Php 16.00
Morphine 30 mg modified-release tablet	Php 41.58

Morphine 60 mg modified-release tablet	Php 108.69
Morphine ampule	Php 124.00
Fentanyl Citrate 50 mcg/2ml	Php 152.00
Fentanyl citrate 50 mcg/ ml 10 ml	Php 577.50
Buprenorphine	Php 1,701.00 to 3,924.00

## PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

There were no studies found regarding patient's values and preference, equity, acceptability, and feasibility for two-step approach vs WHO-3 step ladder approach.

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## 4.5 Effectiveness of transdermal opioid patch vs subcutaneous opioid administration in symptom control

**Question 5: Among adult cancer patients, without intravenous and enteral access, is transdermal opioid patch more effective than subcutaneous opioid administration in symptom (pain and dyspnea) control?**

### RECOMMENDATIONS

1. Among adult opioid-tolerant cancer patients without intravenous or enteral access, **we suggest transdermal fentanyl patch to control pain.** (*Weak recommendation, very low certainty of evidence*)
  
2. Among adult cancer patients without intravenous or enteral access, **we suggest subcutaneous morphine to alleviate dyspnea.** (*Weak recommendation, very low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The panel discussed offering a transdermal opioid patch for patients who cannot tolerate oral medications or refused to have nasogastric tube insertion or maintaining intravenous line, or giving opioids subcutaneously. They further discussed that families prefer the transdermal medications such as transdermal fentanyl patch over subcutaneous medications as it means they can give it at home.
- The representative from the Philippine Alliance of Patient Organization (PAPO) highlighted that the cost and accessibility of transdermal fentanyl patch is a problem. Another panel member further highlighted that the transdermal fentanyl patch is not included in the Philippine National Drug Formulary. With this CPG, the panel hopes PhilHealth will support expenses in procuring the patch.
- Furthermore, the decision of who can administer the subcutaneous medications at home and its cost, should be

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considered part of the decision-making shared between the healthcare team, the family and the patient, with the goal of achieving comfort.

## Key Findings

- There was one retrospective cohort study and one crossover RCT that evaluated the use of transdermal and subcutaneous opioids for relief of pain and dyspnea.
- There were no significant differences in pain control during the 4-hourly monitoring in the last 48 hours prior to death, except on the 20<sup>th</sup> and 8<sup>th</sup> hour prior to death, where fentanyl given transdermally as a patch showed significant pain control compared to diamorphine given subcutaneously. There were no significant differences in breakthrough pain relief between fentanyl and diamorphine groups when given rescue opioids, which was either “as required” diamorphine or immediate-release oral morphine, in the last 72 hours prior to death. Patients on fentanyl received significantly lower mean number of doses of “as required” diamorphine and immediate-release oral morphine in the last 24 hours prior to death.
- For breakthrough pain even after giving two doses of rescue opioids over a 24- hour period, significant relief with an additional dose of diamorphine was observed in the fentanyl group compared to diamorphine group.
- There was relief of dyspnea with both subcutaneous morphine and nebulized morphine, although there was no significant difference. There were also no significant differences in adverse events, which were wheezing, nausea, and sedation.
- Overall certainty of evidence was downgraded to very low as there were concerns with allocation concealment, blinding of outcome assessors, confounding bias, indirectness, and imprecision with small sample size.
- There was no evidence found on quality of life.

## Background

Pain is experienced by 55% of patients undergoing anti-cancer treatment and by 66% of patients who have advanced, metastatic, or terminal disease<sup>1</sup>. The goal of pain management is to relieve pain to a level that allows for an acceptable quality of life.

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Treatment is generally based on the World Health Organization (WHO) pain relief ladder, which proposes a three-step sequential approach corresponding to drugs with increasing efficacy<sup>2</sup>. Opioids bind to mu, kappa and delta receptors resulting in analgesic and antidepressant effects. Activation of the receptors can also lead to sedation, respiratory depression, constipation, and physical dependence. Oral administration of opioids is usually preferable to avoid discomfort, inconvenience and expense of parenteral administration. However, cancer patients often become unable to take oral medicines, or do not have enteral access, hence other routes of opioid administration are often needed. Transdermal (TD) opioid delivery avoids first-pass metabolism by the liver, increasing bioavailability and limiting variation in plasma concentration. TD opioid is usually the treatment of choice for patients who are unable to swallow, or with poor compliance<sup>3</sup>. However, TD opioids require a long lag period for dose stabilization and elimination, hence are unsuitable for acute or unstable pain, and may result in prolonged side effects.<sup>[3]</sup> When transdermal routes are not possible, the subcutaneous route is recommended based on observational non-analytic studies<sup>4,5</sup>.

## **Review Methods**

A systematic search was independently performed by two reviewers in PubMed, Cochrane Europe PMC, Cochrane Central Register of Controlled Trials (CENTRAL), MedRxiv, and ClinicalTrials.gov for citations published up to February 23, 2023. The search terms were: “subcutaneous” “transdermal”, “buprenorphine”, “oxycodone”, “methadone”, “fentanyl”, “sulfentanil”, “morphine”, “hydromorphone”, cancer pain, “dyspnea” “randomized”. The search included non-English publications and was limited to studies in human beings and NOT “non-cancer pain.” In the absence of RCT, NOT “randomized” was added to the search. The reference lists of relevant articles were hand searched to identify eligible articles.

## **Study Eligibility**

Articles included in the analysis were RCT on the use of transdermal opioid compared with subcutaneous opioids for the relief of cancer pain and dyspnea in adults. Observational studies were planned to be included in the absence of an RCT. Articles excluded from the analysis were study protocol/design, letters, commentaries/news, case reports, patient surveys, and narrative reviews. The following inclusion criteria were considered: (a) RCTs investigating the efficacy of transdermal opioids in relieving symptom of dyspnea or pain in adult patients with any type of cancers; (b) any

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subcutaneous opioids as comparator; (c) studies reporting at least one of the following outcomes: symptom control (pain or dyspnea), adverse events, and quality of life. Exclusion criteria were as follows: (a) studies without available data for synthesis; (b) reviews, case reports, case series, editorials, and conference abstracts.

## Data extraction

Data collected included first author, publication year, country, study design, number of patients, patient characteristics, intervention and control characteristics, and results/endpoints. Outcomes examined included any measure of analgesic efficacy (pain or dyspnea scores, pain intensity difference [PID], proportion of responders, need for rescue opioid), quality of life, and safety. Two independent reviewers extracted the data on outcomes of each study independently. Consultation with a third reviewer was planned for unresolved discrepancies. Risk of bias of individual studies included in the review was appraised using the Cochrane Tool to Assess Risk of Bias in Cohort Studies.

Meta-analysis was planned using Review Manager 4. Results were pooled using a fixed effects model. In the presence of significant heterogeneity, the random effects model was planned with sensitivity analysis and subgroup analysis stratified by age, and stage of cancer. Mean difference (Standard Deviation) and Risk Ratio (95% CI) were reported. Certainty of evidence was rated using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

## Results

### Characteristics of included studies

There was one retrospective cohort study<sup>6</sup> and one crossover RCT<sup>7</sup> included in the review. The effectiveness and safety of fentanyl given transdermally as a continuous patch were compared with diamorphine given as a 24-hour subcutaneous infusion in 94 dying cancer patients from one specialist palliative care unit. Cancer types included lung, which was the most common, prostate, breast, colon, stomach, rectum, pancreas, and others. The mean number of days prior to death from being placed on the Liverpool Care Pathway for the Dying Patient was 2.64 days (range 1-10 days). The doses of fentanyl and diamorphine were based on dose conversion to and the dose equivalent to oral morphine, respectively. The 24-hour equivalent opioid dose was greater in the fentanyl group compared with the

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diamorphine group by a ratio of approximately 2:1. (50 ug/hr for fentanyl and 30 mg/day for diamorphine)<sup>6</sup>. There was one crossover, placebo controlled RCT on the efficacy and safety of morphine given subcutaneously compared to if given through nebulization in 11 patients with primary or metastatic lung cancer. Patients had resting dyspnea intensity of  $>/= 3$  in a 0 to 10 scale, with 0= no shortness of breath to 10 = most severe shortness of breath. Patients were on maintenance opioids without dose adjustment for at least 72 hours prior to the study. Patients were randomly assigned to receive either (1) morphine given subcutaneously and nebulized saline for one day or (2) morphine given through nebulization and subcutaneous saline for one day. This was followed by a crossover on day 2. A median daily dose of 45 mg of morphine was the morphine equivalent of half of their maintenance opioid dose. Patients continued to receive half their maintenance dose as oral morphine equivalent<sup>7</sup>.

Outcomes were pain and dyspnea control, need for rescue opioid for breakthrough pain relief, increase in opioid doses for breakthrough pain, change in intensity of dyspnea, and incidence of adverse events.

### **Fentanyl given transdermally vs diamorphine given subcutaneously**

#### **Effectiveness**

There were no significant differences in pain control during the 4-hourly monitoring in the last 48 hours prior to death, except in the 20<sup>th</sup> hour and 8<sup>th</sup> hour prior to death, where fentanyl given as transdermal patch showed significant pain control compared to diamorphine given subcutaneously (RR 1.31, 95% CI 1.11, 1.56)<sup>6</sup>.

There was significantly lower mean number of “as required” diamorphine AND immediate release oral morphine doses for relief of breakthrough pain in the fentanyl group compared with diamorphine group in the last 24 hours prior to death (Independent t test of 12.61, p value of 0.001)<sup>6</sup>.

There were no significant differences in breakthrough pain relief between fentanyl and diamorphine groups with either “as required” diamorphine with RR of 1.07 (95% CI 0.60, 1.90) 72 hours prior to death, RR of 1.35 (95% CI 0.84, 2.18) 48 hours prior to death, and RR of 0.82 (95% CI 0.37, 1.79) 24 hours prior to death OR immediate-release oral morphine with RR of 0.93 (95% CI 0.51, 1.71) 72 hours prior to death, and RR of 0.70 (95% CI 0.29, 1.68) 48 hours prior to death.

There was significant breakthrough pain relief in the fentanyl group compared to the diamorphine group with an additional dose of subcutaneous diamorphine during the last 72 hours prior to death (RR 1.82, 95% CI 1.31, 2.52).

### Quality of Life

Not reported.

### Serious Adverse Events

Not reported.

### GRADE Summary of Findings Table

**Table 12. Transdermal fentanyl vs Subcutaneous diamorphine**

CRITICAL OUTCOMES	BASIS (No and Type Of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>EFFECTIVENESS</b>					
<b>Pain Control (controlled or uncontrolled)</b>					
48 hours prior to death	1 cohort n= 94	RR 1.03	0.85, 1.24	Inconclusive	Very low
24 hours prior to death	1 cohort n= 94	RR 1.03	0.86, 1.22	Inconclusive	Very low
8 hours prior to death	1 cohort n=94	RR 1.31	1.11, 1.56	Benefit	Very low
<b>Breakthrough pain relief (diamorphine)</b>					
72 hours prior to death	1 cohort n= 94	RR 1.07	0.60, 1.90	Inconclusive	Very low
	1 cohort	RR	0.84,	Inconclusive	Very low

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48 hours prior to death	n= 94	1.35	2.18		
24 hours prior to death	1 cohort n= 94	RR 0.82	0.37, 1.79	Inconclusive	Very low
<b>Relief of Breakthrough pain (immediate- release oral morphine)</b>					
72 hours prior to death	1 cohort n= 94	RR 0.93	0.51, 1.71	Inconclusive	Very low
48 hours prior to death	1 cohort n= 94	RR 0.70	0.29, 1.68	Inconclusive	Very low
24 hours prior to death	1 cohort n= 94	RR 0.14	0.01, 2.70	Inconclusive	Very low

## Morphine given subcutaneously vs Morphine given through nebulization

### Efficacy

There was no difference in relief of dyspnea between morphine given subcutaneously and morphine given through nebulization one hour-post administration of morphine (MD 0.00, SD -0.61, 0.61). Both routes similarly demonstrated a reduction in dyspnea scores pre vs post treatment.

### Quality of life

Not reported.

### Safety

There were no significant differences in wheezing (MD 0.00, SD -1.15, 1.15), nausea (MD 0.00, SD -1.08, 1.08), and sedation (MD 1.00, SD -0.52, 2.52) between morphine given subcutaneously and morphine given through nebulization two hours post-administration of morphine.

## GRADE Summary of Findings Table

**Table 13. Subcutaneous morphine vs Nebulized morphine**

OUTCOME	BASIS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>Efficacy</b>					
<b>Dyspnea Relief (Dyspnea Scale*)</b>					
subcutaneous vs nebulized morphine	1 cross-over RCT n=11	MD 0	-0.61, 0.61	Equivalent**	Very low
<b>Safety</b>					
*Wheezing	1 cross-over RCT n=11	MD 0.00	-1.15, 1.15	Inconclusive	Very low
*Nausea	1 cross-over RCT n=11	MD 0.00	-1.08, 1.08	Inconclusive	Very low
*Sedation	1 cross-over RCT n=11	MD 1.00	-0.52, 2.52	Inconclusive	Very low

\*Using a scale from 0 (no symptom) to 10 (worst possible symptom)

\*\*Both routes similarly demonstrated a reduction in dyspnea scores pre vs post treatment

### Certainty of Evidence

Overall certainty of evidence was rated very low. Downgrading was based on serious risk of bias as there were concerns in non-matching or non-adjustment of prognostic factors other than age, sex and diagnosis, and imprecision with small sample size in the study comparing transdermal

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fentanyl and subcutaneous diamorphine.

Certainty of evidence was rated very low as there were concerns in allocation concealment, blinding of outcome assessors, indirectness, and imprecision with small sample size in the study comparing subcutaneous morphine and nebulized morphine.

## RECOMMENDATIONS FROM OTHER GROUPS

GROUP OR AGENCY	RECOMMENDATION	STRENGTH OF RECOMMENDATION/ CERTAINTY/QUALITY OF EVIDENCE
ESMO <sup>8</sup>	Recommends the use of TD buprenorphine and TD fentanyl as the safest opioids of choice in patients with renal impairment without dose adjustment (Ahn #31,45,46)	A
ESMO  European Association for Palliative Care (EAPC) Feb 04, 2022 <sup>9</sup>  UK National Health System	Transdermal opioids are the preferred treatment in patients who are unable to swallow (Ahn #7,9,26)	
National Comprehensive Cancer Network (NCCN) <sup>10</sup>	Transdermal opioids can be used as indicated to maximize patient comfort (Ahn #1)	
WHO <sup>2</sup>	Best Practice statement  When oral or transdermal routes are not possible, the subcutaneous route is preferred over intramuscular injection as the subcutaneous route is less painful for the patient.	

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<p>German Guideline Program in Oncology (GGPO), The Association of the Scientific Medical Societies in Germany (AWMF), The German Cancer Society (DKG) and the German Cancer Aid (DKH) (cited EAPC) [9,11]</p>	<p>TD fentanyl and buprenorphine can be alternative to oral opioids as the preferred step III opioid for some patients with cancer pain</p> <p>For patients with cancer pain unable to swallow, transdermal opioids can be given as an effective, non-invasive means of opioid delivery</p> <p>The subcutaneous route for administering morphine and hydromorphone shall be the first choice alternative for patients unable to receive opioids by oral or transdermal routes.</p> <p>IV and subcutaneous infusions can be used to achieve optimum pain control inpatients unable to achieve adequate analgesia with oral and transdermal administration.</p>	<p>*GoR (0) **LoE (1)</p> <p>*GoR (0) **LoE (1)</p> <p>*GoR (A) **LoE (1+)</p> <p>*GoE (0) **LoE (3)</p>
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## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

One RCT examined the treatment costs of TD fentanyl compared with oral morphine, specifically the costs of pharmacological cancer pain management, including opioids, symptomatic drugs (i.e., those used to control opioid- induced AEs), and non- opioid drugs. The costs were significantly higher with TD fentanyl than oral morphine with a MD of \$ 11.8 (SD 11.01, 12.59). The mean difference is equivalent to twice the amount of fentanyl compared to morphine. However, the authors noted that other relevant costs (i.e., hospital admissions, visits, contacts, transportation, educational materials, and domestic support) were not included in the analysis<sup>12</sup>.

There were no studies found on subcutaneous opioids.

### PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Two RCTs comparing TD fentanyl vs oral morphine showed that among those receiving TD fentanyl, 26% (43/168) showed preference for it, while

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among those receiving oral morphine, 48% (80/165) preferred it. The opioids were given for two to four weeks and they were assessed of their preference at the end of the study (two to four weeks). [13,14] An overall rating that included pain control, good night sleep, interruption of daily activities of the patient, interruption of caregiver's activities, and troublesome side effects showed no difference between TD fentanyl and oral morphine (MD 1.00, 95% CI -0.77, 2.77)<sup>14</sup>.

There were no studies found on subcutaneous opioids.

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## 4.6 Psychosocial and spiritual care

**Question 6: Among adult cancer patients, will psychosocial and spiritual care improve symptom control, quality of life and coping with permanency of outcome?**

### RECOMMENDATIONS

1. Among adult cancer patients, **we suggest giving psychosocial care in improving quality of life and reducing maladaptive coping response.** (*Weak recommendation, very low certainty of evidence*)
2. Among adult cancer patients, **we suggest giving spiritual care in improving quality of life and quality of end-of-life care.** (*Weak recommendation, very low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- A panel member highlighted that one has to assess the psychosocial needs and intervention suitable and effective for the patient. The panel further discussed that psychosocial and spiritual care involves a multidisciplinary approach involving psychiatrists, chaplain, support groups, etc. tailored to the patient based on the needs assessment. They emphasized the need to establish a process in implementing psychosocial and spiritual care including identifying the people who will render it to the patients and their families.
- Some panel members also shared their experiences in talking and providing psychosocial and spiritual support to their patients. Patient support groups is an opportunity for patients to learn from each other and gain emotional support. One member also shared that families appreciate the suggestion of being visited by a chaplain or a spiritual leader (i.e. for anointing of the sick).
- Based from the included studies, suggested psychosocial care interventions include but not limited to (1) Cognitive behavioral therapy (Psychological support group, self-management in multimodal comprehensive coping strategy program, structured multidisciplinary intervention and web-based collaborative care intervention), (2) Music Therapy (Western Music Therapy, CM5-

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Element Music Therapy), and (3) Education (Communication Support Program, Patient-centered communication), and spiritual care interventions include but not limited to meaning-enhancing therapy, life review, dignity therapy, meditation, narrative, intercessory prayer and spiritual growth group.

## Key Findings

- There were 33 RCTs identified that evaluated the efficacy of psychosocial and spiritual care in adult cancer patients.
- Psychological intervention demonstrated improvement in quality of life, compared with usual care. It also showed benefit in reducing maladaptive coping responses. Psychological interventions did not show significant differences with usual care in reducing anxiety, avoidant coping, caregivers' burden and hopelessness, and in improving the quality of relationships, dyadic support, and caregiver's quality of life.
- Spiritual care demonstrated better quality of life and end-of-life experiences compared with usual care. It did not show a significant difference with usual care in reducing distress and anxiety.
- The overall certainty of evidence was rated very low due to non-blinding of participants, participant-reported outcomes, attrition bias, inconsistency, publication bias, and imprecision.
- There was no evidence found for peaceful death-related outcomes.

## Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. (WHO) Cancer diagnosis and treatment are often associated with substantial physical and psychosocial challenges. Psychosocial and spiritual well-being are important aspects of patients' coping with cancer and its treatment. Several psychosocial and spiritual interventions have been evaluated in cancer patients. Psychosocial interventions include theoretical approaches and therapeutic orientations such as cognitive-behavioral, psychotherapy, or non-behavioral counseling, social support, complementary or alternative mind-body and multi-component approaches<sup>1</sup>. On the other hand, spiritual care includes meaning-enhancing therapy, dignity therapy, mediation

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therapy, intercessory prayer, and spiritual care groups. Studies have shown that interventions addressing these aspects are associated with clinically relevant outcomes, including depression, end-of-life coping, and caregiver well-being<sup>2,3</sup>. Previous study limitations include varied cancer stages and small study populations. Hence, a meta-analysis may address these, and provide evidence-based efficacy for the interventions. As rates of cancer survivorship increase, psychosocial and spiritual care may equip patients to manage cancer and its treatment.

## **Review Methods**

A literature search was conducted last 04 June 2023 from database inception until June 04, 2023, through MEDLINE using the combined MeSH and keywords search on psychosocial, spiritual, cancer, and palliative care or end-of-life care. A filter was placed to include only systematic reviews, meta-analyses, clinical practice guidelines, and human studies. Only studies with outcomes of interest were included. The references to the included studies were also hand-searched to identify additional studies that may not have appeared in the database search. No language restrictions were applied. The complete search strategy is presented in the Appendix.

One systematic review was identified that could address the research question. Another search was conducted on July 9, 2023 from 01 January 2017 to 09 July 2023 through MEDLINE to update the identified systematic review. The review used the search terms for psychosocial intervention, cancer, and cancer staging. A filter was placed to include only human studies, randomized controlled trials, and clinical studies. The complete search strategy was also presented in the Appendix.

Citations were screened for eligibility based on (a) Population- adult cancer patients, (b) Intervention- psychosocial or spiritual care, (c) Control- standard care or usual care, (d) Outcome- quality of life, symptom control, coping, end-of-life care experience of patient and caregiver (e) experimental studies. Observational studies were planned to be considered in the absence of experimental studies. Pilot studies and studies with incomplete data were excluded. Risk of bias was assessed using the Cochrane Risk of Bias tool (Risk of Bias 2). Random effects meta-analysis using the inverse variance method was performed in RevMan 5.4. Pooling of results was done when possible. Adjusted effect estimates were chosen if presented. For studies with several

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post-intervention measurements, the identified primary endpoint was chosen. Significant heterogeneity was reported for I<sup>2</sup> statistic values > 50% and its sources were identified through sensitivity analysis for outlying studies. A subgroup analysis was also planned for the intervention category. The certainty of evidence was determined using the GRADE approach.

## Characteristics of Included Studies for Psychosocial Care

We identified 18 RCTs for this review. There were a total of 2,526 randomized patients and 678 caregivers. The studies included adult patients with different cancer diagnoses (colorectal, prostate, lung, breast, brain, hepatocellular, cholangiocarcinoma, gallbladder, neuroendocrine, pancreatic), with or without metastasis. There were several psychosocial interventions (Table 14) categorized into cognitive behavioral therapy (n=14 studies)<sup>4,5,6,7,9,10,11,12,15,16,17,18,19,20</sup>, counseling (n=1)<sup>14</sup>, education (n=2)<sup>8,21</sup>, and music (n=1)<sup>13</sup>. These interventions were compared with usual care. Outcomes included quality of life, distress, anxiety, and the coping strategies of patients and caregivers. Follow-up was from 2 weeks to 24 months. Anxiety was assessed using Depression Anxiety Stress Scale (DASS-21), on a 0 to 42 scale, and defined by a score of > 7. Other anxiety measures were Generalized Anxiety Disorder-7 (GAD-7) and Hospital Anxiety and Depression Scale Anxiety (HADS-A) with higher scores interpreted as greater anxiety. Distress was measured on a 0 to 10 scale, with higher scores interpreted as greater distress. Quality of Life was assessed using European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire PAL 15 (EORTC QLQ-C15-PAL), EORTC QLQ Version 1, EORTC QLQ C33, EORTC QLQ C30, FACT-G Health-related Quality of Life, Hospice Quality of Life Index-Revised (HQOLI-R), McGill Quality of Life Questionnaire (MQOL), Quality of Life Index—Cancer Version (QOLI-CV). These measures were interpreted as higher the level of functioning with higher scores, ranging from 0 to 100 and 0 to 280. Caregiver's difficulty was assessed using the caregiver's burden scale on a 0 to 70 scale, interpreted as greater burden with higher scores. Maladaptive Coping Response was used to measure Maladaptive Coping strategies, with a score range from 0 to 36, with higher score interpreted as making use of such coping strategies. Patient autonomous motivation for self-care was assessed on a 1 to 7 scale; higher scores indicate greater endorsement.

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**Table 14. Types of Psychosocial Intervention**

<b>Cognitive Behavioral Therapy</b> <ul style="list-style-type: none"><li>- Cognitive Behavioral therapy</li><li>- Mindfulness-based cognitive therapy</li><li>- Psycho-educational intervention</li><li>- Structured multi-disciplinary intervention</li><li>- Group cognitive behavior therapy</li><li>- Breathlessness intervention service</li><li>- Self-management multimodal comprehensive coping strategy program</li><li>- Individual or group support rehabilitation</li><li>- Mindfulness-based stress reduction</li><li>- Brief/ Extensive Focus</li><li>- Home-based Making Sense of Brain Tumor Program</li><li>- Individual cognitive therapy</li><li>- Psychological support group</li><li>- Web-based collaborative care intervention</li></ul>
<b>Music intervention</b> <ul style="list-style-type: none"><li>- CM five-element music therapy</li><li>- Western music therapy</li></ul>
<b>Educational Intervention</b> <ul style="list-style-type: none"><li>- Patient- centered communication intervention</li><li>- Communication-support program</li></ul>
<b>Counseling</b> <ul style="list-style-type: none"><li>- Emotionally-focused therapy</li></ul>

## Certainty of Evidence

Using the GRADE approach, we identified sources of bias, which included non-blinding of participants, participant-reported outcomes, attrition, which ranged from 20% to 64%, inconsistency, and imprecision due to small study populations ( $n < 50$ ).

## Characteristics of Included Studies for Spiritual Care

We found 15 unique studies that included 2,495 adult people living with cancer. These studies investigated the effect of spiritual care compared to usual care on patient-important outcomes identified as critical to decision making (See Table 15). There were 12 RCTs<sup>22,24, 25, 26, 27, 29, 30, 31, 32, 33, 36</sup>, two clustered RCT<sup>23, 35</sup>, and one crossover RCT<sup>28</sup>.

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All studies included adult persons living with advanced cancer. Most of the studies included participants with different types of cancer. Care settings were mostly outpatient<sup>23,35</sup>, while two (2) studies were inpatient<sup>27,36</sup> and one (1) study was from a hospice facility<sup>37</sup>. The other studies did not mention the care setting.

Spiritual care was categorized as meaning-enhancing therapy, dignity therapy, life review therapy, meditation therapy, intercessory prayer, and spiritual growth groups. Studies were categorized based on the intervention they investigated.

The initial outcomes rated as critical by the consensus panel include patient comfort and distress or anxiety. The outcome of patient comfort was merged with patient distress or anxiety since the two outcomes are related. There were no studies that investigated the composite outcome of patient distress or anxiety; hence, this evidence summary looked for studies that considered patient distress and patient anxiety as two separate outcomes. Repeated measures of the outcomes were reported in the studies. The time points seen as clinically relevant were outcomes measured immediately after the intervention and up to 3 months, whichever comes first.

**Table 15. Patient Important Outcomes**

OUTCOMES	STUDIES
Quality of Life	Chochinov et al. (2011), Hall et al. (2011), Kleijin et al (2018), Xiao et al. (2013), Cole et al. (2012), Jafari et al. (2013), Amir et al. (2015), Breitbart et al. (2018), Hansen et al. (2009), Piderman et al. (2014), Rodin et al. (2018), Duggleby et al. (2007), Olver (2012)
Patient Distress	Chochinov et al. (2011), Hall et al. (2011), Vuksanovic et al. (2016), Kleijin et al. (2018), Xiao et al. (2013), Breitbart et al. (2018), Rodin et al. (2018)
Patient Anxiety	Chochinov et al. (2011), Hall et al. (2011), Vuksanovic et al. (2016), Kleijin et al. (2018), Breitbart et al. (2018), Rodin et al. (2018), Moeini et al. (2014)
Patient autonomy in end-of-life decisions	None
Peaceful death/dignified death	None
Quality of end-of-life care (patient)	Cole et al. (2012)

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Quality of end-of-life care (family)	None
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Different tools were used in the included studies to measure the outcomes. Quality of life measures were the McGill Quality of Life Scale, the EORTC Quality of Life C-30 Questionnaire, the Quality of Life Rating, and FACIT, which can be interpreted as the higher the score, the better the quality of life. Patient distress was measured using the Death and Dying Distress Scale (DADDS), Dignity-related distress (Patient Dignity Inventory), and Hospital Anxiety and Depression Scale (HADS) total, which can be interpreted as the higher the score, the greater the distress. For patient anxiety, it was measured using the HADS-Anxiety subscale and Generalized Anxiety Disorder-7 (GAD-7), which can be interpreted as the higher the score, the greater the anxiety. The quality of end-of-life care (patient's experience) was evaluated using a post-session evaluation using a 7-point scale, with higher scores indicating a more positive endorsement.

## Efficacy Outcomes for Psychosocial Care

### Quality of Life

Our findings on the quality of life suggested benefit for patients assigned to psychosocial interventions (cognitive behavioral therapy, education, and music) compared with usual care ( $SMD\ 0.77$ , 95% CI  $0.25$ ,  $1.30$ ;  $I^2= 94\%$ , 10 RCTs,  $n=1,190$ , very low certainty of evidence). We did not identify studies on other psychosocial interventions, like counseling, and writing on its efficacy in improving quality of life.

### Anxiety and Distress

Findings from our meta-analysis did not support the efficacy of psychosocial intervention for reducing anxiety ( $SMD\ -0.42$ , 95% CI  $-1.01$ ,  $0.18$ ), 7 RCTs,  $n=919$ ,  $I^2=94\%$ , very low certainty of evidence) and distress ( $MD\ -0.99$ , 95% CI  $-2.58$ ,  $0.60$ , 1 RCT,  $n=54$ , very low certainty of evidence)

### Peaceful death/ dignified death

No studies were identified.

### Patient's autonomy in end-of-life decisions

Our findings did not support the efficacy of psychosocial intervention (behavioral cognitive therapy) for increasing autonomy ( $MD\ 2.61$ , 95% CI  $-3.88$ ,  $9.10$ , 1 RCT,  $n = 203$ , very low certainty of evidence).

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## **Quality of end-of-life care (patient experience)**

Our findings demonstrated benefit for reducing maladaptive coping responses (MD -0.21, 95% CI -0.33, -0.09, 1 RCT, n = 30, low certainty of evidence) for patients assigned to psychosocial intervention (cognitive behavioral therapy) compared to usual care.

It did not support the intervention's efficacy for (a) improving active behavioral coping of patients (SMD 1.13, 95% CI -0.26, 2.52, 4 RCTs., n=509, very low certainty of evidence) (b) avoidant coping (aMD -0.06, 95% CI -0.15, 0.04,  $I^2 = 0\%$ , 1 RCT, n=203, very low certainty of evidence), (c) quality of relationship (MD 0.51, 95% CI -0.44, 1.45,  $I^2 = 0\%$ , 1 RCT, n=203, very low certainty of evidence), and (d) dyadic support (aMD 0.05, 95% CI -0.07, 0.18,  $I^2 = 0\%$ , 1 RCT, n=203, very low certainty of evidence).

## **Quality of end-of-life care (family experience)**

Our findings did not support the efficacy of psychosocial intervention (behavioral cognitive therapy and counseling) for improving the quality of life of caregivers (MD 0.30, 95% CI -7.07, 7.67, 1 RCT, n = 116, low certainty of evidence) and reducing caregiver's difficulty (MD -0.14, 95% CI -0.77, 0.49, 1 RCT, n = 72, very low certainty of evidence) and hopelessness (MD 1.55, 95% CI -0.63, 3.73, 1 RCT, n = 72, very low certainty of evidence).

## **Summary of Findings Table**

**Table 16. Psychosocial Intervention vs Usual Care**

<b>CRITICAL OUTCOMES</b>	<b>BASIS (No and Type Of Studies, Total Participants)</b>	<b>EFFECT SIZE</b>	<b>95% CI</b>	<b>INTERPRETATION</b>	<b>CERTAINTY OF EVIDENCE</b>
Quality of Life (Patient)	10 RCTs n=1,190	SMD 0.77	0.25, 1.30	Benefit	Very low
Anxiety	8 RCTs n=973	SMD - 0.39	-0.93, 0.15	Inconclusive	Very low
Physical distress	1 RCT n=54	MD - 0.33	-0.87, 0.21	Inconclusive	Very low

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	1 RCT n=35	U-test score 149 Median I-25 C-27	p 0.90	Inconclusive	Very low
Autonomy	1 RCT (2 intervention arms)  n=203	aMD 2.61	-3.88, 9.10	Inconclusive	Very low
Maladaptive coping response	1 RCT n=30	MD - 0.21	-0.33, - 0.09	Benefit	Low
Active behavioral coping	4 RCTs n=509	SMD 1.13	-0.26, 2.52	Inconclusive	Very low
Avoidant coping	1 RCT (2 intervention arms) N=203	aMD - 0.06	- 0.15,0.04	Inconclusive	Very low
Quality of Relationship	1 RCT (2 intervention arms) n=203	aMD 0.51	-0.44, 1.45	Inconclusive	Very low
Dyadic support	1 RCT (2 intervention arms) n=203	aMD 0.05	-0.07, 0.18	Inconclusive	Very low
Quality of Life (Caregiver)	1 RCT n=116	MD 0.30	-7.07, 7.67	Inconclusive	Low
Caregiver's Difficulty	1 RCT n=72	MD - 0.14	-0.77, 0.49	Inconclusive	Very low

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Caregiver's hopelessness	1 RCT n=72	MD 1.55	-0.63, 3.73	Inconclusive	Very low
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## Certainty of Evidence for Psychosocial Care

We considered the overall certainty of the evidence for our critical outcomes to be very low. Non-blinding of participants, use of participant-reported outcomes, attrition, inconsistency, and imprecision owing to a small sample size resulted in the downgrading of the certainty of evidence.

## Efficacy Outcomes for Spiritual Care

### Quality of Life

Based on 13 RCTs, the effect size showed a beneficial effect of spiritual care on the quality of life of adult persons living with advanced cancer compared to usual care (SMD 0.44, 95% CI 0.13, 0.75,  $I^2 = 86\%$ ). Sub-grouping based on the type of spiritual care that was given showed that dignity therapy (SMD -0.02, 95% CI -0.27, 0.23,  $I^2 = 0\%$ ) and intercessory prayer (SMD -0.06, 95% CI -0.21, 0.10) revealed harmful effects, but results were inconclusive. While life review therapy (SMD 0.87, 95% CI, -0.69, 2.43,  $I^2 = 96\%$ ), meditation therapy (SMD 1.23, 95% CI -0.57, 3.03,  $I^2 = 93\%$ ), narrative therapy (MD 0.44, 95% CI -0.08, 0.96) and meaning-enhancing therapy (SMD 0.22, 95% CI, -0.17, 0.61,  $I^2 = 79\%$ ) revealed beneficial effects, the results were inconclusive.

### Patient Distress

Based on 7 RCTs, psychosocial care showed harmful effects (SMD 0.15, 95% CI, -0.14, 0.43,  $I^2 = 73\%$ ), although the result was inconclusive. Sub-grouping based on the type of spiritual care given showed that dignity therapy (SMD 0.05, 95% CI -0.19, 0.28,  $I^2 = 0\%$ ) and life review therapy (SMD 0.43, 95% CI -0.40, 1.27,  $I^2 = 88\%$ ) revealed harmful effects but inconclusive results, while meaning-enhancing therapy (SMD -0.13, 95% CI -0.33, 0.07,  $I^2 = 0\%$ ) revealed benefit but results were inconclusive.

### Patient Anxiety

Based on 7 RCTs, the effect size showed beneficial effects (SMD -1.14, 95% CI, -2.34, -0.06,  $I^2 = 82\%$ ) but an inconclusive result. Sub-grouping based on the type of spiritual care given showed that dignity therapy (SMD 0.25, 95% CI -0.28, 0.77,  $I^2 = 0\%$ ) revealed harmful effects but inconclusive results. While life

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review therapy (SMD -0.70, 95% CI, -2.28, 0.88) revealed beneficial effects but an inconclusive result, meaning-enhancing therapy (SMD -3.04, 95% CI, -5.52, -0.56,  $I^2=86\%$ ) revealed beneficial results.

### **Quality of end-of-life care (patient's experience)**

One cross-sectional study done among patients included in an RCT investigated the quality of end-of-life care of the participants after receiving the intervention, and it revealed that 78% (36 of 46) preferred programs that included spirituality, 2% (1 of 46) preferred secular programs, and 29% (9 of 47) had no preference. Program evaluations were equivalent for both intervention conditions regarding how helpful and relaxing sessions were, how close they felt to the therapist, and how helpful the person was<sup>25</sup>.

No studies were found that investigated the quality of end-of-life care (family's experience), patient autonomy in end-of-life decisions, peaceful or dignified death, or safety outcomes.

**Table 17. Spiritual Care vs Usual Care for Adults with Cancer**

CRITICAL OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Quality of Life 1-28 days of follow-up	13 RCTs (n=1,794)	SMD 0.44	0.13, 0.75	Benefit	Very low
Patient Distress 1-90 days of follow-up	7 RCTs (n= 862)	SMD 0.15	- 0.14, 0.43	Inconclusive	Low

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Patient Anxiety	7 RCTs (n=805)	SMD - 1.14	-2.34, 0.06	Inconclusive	Very low
Quality of end-of-life care (patient experience)  1 day of follow-up	1 RCTs	The study of Cole (2012), revealed that 78% (36 of 46) preferred programs that included spirituality, 2% (1 of 46) preferred secular programs, and 29% (9 of 47) had no preference.  Program evaluations were equivalent for both intervention conditions regarding how helpful and relaxing sessions were, how close they felt to the therapist, and how helpful the person was.		Benefit	Moderate

## Certainty of Evidence of Spiritual Care

The overall certainty of evidence across all the critical outcomes for spiritual care vs. usual care is very low. Most of the studies had a serious risk of bias; a particular concern is the lack of blinding. Thus, introducing performance and detection bias. Inconsistency was serious due to substantial heterogeneity; point estimates across studies varied widely, and interval estimates showed minimal overlaps. Indirectness and imprecision among the included studies were not serious. Publication bias is present in some of the pooled studies.

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## RECOMMENDATIONS FROM OTHER GROUPS

GROUP OR AGENCY	RECOMMENDATION	QUALITY OF EVIDENCE (QE), STRENGTH OF RECOMMENDATION (SR)
Evidence-based European guidelines on the management of depression in palliative cancer care	Clinicians should consider psychological therapy for the treatment of depression in palliative care.	QE: High SR: Strong
American Society of Clinical Oncology (ASCO) 2018	There should be access to spiritual care from professionals who have the necessary training in all contexts, whether locally or through referral. In addition to providing direct patient care, spiritual care providers may advise and support the care team in supporting the patients and their families. Nurses or counselors may be trained to assess the spiritual needs of patients and their families. Providers should be observant of and sensitive to the religious norms of patients and families.	QE: insufficient SR: weak
Clinical practice guideline for oncology nurses in Iran (2020)	<p>1. All healthcare centers in the second and third levels of the healthcare system, including Public hospitals, specialized hospitals, hematology, and oncology wards, and palliative care units, specialized clinics, and centers for taking care of cancer patients, should be able to present some level of spiritual care alongside other care dimensions for patients with cancer, both inpatient and outpatient.</p> <p>2. Spiritual care for patients with cancer can be provided while providing hospital-based or community-based home care.</p> <p>3. The spiritual care team can work at the country's third healthcare system level (oncology wards and palliative care units of specialized hospitals) and at the community</p>	QE: IV SR: weak  QE: IV SR: weak  QE: IV SR: weak

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	level to provide home care services.	
ESMO 2023	<p>The combination of psychotherapeutic and psychopharmacological modalities for treating anxiety and depression is more efficacious than single treatment alone and is therefore recommended [I, A].</p> <p>In patients with anxiety and depressive symptoms, the following therapies should be considered: CBT, MBT, psychoeducation, and supportive-expressive therapies.</p> <p>Meaning-centered therapy and dignity therapy are recommended in specific cancer settings (e.g., end-of-life)</p>	<p>QE: I SR: A</p> <p>QE: I SR: B</p> <p>QE: I SR: A</p>

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION PHASE

### COST (Resources Required)

No direct evidence is available for people living with cancer who suffer from mental, psychosocial, and/or spiritual illness. The data on cost is based on the data on general mental illness from a societal perspective.

#### Economic Burden of Mental Health

##### *Direct costs*

The total Philippine budget for mental health (excluding PhilHealth, capital costs, and infrastructure) was 2 590.6 million PHP (US\$ 51.4 million) in 2019. Total PhilHealth subsidies for inpatient and outpatient mental health care during 2019 amounted to 99.6 million PHP (US\$ 2 million). It was not possible to break down government health spending by mental health issues.

##### *Indirect costs*

The indirect economic losses caused by mental health conditions were estimated as the sum of losses due to absenteeism, presenteeism, and premature death. The total number of working days absent was estimated to be 36.2 million for absenteeism and 19.9 million for presenteeism. Absenteeism and presenteeism costs are the highest for anxiety disorders.

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Although anxiety is associated with fewer days off work than depression for the average individual, the estimated prevalence of anxiety in the Philippines is much higher than that for depression. The total costs of premature death due to mental health conditions were estimated to be 10,140 million PHP (US\$ 201 million) in 2019.

The table shows the total direct and indirect costs of mental health conditions in the Philippines. The indirect economic losses are much higher than the direct losses. Total Government expenditure on health care for mental health conditions was 2,591 billion PHP (US\$ 51.4 million), and PhilHealth provided 100 million PHP (US\$ 2.0 million) in health care subsidies. In addition, the economic losses due to absenteeism, presenteeism, and premature death amounted to 66.2 billion PHP (US\$ 1.31 billion).

**Table 18. Economic burden of mental health conditions in the Philippines (2019 PHP, millions)**

COST	TOTAL COST (2019 PHP, MILLIONS)	TOTAL COST (2019 US DOLLAR, MILLIONS)
<b>Direct Cost</b>		
Health care		
Health care expenditure	2,591	51.4
Disability support payments	100	2.0
Total direct costs	2,691	53.4
<b>Indirect costs</b>		
Absenteeism	36,170	717.7
Presenteeism	19,861	394.1
Premature deaths	10,140	201.2
Total indirect costs	66,171	1,312.9
<b>TOTAL</b>	<b>68,861</b>	<b>1,366.3</b>

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The total economic burden of the selected mental health conditions on the Philippine economy in 2019 was 68.9 billion PHP (US\$ 1.37 billion), equivalent to 0.41% of the GDP in 2018.

### **Costs of Intervention**

The costs of the interventions were estimated for the period 2020–2024. The table shows the absolute costs during the first five years of this period plus the 10-year and 20-year total costs. Data for other mental health illnesses was not included in the data presented in the table below.

Interventions involving intensive psychosocial treatment and anti-depressant medication have large, planned costs. Nevertheless, numerous low-cost interventions exist, including basic psychosocial treatment (for anxiety disorders and depression in particular).

**Table 19. Estimated absolute costs of interventions (PHP, millions), 2020–2040**

MENTAL HEALTH INTERVENTION PACKAGE	2020	2021	202 2	2023	202 4	TOTAL FOR 10 YEARS	TOTAL FOR 20 YEARS
Anxiety disorders	203	344	488	634	783	10,438	24,671
Depression	202	289	380	472	567	7,410	16,859

### **Cost-effectiveness**

No cost-effectiveness studies were found

### **EQUITY**

There is no direct evidence regarding the availability of mental and psychosocial care services for adults living with cancer. The data that will be presented is about the general mental health services provided in the Philippines. In a joint effort between the Psychosocial Support and Children's Rights Resource Center and the Mental Health and Psychosocial Support Network, in collaboration with the Department of Health (National Center for Mental Health) and with funding from the World Health Organization (WHO), Philippines attempted to map and assess the mental and psychosocial support in the country in 2014 after Typhoon Haiyan (Yolanda) struck the country. The mapping was done in order to have a better understanding of the situation. Due to the fact that most government

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institutions, as well as foreign and local non-governmental groups, were occupied with disaster and relief responses, it was challenging to gather accurate data for the country. The NCR, Region IV B, Region VI, Region VII, Region VIII, and the Hong Kong consulate have responded. These regions of the country have 77 significant players in mental health and psychosocial assistance and ten collaborating partners, according to the findings. Psychosocial work (person-focused), psychological therapies, and general MHPSS support activities were the main activities given to patients. Learning about and, when appropriate, partnering with local, indigenous, and traditional health systems to reduce the harm caused by drinking and other drug use, the coordinated inclusion of certain social factors (safe, respectful, culturally, and societally appropriate support) in site planning and shelter supply, as well as the provision of water and sanitation, were among the activities that none of the agencies mentioned they provide.

## ACCEPTABILITY

The United Nations on the Rights of Persons with Disabilities states that it is important to safeguard all people with disabilities from prejudice based on their conditions. Long-term physical, mental, intellectual, or sensory impairments are among those that define a person with a disability. In addition, the Universal Declaration of Human Rights guarantees everyone the right to a standard of living sufficient for their own health and well-being and that of any members of their family. This covers necessities, including food, clothing, housing, health care, and social services. Additionally, encouraged is the right to security in case of illness or incapacity.

The Sustainable Development Goals include mental health as one of their goals under the target to strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful alcohol use, as an essential component of universal health coverage and the target to reduce premature mortality from non-communicable diseases by one-third through prevention and treatment.

In the Philippines, Republic Act No. 11038 (2018), also known as the Mental Health Act, establishes a national mental health policy to ensure that all Filipinos have access to the fundamental right to mental health and to protect those who need services to be made available to the general public. It also mandates the education and promotion of mental health in workplaces and educational institutions, as well as the requirement to conduct research and development on the topic.

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The Magna Carta for Persons with Disabilities (RA No. 10754), the Universal Health Act (RA No. 11223), the Operational Framework for the Sustainable Establishment of a Mental Health Program (DOH AO No. 2007-0009), and the Revised Operational Framework for a Comprehensive National Mental Health Program are additional laws and regulations.

## FEASIBILITY

The DOH's Mental Health Strategic Plan 2019–2023 (2019) states that mental healthcare is not given high priority in the Philippines. A study sponsored by the Philippine Consortium for Health Research Development (PCHRD) that intended to outline the country's mental health research agenda identified significant gaps in the mental health program and services. The identified deficiencies include inadequate mental health data for program design and implementation as well as service delivery, poor mental health governance, and a lack of mental health services relative to the high demand from the 110 million Filipinos. The absence of proactive efforts to advance mental health and well-being and avoid mental diseases is a critical gap.

In the Philippines, there are a pitiful number of mental health specialists who offer mental and psychological care. According to the strategic plan, there are 2,051 paid mental health employees in government and private institutions, including psychiatrists, child psychiatrists, doctors, nurses, psychologists, social workers, occupational therapists, and other paid mental health specialists. According to this information, there would be 2.02 mental health professionals for every 100,000 Filipinos (WHO, 2018). According to data broken down by type of mental health care provider, there were 0.518 psychiatrists, 0.885 psychologists, 0.30 occupational therapists, and 0.26 speech therapists per 100,000 people in the mental health sector. Comparing these figures to the WHO's global aim of ten psychiatrists per 100,000 people sheds light on the lack of a health workforce for mental health. To compound the issue, most psychiatrists are headquartered in urban regions, particularly in the national capital region, and work in for-profit organizations or private clinics<sup>45</sup>.

The accessibility of mental health care in the Philippines is inadequate. Additionally, it has been demonstrated that perceived or internalized stigma prevents Filipinos from getting help, much as it does for Western populations<sup>45</sup>. Filipinos may struggle to acknowledge mental health issues or seek help because of the cultural need to "save face" when one's social standing is threatened or lost. Since there is a strong sense of family in the Philippines, people will first resort to their family and peer networks when they believe their problems are social in nature<sup>49</sup>.

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## 4.7 Advance Care Planning and satisfaction and perception of care

**Question 7: Among adult cancer patients, will advance care planning increase patients' and families' satisfaction and perception of care?**

### RECOMMENDATION

**We suggest that advance care planning be offered early to adult cancer patients and their families.** (*Weak recommendation, very low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The panel highlighted that the advance care planning is done to enable any person to express their values and preferences for their end-of-life care.
- Advance Care Planning doesn't have to be offered only at the end-of-life. It can also be discussed during the early course of the disease. However, consideration be given to families who may not be comfortable in discussing these concepts early on.
- The panel had a discussion on who to consider part of the patient's family. In advance care planning it is the patient and the family who decide/give consent. In case the patient is no longer able, the law determines who will make the decision for the patient.
- Advance Care Planning could be initiated by anyone who is knowledgeable and comfortable on how to do it. However the panel emphasized that not all public hospitals underwent training on palliative care. There is a need to equip the healthcare providers with knowledge and skills in Advance Care Planning.

### Key Findings

- Included in this evidence summary are four randomized controlled trials and one nonrandomized controlled trial.
- On the outcome of families' distress or anxiety, one study showed benefit in the context of meetings when given advance care planning, while another showed inconclusive results.
- On the outcomes of quality of life, patient and family/caregiver

satisfaction with healthcare, patient autonomy, and having a peaceful/dignified death, studies reviewed showed inconclusive results to support the use of ACP.

- Three studies had a high risk of bias issues as there were concerns about missing outcome data and blinding.
- Overall certainty of the evidence for all outcomes was downgraded to very low due to varying risks of bias and imprecision.

## **Background**

According to a study by Lanaban et al., there are three interrelated notions of a good death and dying among patients with cancer and their caregivers and among health care providers, namely—the recognition that something external to the self is controlling life and death, including the time and place of death and the circumstances around it; one can have a good death if one is ready for it; and, physical and emotional comfort while one is dying makes for a good death<sup>1</sup>. The cancer patient's values and preferences regarding end-of-life (EOL) decisions can be discussed through advanced care planning (ACP).

Advanced care planning is a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. It is generally recommended as part of routine palliative care, but good-quality evidence must still be provided to support these recommendations. In palliative care, it is logical that advanced care planning must be done. However, it is also logical that patients and their families will feel intense emotions when facing these concepts. Recent RCTs have yet to improve QOL with the application of advanced care planning.

## **Review Methods**

A systematic search was done from the date of the last search, February 6-March 14, 2023, using Medline, Cochrane Library, Ovid, and Google Scholar with a combined MeSH and free text search using "advance care planning" OR "advance directives" OR "living will" OR "goals of care" OR "anticipatory care" OR "healthcare directive" OR "healthcare decisions at the end-of-life" AND cancer AND satisfaction.

Studies included are randomized controlled trials and non-randomized controlled trials comparing advance care planning to no advance care

planning or usual care planning. Trials that included adults, 18 years old and above, with cancer regardless of histologic type or stage, their families, and healthcare providers were included. Only data from cancer patients were included in trials that included both cancer and non-cancer patients. Studies whose intervention included discussions with patients and/or their representatives about the goal and desired direction of patient care, particularly end-of-life care, in the event the patient is or becomes incompetent compared to usual care or no advanced care planning was included. Outcomes identified as critical and considered included are patient or family satisfaction, quality of life, perception of care, patient or family's distress or anxiety, peaceful or dignified death, patient autonomy for end-of-life decisions, and well-coordinated care.

Risk of bias assessment using the revised Cochrane risk-of-bias assessment tool (ROB 2) was done in the included studies. A narrative synthesis was created using the evidence gathered. Pooling of results was planned.

## Results

We found four (4) RCTs and one (1) non-RCT that included 648 cancer patients and their family members/caregivers. One trial from Denmark included patients with lung, heart, and cancer diseases with an estimated lifespan of up to 12 months<sup>2</sup> but only data from cancer patients were extracted. Another RCT from the United Kingdom included patients who had completed a primary course of treatment for cancer but still had clinically detectable, active, progressive disease<sup>3</sup>. A feasibility randomized trial from Scotland included patients starting palliative oncology treatment for newly diagnosed incurable pancreatic or upper gastrointestinal cancer in the primary care setting<sup>4</sup>. A study from Taiwan included patients from a medical center identified by their oncologist as having terminal cancer<sup>5</sup>.

Intervention in one trial consisted of a one-to-one conversation with a trained care planning mediator using a checklist of topic domains. Discussions explored patients' perceptions of their current situation, their communication with health professionals and significant others, and their hopes and fears for the future and about making future healthcare decisions<sup>3</sup>. The intervention in another trial consisted of a single discussion between the first author and the patient inspired by other ACP programs (Gold Standard Framework, 2016)<sup>2</sup>.

Patients were encouraged to reflect on end-of-life issues, concerns in general, preferred place of care (PPOC), preferred place of death (PPOD), preferences for life-prolonging treatment, and cardiopulmonary resuscitation<sup>2</sup>.

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The trial by Tang et al. used a theory-based, individualized, interactive ACP intervention that has five (5) major components: (1) repeated assessments of participants' readiness to engage in ACP, (2) specific sub-interventions tailored to participants' readiness to engage in ACP, (3) facilitation physician-patient EOL care discussions, (4) use of a booklet and video educational aid to facilitate understanding of ACP and Life Sustaining Therapies (LSTs) at EOL, and (5) psychological support of participants while engaged in EOL care decision-making.<sup>5</sup>

The RCT of Canny et al., the intervention was a personal letter developed with a patient-public involvement (PPI) group signed by their oncologist to help them make an appointment to discuss ACP with their general practitioner (GP). The GP follows the Scotland 'RED-MAP' communication framework (2019) for ACP discussion.

Quality of life (QOL) outcomes were measured using a validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15. This questionnaire was developed for patients with advanced cancer in palliative trajectories. All items are rated on 4-point Likert scales that range from 1 (not at all) to 4 (very much), with the exception of the global health/quality of life scale, which is rated from 1 (very poor) to 7 (excellent). The higher the score, the better. Another tool that was used was the EuroQol EQ-5D-5L. EQ-5D-5L, the descriptive system, comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patients in the study were asked to indicate their health state to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. EQ VAS is scored from 0 to 100, where 0 is the worst health you can ever imagine and 100 is the best health you can ever imagine.

The patient's distress and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS). This standardized tool measures anxiety (seven items) and depression (seven items) with good reliability and validity. Data from the subscale of anxiety was extracted from the study. Results can range from 0-21, with a higher score meaning more anxiety symptoms. In one trial, subscales from the validated scale, Symptom Checklist, 92-item version (SCL-92), were used. Each item's responses were scored on a five-point rating scale ranging from 0 ('not at all') to 4 ('extremely'). The SCL-92 applies to both

patients and relatives.

Patients' perception of care and satisfaction in one trial was measured using five statements the authors made about the degree of healthcare satisfaction. Each word was scored on VAS 0-10 in the direction of increasing satisfaction<sup>3</sup>. In another trial, patient satisfaction was measured using the 16-item FAMCARE-Patient scale. This scale is a self-reported questionnaire using a five-point Likert scale from 1 ('very dissatisfied') to 5 ('very satisfied').

Patients' autonomy for end-of-life decisions in one trial was measured using ICECAP-SCM well-being measures. The ICECAP-SCM has seven well-being domains, and the domain of choice ("having a say") was considered to reflect the patient's autonomy<sup>4</sup>. The study of Jones et al. used VAS (0-10) on five statements that the authors made about discussions with professionals, family, and friends about the future in the direction of increasing discussion.

Peaceful death/Dignified death was measured using ICECAP-SCM well-being measures. We used the domain of dignity (being able to maintain my dignity and self-respect) to determine this outcome.

The family's distress or anxiety was measured using the Symptom Checklist, a 92-item version (SCL-92), and HADS A.

Family's perception of care and satisfaction was measured in one trial using a 19-item FAMCARE scale, a self-reported questionnaire using a five-point Likert scale from 1 ('very dissatisfied') to 5 ('very satisfied').

Well-coordinated care/better interdisciplinary care, one study measured the time in weeks between multidisciplinary cancer team meetings and events (first GP contact, death, specialist palliative care referral). Another study used VAS (0-10) on the authors' statements about communication levels with professionals. The higher the score, the better. Another study used CollaboRATE; it used a 0-9 scale where 0 (no effort made) to 9 (every effort was made).

## **Effectiveness of ACP vs. No ACP or Usual Care**

### **Quality of Life**

Two RCTs have studied ACP's effects on cancer patients' quality of life with 99 participants<sup>2,4</sup>. One RCT evaluated QOL using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15<sup>2</sup>. Another RCT used the EuroQol EQ-5D-5L<sup>4</sup>. Results of

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both studies in all follow-ups showed that the ACP group had a better quality of life than the control group, but the results were inconclusive (See Table 20). The results at six weeks of the two studies were not pooled because one study did not have the measure of variation of its mean.

### **Patient's Distress or Anxiety**

Two studies (RCTs) reported the effect of ACP on the anxiety of 95 cancer patients<sup>2,3</sup>. The study by Jones et al. used Hospital Anxiety and Depression Scale (HADS); the results were equivalent. Anxiety symptoms in the study of Skorstengaard et al. were measured using subscales from the validated scale Symptom Checklist, 92-item version (SCL-92); results were equivalent (See Table 20).

### **Patient's Perception of Care and Satisfaction**

Two RCTs had data that studied the effect of ACP on 102 cancer patients' satisfaction with healthcare<sup>2,3</sup>. Jones et al. used five statements the authors made about the degree of healthcare satisfaction; the results were inconclusive. The study of Skorstengaard et al. measured patient satisfaction with healthcare using the 16-item FAMCARE-Patient scale. Results showed that patients who did not receive ACP were more satisfied than those receiving ACP, but the results were inconclusive (See Table 20).

### **Patient Autonomy for End-of-life Decisions**

Two RCTs had data that studied the effects of ACP on 71 cancer patients' autonomy<sup>3,4</sup>. Canny et al. used the ICECAP-SCM well-being measures. Results showed inconclusive findings. The other study by Jones et al. used VAS (0-10) on five statements the authors made about discussions with professionals, family, and friends about the future; the results were inconclusive (See Table 20).

### **Peaceful Death/Dignified Death**

One RCT had data that studied the effect of ACP on having a dignified death<sup>4</sup>. The study used ICECAP-SCM well-being measures. The results were inconclusive.

### **Family's Distress or Anxiety**

Two RCTs had data that studied the effects of ACP on family distress or anxiety<sup>2,5</sup>. The study of Skorstengaard used the Symptom Checklist, a 92-item

version (SCL-92); results showed that patients in the ACP group had more anxiety symptoms than the control group during 4-5 weeks of follow-up, but the results were inconclusive. Tang et al. used Hospital Anxiety and Depression Scale (HADS) of combined patients and family members. The result of the scale of anxiety was considered in this review. The study Tang showed beneficial effects of ACP, where they observed fewer anxiety symptoms in the ACP group at 5-6 follow-up periods ( $\beta=0.58$ , 95% CI -0.98, -0.19) (See Table 21).

### **Family's Perception of Care and Satisfaction**

One RCT with 125 participants had data that studied the effect of ACP on family satisfaction with care<sup>2</sup>. The study used the 19-item FAMCARE scale. The study reviewed showed that families who did not receive ACP were more satisfied than those who received it, but the results were inconclusive.

### **Well-coordinated Care/Better Interdisciplinary Care**

Two RCTs and one non-RCT with 133 participants had data that studied the effect of ACP on well-coordinated care/better interdisciplinary care<sup>3,4</sup>. One study measured the time between multidisciplinary cancer team meetings and events (first GP contact, death, specialist palliative care referral), results showed that patients who received ACP had a shorter time in weeks to have first GP contact which the effect of intervention favors ACP, and death but results were inconclusive. While having a specialist palliative care referral took longer for the ACP group, the impact of intervention favors usual care. With the use of CollaboRATE tool, patients who received ACP thinks that every effort was made to arrive at a shared decision compared to those who did not receive it during the 12 and 24-week follow-up period but felt otherwise during the six and 48-week follow-up, but the results showed inconclusive findings. The other study used VAS (0-10) on the authors' statements about communication levels with professionals<sup>3</sup>. Results showed patients who received ACP are more happy with the level of communication with professionals compared to those who did not have ACP, but the results were inconclusive.

## GRADE Summary of Findings

**Table 20. Advance Care Planning vs. No Advance Care Planning/Usual Care for Patients with Cancer**

CRITICAL OUTCOME	BASIS (no. and type of studies, Total participants)	EFFECT SIZE	95% CI	INTERPRE-TATION	CERTAINTY OF EVIDENCE
<b>Quality of Life</b>					
ff-up 4-5 weeks	2 RCT, 99	MD - 0.13	-0.90, 0.64	Inconclusive	Very low
ff-up 6 weeks		MD - 0.05	-0.17, 0.07	Inconclusive	Very low
ff-up 12 weeks		MD 0.09	-0.09, 0.27	Inconclusive	Very low
ff-up 24 weeks		MD 0.12	-0.08, 0.32	Inconclusive	Very low
ff-up 48 weeks		MD - 0.33	-1.23, 0.57	Inconclusive	Very low
<b>Patient's distress or anxiety</b>					
ff-up 4-5 weeks	2 RCT and 1 non-RCT, 133	MD - 0.01	-0.24, 0.22	Equivalent	Very low
ff-up 8 weeks		MD 0	-1.34, 1.34	Inconclusive	Low
<b>Patient's perception of care and satisfaction with healthcare</b>					
ff-up 4-5 weeks	2 RCT, 102	MD 0.07	-0.15, 0.98	Inconclusive	Very low

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ff-up 8 weeks		MD 2.1	-1.31, 5.51	Inconclusive	Low
<b>Patient's Autonomy</b>					
ff-up 8 weeks	2 RCT and 1 non-RCT, 129	MD - 0.9	-7.05, 5.25	Inconclusive	Low
ff-up 6, 12, 24, 48 weeks		Regarding the domain of choice in the ICECAP-SCM, the majority in both groups stated, "I am able to make decisions that I need to make about my life and care most of the time" during the follow-up periods (100% vs. 100%). Except for week 12, where some of the participants in both groups stated, "I am able to make decisions that I need to make about my life and care some of the time" (8% vs. 17%)		Inconclusive	Very low
<b>Peaceful Death or Dignified Death</b>					
ff-up 6, 12, 24, 48 weeks	1 RCT, 33	Regarding the domain of dignity in the ICECAP-SCM, all participants in both groups stated, "I am able to maintain my dignity and self-respect most of the time" during the follow-up		Inconclusive	Very low

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		periods (100% vs. 100%). Except for weeks 6 and 12, where some of the participants in the ACP group stated, "I am able to maintain my dignity and self-respect some of the time" (6% vs. 0%) and (15% vs. 0%), respectively		
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**Table 21. Advance Care Planning vs. No Advance Care Planning/ Usual Care for Cancer Patients and their Caregiver/Family**

CRITICAL OUTCOME	BASIS (no. and type of studies, Total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>Anxiety</b>					
ff-up 4- 5 weeks	2 RCT, 495	MD -0.07	-0.36, 0.22	Inconclusive	Very low
ff-up 5-6 weeks		$\beta$ - 0.58*	-0.98, - 0.19	Benefit	Moderate
<b>Family's Perception of Care and Satisfaction</b>					
ff-up 4-5 weeks	1 RCT, 127	MD 0.12	-0.10, 0.35	Inconclusive	Very low

\*negative beta coefficient indicates lower anxiety scores in the intervention group

**Table 22. Advance Care Planning vs. No Advance Care Planning/Usual Care for Healthcare Providers Giving Care to Cancer Patients**

CRITICAL OUTCOME	BASIS (no. and type of studies, Total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>Well-coordinated Care/Better Interdisciplinary Care</b>					
MDT* review meeting to first GP contact	2 RCT and 1 non-RCT, 133	MD 4.8	0.17, 9.42	Benefit	Very low
MDT review meeting to death		MD 0.7	-10.58, 11.97	Inconclusive	Very low
MDT review meeting to SPC referral		MD - 12.3	-22.23, -2.37	Harm	Very low
CollaboRATE ** Ff-up 6 weeks		MD 0.86	-6.56, 8.28	Inconclusive	Very low
Ff-up 12 weeks		MD – 3.3	-11.92, 5.32		
Ff-up 24 weeks		MD – 2.78	-10.40, 4.84		
Ff-up 48 weeks		MD 11.11	-15.61, 37.83		
Happiness with communication with		MD - 0.4	-3.13, 2.33	Inconclusive	Low

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professionals					
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\*MDT, Multidisciplinary Team, GP, General Practitioner, SPC, Specialist Palliative Care

\*\*CollaboRATE Mean Score: Higher scores represent more shared decision making (range 0-100).

### Certainty of evidence

Three of the four studies retrieved had a high risk of bias due to missing outcome data and issues with blinding. Overall certainty of evidence for all outcomes was downgraded to very low due to varying risks of bias and imprecision.

### RECOMMENDATIONS FROM OTHER GROUPS

GROUP	RECOMMENDATION	STRENGTH OF RECOMMENDATION/CERTAINTY/QUALITY OF EVIDENCE
NCCN	The oncology team should initiate discussions of personal values and preferences for end-of-life care while patients have a life expectancy of years to months.	Category IIA - Based upon lower-level evidence, there is a uniform NCCN consensus that the intervention is appropriate.

### ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

#### COST

There were no studies on the cost of ACP services in the Philippines and its cost effectiveness.

#### PATIENT'S VALUES AND PREFERENCE

A systematic review by Matina et al. showed that 39-90% of South/South-

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East/East Asian patients agreed that advance care planning was necessary. [6] The main motive for their engagement in it concerned its benefits, such as promoting autonomy, allowing a comfortable end-of-life, avoiding burden on family members, and facilitating shared understanding with family members. Conversely, a range of motives characterized those who were unwilling to engage in it: patients' lack of understanding of their disease, their misperceptions about advance care planning, and the following beliefs: that it was not beneficial, that it was potentially harmful, that it was not consistent with their religious beliefs or with the wishes of their family or healthcare professionals, and that there were various barriers to it.

When faced with a significant or life-threatening sickness, many Filipinos hold fatalistic perceptions known as "Bahala Na" (what is destined or inevitable; illness is always "the will of God")<sup>7,8,9</sup>. A descriptive, correlational, cross-sectional study of 22 critically ill Filipino Americans aged 55 and older and their family members regarding attitudes toward advance directives revealed that overall attitudes toward advance directives were positive, particularly among acculturated and highly educated families. Patients' completion rates were low (10%), most likely due to their fatalistic assumption that sickness is destined or unavoidable, rendering advance directives unnecessary<sup>10</sup>.

## ACCEPTABILITY

The family serves as the primary caregiver, patient advocate, and decision-maker in treating the dying or critically ill. Patients assume a passive position and readily accept a loss of autonomy as they entrust their care to their families. Religious convictions and cultural values impede conversations about advance directives. Filipino families are influenced by filial piety, a religious duty to preserve the gift of life, and a belief in God as the arbiter of life and death to leave the time and manner of a person's demise in God's hands. In most cases, aggressive medical interventions are preferred to withholding or removing extraordinary life-sustaining measures from terminal patients. Filipino families are expected to do everything possible to prolong the life of a terminally ailing family member until God intervenes to end the patient's suffering<sup>11</sup>.

When family members are gravely ill or dying, Filipino families may have difficulty or try to avoid discussing advance directives and life support decisions. Culture and beliefs also determine the rules for disclosing or telling the truth about terminal health diagnoses and prognoses. Protecting the patient, sustaining hope, and ensuring a dignified passing are tenets of

the Filipino tradition of filial obligation. Discussions about end-of-life issues and advance directives should be approached with caution, as discussing such sensitive topics may raise the fear that the discussion itself could contribute to or invoke undesirable outcomes<sup>12</sup>.

Advanced care planning is essential in end-of-life care, but many Filipinos are unaware of it. In a study conducted among 341 acute care, breast cancer, and general ambulatory care patients, 72 lay caregivers and 63 physicians at the Philippine General Hospital (PGH) through personal interview about their knowledge, attitude, and behavior regarding living wills, 47% of patients and 2.8% of caregivers were aware of advanced directives<sup>13</sup>. In a study conducted among 90 Filipino patients with Chronic Obstructive Pulmonary Disease, nearly all were unfamiliar with the terms ACP (95.55%), end-of-life care (95.55%), and do not resuscitate order (100%). However, the majority of them desired to have ACP discussions (94.44%) which were not viewed as distressing and were deemed beneficial (96.67%)<sup>14</sup>.

There are no studies on the equity and feasibility of ACP services in the Philippines.

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## 4.8 Parenteral and Enteral Nutrition in the last six months of life

**Question 8: Among adult cancer patients in the last six months of life, will parenteral or enteral nutrition improve quality of life and increase survival time?**

### RECOMMENDATION

**Among adult cancer patients with poor performance status and with life expectancy of a few months, or actively dying, we do not suggest routinely offering artificial nutrition and hydration.** (*Weak recommendation, low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The panel discussed that not all patients with Stage IV or advanced or metastatic cancer and are incurable, are with poor performance status. A “poor status” patient is defined as Eastern Clinical Oncology Group (ECOG) 3, Karnofsky performance of less than 70 and with a life expectancy of a few or three months .
- The panel considered the high cost of artificial nutrition which may pose financial challenges for many families.

### Key Findings

- There were 17 cohort studies, 2 randomized trials, 2 case series and 3 qualitative studies that investigated the effects of parenteral or enteral nutrition on the quality of life and survival time of adult cancer patients in the last six months of life.
- There are no direct studies that reported on the effect of enteral or parenteral nutrition in the quality of care. **Six cohort studies showed that oral intake of small solids and liquids can alleviate symptoms of hunger and thirst but it does not provide better comfort care. Enteral feeding via nasogastric tube does not statistically increase albumin levels; however the serum albumin levels of patients on artificial hydration are significantly lower compared to those not on artificial hydration.** Patients with percutaneous endoscopic gastrostomy tube have shorter length of hospital stay compared to patients on nasogastric tube and on nothing per orem. The percentage of patients with deterioration in dehydration score in the final 3

- weeks was higher in the non-hydration group than the hydration group.
- Four cohort studies and two case series report that parenteral or enteral nutrition has no significant change in providing comfort in cancer patients.
- Three cohort studies reported that the quality of life of cancer patients on artificial nutrition did not change significantly compared to those without.
- Six cohort studies showed that artificial hydration has no significant effect on symptoms of edema, ascites and nausea and vomiting; however, artificial hydration increases risk of respiratory secretions.
- There are no direct studies that assess the effect of parenteral and enteral nutrition on the autonomy of cancer patients for end-of-life decisions. Two cohort studies and 1 randomized cluster trial reported that cancer patients have autonomy in deciding whether to receive nutrition and hydration.
- Four cohort studies reported that artificial hydration does not have any effect on the anxiety, agitation and restlessness of patients.
- Three qualitative studies showed that patients and relatives identify that oral intake is important especially towards the end-of-life. They also believe that parenteral nutrition is beneficial and considered as part of standard medical practice.
- Six cohort studies and 1 RCT reported that enteral or parenteral nutrition has no significant effects on the overall survival of cancer patients.

## **Background**

End-of-life care for cancer patients consists of complex, personal and health care decisions that attempts to balance palliative care and reduction of invasive treatments.<sup>1</sup> Collaboration with the healthcare provider, patients and family members are important for important decision-making to promote quality end-of-life care and decrease any discomfort, anxiety and stress to the dying patient. Decisions also include whether or not to implement artificial hydration and nutrition.

The role of nutrition support in cancer patients in their last months of life in palliative care is a controversial topic. Artificial nutrition and hydration through enteral or parenteral access can be integrated in a palliative care program when a positive effect can be influenced in the patient's quality of life and the risk of dying from malnutrition is higher than cancer progression.<sup>1</sup> Enteral nutrition is frequently used when the gastrointestinal tract is intact and functional. Placement of a nasogastric, nasojejunal tube or percutaneous endoscopic gastrostomy tube may be a suitable strategy to allow enteral access for nutrition. When enteral nutrition is contraindicated or unfeasible, parenteral nutrition can be considered.

Enteral and parenteral access for nutrition and hydration has both its benefits and complications. The impact of nutritional support through artificial means may come with adverse effects and can cause discomfort and anxiety for the patient. Trying to make a patient eat when he or she has marked appetite loss can lead to increased distress with interactions with his or her relatives or caregivers.<sup>2</sup> The opposite spectrum of not feeding or hydrating the patient may lead to increase in deterioration and may cause hunger and thirst to the patient.

The purpose of this Evidence Summary is to provide evidence and recommendations for the healthcare provider on the impact of enteral or parenteral nutrition on the quality of life and survival time of cancer patients in their last six months of life.

### **Definition of Terms**

- a. **Enteral nutrition** – receiving nutrition through access using the gastrointestinal tract (ex. Oral route, nasogastric tube, nasojejunal tube, percutaneous endoscopic gastrostomy)<sup>2</sup>
- b. **PARENTERAL NUTRITION** – receiving nutrition through access via the intravenous route<sup>2</sup>
- c. **Quality end-of-life care** – addresses a patient's psychosocial, spiritual and clinical needs and considering the needs of those close to them.<sup>3</sup> Parameters that may measure the care provided are taking a look at measurements that may address the patient's condition, such as presence of hunger and thirst may affect the psychosocial behavior of patients. The hydration status and albumin level also correlates to the clinical parameters of patients pertaining to nutrition, mortality and prognosis of patients.
- d. **Patient comfort** – transient and dynamic state characterized by ease from pain, emotional and physical distress with a developing sense of positivity, safety, strength and acceptance of one's situation that is underpinned and sustained by the feeling of being valued, cared for and the accompanying impression of confidence and acceptance of treatment by choice.<sup>4</sup>
- e. **Quality of life** – individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns<sup>5</sup>
- f. **Symptom control** – relief of physical symptoms and emotional and spiritual support for the patient<sup>6</sup>
- g. **Patient autonomy for end-of-life decisions** – making choices and decisions about treatment and care and support on the patient's engagement in daily activities, in contributing to others and in active preparation for dying.<sup>7</sup>
- h. **Patient's distress or anxiety** – feeling of helplessness or fear often related to the sense of losing control that accompanies life with

- illness<sup>8</sup>
- i. **Patient's perceptions of care and satisfaction** – measure of the extent to which a patient is content with the health care they received from their health care provider.<sup>9</sup>

## Review Methods

A comprehensive, systematic search was done from November 23, 2022 until February 25, 2023 using Medline, Cochrane Library and Google Scholar with a combine MeSH and free text search using the terms: cancer patients, end-of-life, palliative care, nutrition, enteral nutrition, parenteral nutrition, quality of life, survival time, cost-effective, benefit, comfort, symptom control, anxiety, distress and perception. We also searched for ongoing studies in the NIH clinicaltrials.gov and various trial registries.

Only studies that evaluated the effects of enteral or parenteral nutrition on patients in the last six months of life were included in the review. Outcomes of interest included quality end-of-life care, patient comfort, quality of life, symptoms control, patient autonomy for end-of-life decision, patient's distress or anxiety and patient's perception of care and satisfaction. Studies that did not include patients at their end-of-life (last six months of life) were excluded.

Quality assessment of the included CPG was performed using the AGREE II tool. Risk of bias assessment for systematic review was done using the AMSTAR 2. For randomized and non-randomized individual studies, the Revised Cochrane risk-of-bias tools for randomized trials (RoB 2) and Risk Of Bias in Non-randomized studies (ROBINS- 1) were used, respectively. Qualitative studies were assessed with the Critical Assessment Skills Programme (CASP) questionnaire.

Results of quantitative studies were combined using random effects model using pooled adjusted odds ratio. Narrative synthesis was created for each outcome measure using synthesized evidences from qualitative and quantitative studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of evidences and to rate the certainty of evidences in the included studies for each specific outcome measures.

## Results

Seventeen cohort studies, 1 cluster randomized trial, 1 phase II randomized trial, 2 case series and 3 qualitative studies were included in this Evidence Summary, comprising of 3,739 participants.

## **Quality End-of-Life Care**

There are no direct studies that reported on the effect of enteral or parenteral nutrition in the quality of care in addressing a patient's psychosocial, spiritual and clinical needs. Six studies indirectly described effects of artificial nutrition on care for end-of-life cancer patients.

One prospective study noted symptoms of hunger and thirst were present initially on the first total days of evaluation; however, 20 of the 32 studies patients did not develop these symptoms later during their final days of life. For the 12 patients who complained of hunger or thirst, small amounts of liquids and solids satisfied their symptoms. Providing food and fluid administration beyond the specific requests of the patient did not provide better comfort to patients.<sup>10</sup>

Two cohort studies evaluated the effect of artificial nutrition or hydration on the level of serum albumin. There was no statistical significant difference in the serum albumin level between patients who was inserted with nasogastric tube for enteral nutrition compared to patients on nothing per orem ( $MD -0.300 \pm 0.174 \text{ g/dL}$  (95% CI -0.6692- 0.0692)).<sup>11</sup> A prospective study reported that the mean difference of serum albumin level of patients given artificial hydration was statistically significantly lower compared to those without artificial hydration ( $MD 0.0 \pm 0.110 \text{ mg/dL}$  (95% CI -0.2175-0.2175) seen 3 weeks before death and  $MD -0.200 \pm 0.090 \text{ g/dL}$  (95% CI -0.3777-0.0223) seen 24 hours before death).<sup>12</sup>

The route of nutritional intake may also affect the duration of hospital stay. Patients on nothing per orem have a significantly longer hospital stay compared to those with nasogastric tube ( $39 \pm 18$  days vs  $19 \pm 15$  days;  $P=0.01$ ).<sup>11</sup> Another cohort study observed that patients on nasogastric tube have longer hospital stay than patients on percutaneous gastric tube (64 days vs 21 days;  $P=0.0372$ ).<sup>13</sup>

Two studies assessed whether artificial nutrition may address dehydration status of cancer patients. The percentage of patients with deterioration in dehydration score in the final 3 weeks was higher in the non-hydration group than the hydration group [(35% vs 14%;  $P=0.002$ )<sup>14</sup>; (35% vs 13%;  $P=0.0027$ )<sup>15</sup>].

## **Patient Comfort**

One systematic review consisting of 2 retrospective cohort studies and 2 case series review reported complications in patients with peritoneal carcinomatosis who were given total parenteral nutrition. The pooled proportion of participants who had complications was 23% (95% CI 4-41%).

The most common complication was catheter-related bloodstream infection<sup>16,17,18, 19</sup>

Two prospective studies and one retrospective study showed that artificial hydration and oral intake of food and water, has no significant change in providing comfort in cancer patients. There was no change in the prevalence of agitation, restlessness or death rattle seen in cancer patients especially during the days before dying.<sup>10,20, 21</sup>

## **Quality of Life**

Three prospective cohort studies analyzed the quality of life of cancer patients on home parenteral nutrition. Using the Rotterdam symptoms checklist (RSCL) questionnaire, Bozzetti et al showed that there is no statistical significance between a change in the quality of life between baseline and after 1 month.<sup>22</sup> This result was also similar to the study by Santarpia et al wherein cancer patients who survived more than 60 days, and those who survived more than 90 days on home parenteral nutrition had no statistical change in their Karnofsky Performance Status (KPS).<sup>23</sup>

Another prospective study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 15-Palliative Care (C15-PAL) also reported that quality of life did not change significantly between baseline and week 3 in patients given enteral feeding.<sup>13</sup>

## **Symptom Control**

One prospective study observed the effects of enteral intake of food and fluids on subjective symptoms of cancer patients. Hunger and thirst was mostly not present among patients on initial examination. Among 32 patients treated in a comfort care unit, only 12 patients (37%) expressed hunger. Eight of these patients drank and ate small amounts of liquid and solids. One patient had symptoms of hunger present until death and was satisfied with small amounts of food up to the last 2 days before death. There were no patients who experienced persistent hunger after eating small amounts of food. Likewise, among the 32 patients, 21 patients (66%) had symptoms of thirst. All patients were relieved of hunger and thirst with oral food and fluid intake.<sup>10</sup>

Four studies compared symptoms of patients on artificial nutrition and patients not on artificial nutrition. Subgroup analysis showed that there is no significant difference between patients given artificial nutrition and those without on the occurrence of edema (OR 1.10 (95% CI 0.20-5.94); P=0.91).<sup>15,24</sup> Subgroup analysis of three cohort studies showed that patients given artificial nutrition have higher risk of increased respiratory secretion (OR 1.65

(95% CI 1.04-2.60); P=0.03).<sup>15,24,25</sup> Subgroup analysis showed that there is no statistical difference between providing artificial nutrition and not on the occurrence of ascites (OR 1.33 (95% CI 0.69-2.59); P = 0.40).<sup>15,24</sup> Finally, subgroup analysis showed that there is no statistical difference between the presence or absence of artificial nutrition in relation to nausea and vomiting in cancer patients (OR 2.25 (95% CI 0.43-11.84); P = 0.34).<sup>12,24,25</sup>

One prospective study reported that patients on total parenteral nutrition develop pain, ascites and vomiting, but the trend of symptom occurrence decreases the longer the survival period.<sup>2</sup>

### **Patient Autonomy for End-of-Life Decisions**

There are no direct studies that assess the effect of parenteral and enteral nutrition on the autonomy of cancer patients for end-of-life decisions. Two prospective studies and 1 randomized cluster trial mentioned the patient's decisions in receiving hydration and nutrition. Based on the three studies, cancer patients have autonomy in deciding whether to receive nutrition and hydration. Patients at their final days of life did not experience hunger and thirst. Among those who have these symptoms, most of the patients requested for small amounts of liquids and solids.<sup>10</sup> Hydration was discontinued due to adverse effects (site problems, localized edema, generalized edema, respiratory secretions, nausea and vomiting).<sup>26</sup>

In a Korean study, intravenous nutrition and hydration was administered to 133 patients (80.6%) on admission, to 125 patients (75.7%) at 1 week, and to 137 patients (83.0%) 2 days before death (p = 0.7). Advanced directives were implanted in 142 patients (86%); however, artificial nutrition and hydration was stopped in only 9% of patients.<sup>27</sup>

### **Patient's Distress or Anxiety**

Three prospective studies and 1 retrospective study observed for the occurrence of distress or anxiety in cancer patients on oral and parenteral hydration. There was no statistical difference between the scores of the Agitation Distress Scale between patients in the hydration group ( $2.1\pm2.8$ ) and non-hydration group ( $2.3\pm2.7$ ) in the last 3 weeks of their lives (P =0.35).<sup>14</sup> In the last 7 days<sup>21</sup> and last 24 hours of life<sup>20,25</sup> oral intake and hydrations did not also have any significant effect in the presence of anxiety, agitation and restlessness.

### **Patient's Perceptions of Care and Satisfaction**

There were no direct studies that evaluated the patient's perception of care and satisfaction towards enteral or parenteral nutrition. Three qualitative studies the beliefs and perceptions of patients and relatives oral intake and

parenteral nutrition. Overall, the three studies identified that for patients and relatives, oral intake is important especially towards the end-of-life. Tailoring of nutrition care to the patient is valued and nutrition goals should be adapted based on patient's habits and preferences.<sup>28</sup> Both patient and relatives agree that their involvement in the nutrition intervention is important. Some relatives perceived that decreasing oral intake as the patient's choice and viewed that maintaining oral intake is part of the battle against the disease.<sup>29</sup> Most patients believe that parenteral nutrition is beneficial and considered as part of standard medical practice. One of the barriers patients and relatives feel is insufficient explanation and poor communication between healthcare provider and patient and relatives.<sup>30</sup>

## GRADE SUMMARY OF FINDINGS

**Table 23. Parenteral Nutrition vs Enteral Nutrition**

CRITICAL OUTCOMES	BASIS (number of studies; n=patients)	RESULTS		INTERPRE-TATION	CERTAINTY OF EVIDENCE			
		Effect Size	95% CI					
<b>1. Quality end-of-life care</b>								
<b>a. Enteral nutrition vs Nothing per orem</b>								
Serum albumin	1 cohort study (n=31)	MD - 0.300 ±0.174g/d L 11	-0.6692- 0.0692 (P=0.105 3 )11	Equivalent	Low			
<b>b. Artificial hydration vs No artificial hydration</b>								
Serum albumin	1 cohort study (n=226)	3 weeks before death: MD 0.0± 0.110mg.d L12  24 hours before death: MD - 0.200± 0.090mg/ d L12	3 weeks before death: -0.2175- 0.2175 (P=1.00) <sup>1</sup> 2  24 hours before death: -0.3777- 0.0223 (P=0.027 8 )12	Equivalent  Harm	Low			

Deterioration in dehydration score	2 cohort studies (n=200)	14% vs 35% <sup>14</sup> 13% vs 35% <sup>15</sup>	P=0.002 <sup>14</sup>  P=0.002 <sup>75</sup>	Benefit	Low
<b>c. Nasogastric tube vs Nothing per orem</b>					
Length of hospital stay	1 cohort study (n=31)	MD - 20.00 ±7.201 days <sup>11</sup>	- 35.0720- -4.9280 (P=0.012 0) <sup>11</sup>	Benefit	Low
<b>2. Patient's comfort</b>					
<b>a. Parenteral nutrition</b>					
Complications	4 (2 cohort studies and 2 case series) (n=248)	23% developed complications <sup>16,17,18,19</sup>	0.04- 0.4 <sup>16,17,18,</sup> 19	Harm	Low
Comfort (agitation, restlessness or death rattle)	3 cohort study (n=32)	No significant change in providing comfort <sup>10</sup>  No change in the prevalence of agitation, restlessness or death rattle seen in cancer patients especially during the days before dying <sup>10,20,21</sup>	Equivalent	Low	
<b>3. Quality of life</b>					
<b>a. Parenteral nutrition</b>					
KPS	1 cohort study (n=152)	The longer the survival, the lower the KPS (P=0.001) <sup>23</sup>	Harm	High	

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Rotterdam symptoms checklist (RSCL)	1 cohort study (n=69)	Changes in quality of life after 1 months on parenteral nutrition showed that at least half of patients deteriorated and 40% improved. <sup>22</sup>  Karnofsky performance status remained stable until 3 months prior to death <sup>22</sup>	Inconclusive	High
<b>b. Enteral nutrition</b>				
European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ CA15-PAL) score	1 cohort study (n=72)	No significant change between baseline and 3 weeks after <sup>13</sup>	Inconclusive	High
<b>4. Symptom control</b>				
<b>a. Artificial nutrition vs No artificial nutrition</b>				
Edema	2 cohort studies (n=313)	OR <sub>1.10</sub> <sup>15,24</sup>	0.20- <sub>5.94</sub> <sup>15,24</sup>	Harm
Respiratory secretions	3 cohort studies (n=593)	OR <sub>1.65</sub> <sup>15,24,25</sup>	1.04- <sub>2.60</sub> <sup>15,24,25</sup>	Harm
Ascites	2 cohort studies (n=133)	OR <sub>1.33</sub> <sup>15,24</sup>	0.69- <sub>2.59</sub> <sup>15,24</sup>	Harm
Nausea and vomiting	3 cohort studies (n=369)	OR <sub>2.25</sub> <sup>12,14,25</sup>	0.43- <sub>1.84</sub> <sup>12,14,25</sup>	Harm
<b>b. Total parenteral nutrition</b>				

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Pain, ascites and vomiting	1 cohort study (n=152)	Developed symptoms but trend of symptom occurrence  Decreases the longer the survival period. <sup>23</sup>	Inconclusive	High
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## 5. Patient's autonomy for end-of-life decisions

### a. Artificial hydration

Decision-making	3 (2 cohort studies and 1 randomized trial) (n=397)	Patients request for small amounts of solids and liquid when feeling thirsty or hungry. <sup>10</sup>  Artificial hydration was discontinued when patient developed adverse effects (site problems, localized edema, respiratory secretions, nausea and vomiting). <sup>26</sup>	Inconclusive	Moderate
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## 6. Distress or anxiety

### a. Artificial hydration vs No artificial hydration

Agitation Distress Scale	1 cohort study (n=226)	MD - 0.200±0.41 <sub>314</sub>	-0.6136-1.0136 (P=0.06860) <sub>14</sub>	Equivalent	Moderate
Anxiety, agitation and restlessness	3 cohort studies (n=1014)	No significant effect in the last 7 days <sup>21</sup> and last 24 hours of life <sup>20,25</sup>		Equivalent	Moderate

## 7. Perception of care and satisfaction

	3 qualitative studies (n=465)	Tailoring of nutrition care is valued and nutrition goals should be adapted based on patient's habits and	Inconclusive	Moderate
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		<p>preferences.<sup>28</sup></p> <p>Both patient and relatives agree that their involvement in the nutrition intervention is important.</p> <p>Decreasing oral intake is the patient's choice and maintaining oral intake is part of the battle against the disease.<sup>29</sup></p>		
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		<p>Parenteral nutrition is beneficial and considered as part of standard medical practice.</p> <p>One of the barriers is insufficient explanation and poor communication between healthcare provider and patient and relatives.<sup>30</sup></p>		
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## 8. Overall survival

### a. Artificial hydration vs No artificial hydration

Kaplan Meier survival curve	1 cohort study (n=238)	No significant survival difference <sup>24</sup>	P=0.9 <sup>24</sup>	Equivalent	Moderate
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### b. Parenteral nutrition vs No parenteral nutrition

Mean survival, days	1 randomized trial (n=31)	MD - 5.00± 2.623 <sup>37</sup>	- 10.3638 - 0.3638	Equivalent	Moderate
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			(P=0.06 65 )37		
<b>c. Nasogastric tube vs Nothing per orem</b>					
Survival, days	1 cohort study (n=21)	122 days vs 51 days <sup>11</sup>	P<0.01 <sup>11</sup>	Benefit	Moderate

## Certainty of Evidence

Of the 21 non-qualitative studies, 11 studies had an overall moderate risk of bias. Nineteen studies had serious issues on confounding due to study design. Twelve studies had moderate risk in selection and eight studies had moderate risk in reporting bias. Due to some questions with indirect evidence, the overall certainty of evidence across all studies is low.

## RECOMMENDATIONS FROM OTHER GROUPS

The European Society of Medical Oncology (ESMO) recommends nutritional interventions with low risk and burden to patients with an expected survival of less than a few months. They recommend that invasiveness of nutritional interventions should be decreased and dietary counseling and oral supplements should be provided. In patients with an expected survival of less than a few weeks, comfort-directed care is the recommended approach, including alleviating thirst, eating-related distress and other debilitating symptoms. Artificial nutrition should not be initiated in the last weeks of life because it does improve or prevent symptoms of thirst.<sup>31, 32</sup>

The American Society of Parenteral and Enteral Nutrition (ASPEN) recommends that nutrition support be withdrawn or withheld under the circumstance of reduced life expectancy, KPS score <50 or ECOG performance status of 3-4, severe organ dysfunction, uncontrolled nutrition-impacting symptoms, or patient-directed wishes for care or any circumstance in which the patient may not benefit from aggressive nutrition interventions.<sup>33</sup>

The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends nutritional interventions in patients with advanced cancer after considering together with the patient the prognosis of the malignant disease and the expected benefit on quality of life and potentially survival as well as the burden associated with nutritional care.<sup>34</sup>

GROUP	RECOMMENDATION	STRENGTH OF RECOMMENDATION
European Society of Medical Oncology (ESMO)	<ul style="list-style-type: none"> <li>Invasiveness of nutritional interventions should be decreased and dietary counseling and oral supplements should be provided</li> <li>In patients with an expected survival of less than a few weeks, comfort- directed care is the recommended approach, including alleviating thirst, eating- related distress and other debilitating symptoms</li> </ul> <p>Artificial nutrition should not be initiated in the last weeks of life because it does improve or prevent symptoms of thirst</p>	IV;B
American Society of Parenteral and Enteral Nutrition (ASPEN)	<ul style="list-style-type: none"> <li>Nutrition support be withdrawn or withheld under the circumstance of <ul style="list-style-type: none"> <li>Reduced life expectancy</li> <li>KPS score &lt;50 or ECOG performance status of 3-4</li> <li>Severe organ dysfunction</li> <li>Uncontrolled nutrition- impacting symptoms</li> </ul> </li> </ul> <p>Patient-directed wishes for care or any circumstance in which the patient may not benefit from aggressive nutrition interventions</p>	
European Society of Parenteral and Enteral Nutrition (ESPEN)	Nutritional interventions in patients with advanced cancer after considering together with the patient the prognosis of the malignant disease and the expected benefit on quality of life and potentially survival as well as the burden associated with nutritional care	Low, Strong

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## **ADDITIONAL CONSIDERATION FOR EVIDENCE TO DECISION (ETD) PHASE**

### **OVERALL SURVIVAL**

Six cohort studies and 1 RCT showed the effects of artificial nutrition in overall survival of cancer patients. One cohort study reported the mean survival of patient on home parenteral nutrition was 4.7 months<sup>35</sup> while another cohort study reported the survival range from 6 to 1269 days (median 45 days).<sup>23</sup>

One cohort study showed that parenteral nutrition requirement may predict survival in patients with advanced cancer;<sup>36</sup> however, two studies have contradicted this result. One cohort study showed Kaplan-Meier survival curves that did not show any significant survival difference ( $P = 0.9$ ) between patients that received and did not receive artificial hydration.<sup>24</sup> A phase II randomized trial also reported that the Median survival for the control was 8 days (95% CI 5.7–10.3 days) and 13 days (95% CI 3.1–22.9 days) in the patients given parenteral nutrition. The difference was not statistically significant ( $P = 0.982$ ).<sup>37</sup>

A cohort study reported patient on nasogastric tube have a longer median survival compared to those on nothing per orem ( $P < 0.001$ ).<sup>11</sup>

### **COST**

There are no cost-effective studies on enteral or parenteral nutrition among cancer patients in their last six months of life.

**Table 24. Estimated Cost based on Route of Artificial Nutrition**

<b>ROUTE OF NUTRITION</b>	<b>ESTIMATED COST</b>
Nasogastric tube	Php 80.00-100.00
PEG tube	Php 2,899.00-12,753.50
Intravenous	Php 15.00-75.00

**Table 25. Estimated Cost of Other Items Used for Artificial Nutrition**

ITEMS USED	ESTIMATED COST
<b>Enteral Nutrition</b>	
Feeding container/bag	Php 341.00-890.00
Feeding pump	Php 21.34-66,751.80
Powdered formula	Php 150.00-3818.00
Liquid formula	Php 152.25-1,840.00
<b>PARENTERAL NUTRITION</b>	
Extension tube	Php 45.00-801.00
Syringe for flushing	Php 3.50-250.00
1 liter of 5% Dextrose in 0.9% Sodium Chloride	Php 22.50-100.00
PARENTERAL NUTRITIONAL SUPPLEMENTATION	PHP 1489.00-6780.50

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## 4.9 Terminal extubation and quality of end-of-life care

**Question 9: Among adult cancer patients at the end-of-life who are on ventilatory support, will terminal extubation improve quality of end-of-life care?**

### RECOMMENDATION

Among adult cancer patients at the end-of-life who are actively dying on ventilatory support, **we suggest multidisciplinary and individualized decision-making regarding the option of terminal extubation.** (*Weak recommendation, very low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The panel highlighted that actively dying is a state where the patient is very close to death and may exhibit signs and symptoms near death such as gasping, vital signs like blood pressure is dropping, organ failure, and not responding to therapies.
- The legality of the terminal extubation in the Philippines was explored. One panel member emphasized that for actively dying patients the goals of care may include allowing a natural course of death. Representative from the PAPO highlighted the recommendation of individualized care plan. Despite very low certainty of evidence, the panel unanimously agreed on a multidisciplinary and individualized approach to terminal extubation for actively dying patients, cognizant of the wishes of the patient and their family.

### Key Findings

- There were 2 studies (case series and observational studies) that investigated the survival outcomes of 32 terminally ill cancer patients undergoing withdrawal of mechanical ventilation which were both done in Asia (Taiwan).
- The median time from extubation to death varies but noted to be within 1 day in majority of the patients with advanced cancer. Overall, it showed that the median time to death after withdrawal

from mechanical ventilator was short. It was also observed that the majority of decisions regarding ventilator withdrawal were taken and decided by people other than the patient.

- In terms of post-extubation symptoms and signs of distress, 7 types of symptoms or signs of distress, which were not specified in the study, were recorded including post-extubation stridor but no seizure episode.
- Awareness of the short survival time after terminal extubation may help medical and health care professionals to plan and provide appropriate end-of-life care to minimize the possible distressing symptoms which may happen during the withdrawal process from mechanical ventilator.
- The findings were based on qualitative studies, which carry higher risk of bias, although in end-of-life care, it is already recognized that conducting randomized controlled trial is quite challenging. Although not with the highest quality and with an overall low certainty of evidence, these 2 studies provided important insights on survival time of patients with terminal stage or advanced cancer.
- A narrative summary was the best approach to bring together findings from these 2 studies.
- There was lack of direct evidence for important impacts of the withdrawal process of mechanical ventilation on quality end-of-life care of the patients but scarce evidences on patient comfort, distress, restlessness, perceptions of care and outcomes on family satisfaction on withdrawal of mechanical ventilation were included.

## Background

Withdrawal of life-sustaining measures including mechanical ventilation is a common event in critical care units in many parts of the world.<sup>1</sup>

Extubation refers to removal of the endotracheal tube. It is the final step in removing a patient from mechanical ventilation. The practice of withdrawing life-sustaining mechanical ventilator (MV) when death is expected is commonly termed as “terminal extubation” (TE) by intensive care unit (ICU) doctors and intensivists. Other terms commonly used include “compassionate extubation” (CE), also known as palliative extubation, is performed by termination of MV and withdrawal of the tube, thus avoiding the prolongation of death. Terminal extubation, in patients whose death is expected to occur in a short time like those with advanced terminal cancers, is performed when there are no curative therapeutic

options left and that it is no longer considered best applied for the patients.

<sup>2</sup>

Another goal of mechanical ventilation withdrawal is to relieve patients' suffering and provide comfortable end-of-life care. It is an important step toward high quality end-of-life care in patients who are terminally ill, on artificial ventilatory support. Benefits of terminal extubation can include offering the patient greater comfort, assistance from the multidisciplinary team, and a better communication between patient and family at this stage.<sup>3-4</sup> There are reasons leading to withdrawal of mechanical ventilation being done that close to patient death were affected by multiple factors related to medical personnel, patients, and their families. One of the studies reviewed revealed that patients and their families often wish to be able to spend the last moments at home, surrounded by family and friends. This setting shows that what patients want is nothing more than comfort, company, good mood, and conversations.<sup>3</sup> However, this issue has rarely been explored in the Asian population as in the Philippine setting because of the lack of consensus regarding the withdrawal of mechanical ventilation between medical personnel and patients/families and resistance from the families.

## Review Methods

The search for articles was done from February 12, 2023 until March 27, 2023 using PubMed, Cochrane, Google Scholar ,society links with a combined MeSH and free text search using the terms: terminal/palliative extubation, palliative care , advanced cancer, quality care, terminally ill, end-of-life care. The Boolean operator AND was used among the descriptors mentioned as search strategy.

Eligibility criteria included the following:

- Population: adults who are advanced cancer patients.
- Phenomenon of interest: terminal/palliative withdrawal of mechanical ventilation, including all forms of terminal withdrawal of mechanical ventilation.
- Types of studies: primary research of all kinds, reviews, case studies or reports.
- Language: English.
- Only the pertinent articles from 2015 onwards which analyzed or presented the impact or mentioned the outcomes of terminal extubation and met the inclusion criteria were included.

Very small quantities of available studies about the topic were obtained. A narrative synthesis was done to bring together the results of the relevant studies.

## **Results**

We found 2 relevant studies, an observational and a case series study that included a total of 32 terminally ill cancer patients withdrawn from mechanical ventilators. Both studies were from Taiwan, the only country in Asia which legalizes compassionate extubation through its Hospice Palliative Care Act implemented and amended since 2013. The case study by Kok included 12 patients (6 cancer patients, 6 non-cancer patients) while the study of Hung included 135 terminally ill patients ( 26 advanced cancer patients and 109 non-cancer patients: 77 chronic disease, 20 newborns and 12 trauma).

### **Survival Time**

From the case study of Kok, the median time to death after terminal extubation was 97 hours (0.3 - 245 hrs) in 5 cancer patients and the longest time to death was 245 hours in a patient with cancer. Family-initiated request for compassionate extubation was the most common setting with 4 from the patient's child, 1 from sibling and 1 from a patient. All immediate extubations, meaning having no prelude of terminal wean, were performed by an intensivist in the ICU.

In the study by Hung, patients with a diagnosis of advanced cancer and withdrawal initiation by the patients themselves had a significantly shorter time interval between receiving life-sustaining treatment and artificial ventilation support to "Withdrawal meeting" compared to those with non-cancer diseases and withdrawal initiation by family or medical personnel. The median survival time was 59 min (95% CI, 0 - 208 min) for patients with advanced cancer. All the patients with cancer died within one week after withdrawal of mechanical ventilation with 69 % who died within 1 day and 31 % who died within 2-7 days. Patients themselves had the highest percentage of initiating the withdrawal process in those with advanced cancer (30.8%), done via verbal consent while they still had clear consciousness or presence of an advance care planning. Patients with terminally ill cancer almost always presented with rapidly deteriorating courses with mostly cancer-related causes of death.<sup>4</sup>

### **Patient Distress**

In terms of post-extubation symptomatology and signs of distress, 7 types

of symptoms or signs of distress, which were not specified in the study, were recorded in the study of Kok. No episodes of seizures were documented in any of the patients. Post-extubation stridor was auscultated in 5 patients. Three patients exhibited 4 or more types of symptoms or signs of distress, but exact symptoms were not specified and if it involved the group of patients with terminal stage of cancer.<sup>2</sup>

### **Patient Comfort and Restlessness**

There are no direct studies that reported on the effect of terminal extubation in the quality of care in addressing patient's comfort. However, there are 2 observational studies and one qualitative study which indirectly described effects of terminal extubation on patients' discomfort and restlessness. In the study of Wiegand and colleagues, they reported that "bad deaths" were associated with signs of discomfort by the patient with one patient's daughter stating that her mother experienced bad death as she was uncomfortable after she was extubated.<sup>5</sup> In the Netherlands study which involved 241 patients who had mechanical ventilation and/or vasoactive medication withdrawn, only 8 % experienced moderate (3 %) and severe (5 %) terminal restlessness.<sup>6</sup> In another observational study, it was reported that half (50 %) of the 451 patients experienced discomfort after the withdrawal of mechanical ventilation. Specifically in this study, more patients who were terminally extubated experienced airway obstruction (65.7 %) and gasping (44.8 %).<sup>7</sup>

### **Patient's Perceptions of Care and Satisfaction**

There are no direct studies that showed patient's perception of care and satisfaction towards terminal extubation but there is one review by Hinkle et al., which showed the perceptions and satisfaction of family and relatives on terminal extubation. This study found that family members reported greater satisfaction when they were allowed to stay longer during decision-making reunions and during the extubation process. The study concluded that good communication, support for shared decision-making and specific patient care measures were associated with greater satisfaction with end-of-life care.<sup>8</sup>

## GRADE Summary of Findings

**Table 26. Survival Time and Post-extubation symptoms and signs of distress**

CRITICAL OUTCOMES	BASIS (No and Type Of Studies, Total Participants)	RESULTS OF THE STUDY	CERTAINTY OF EVIDENCE
Survival Time	1 case - series study, 1 observational n=32	<p>Time of death varies according to the disease, 97 hours in patients in advanced cancer stages.</p> <p>The median survival time was 59 min (95% CI, 0 - 208 min) for patients with advanced cancer. All the patients with cancer died within one week after withdrawal of mechanical ventilation with 69 % who died within 1 day and 31 % who died within 2-7 days.</p> <p>Patients themselves had the highest percentage of initiating the withdrawal process in those with advanced cancer (30.8%),</p>	Very low
Post - extubation symptoms and signs of distress	1 case-series study (n= 6 )	<p>Seven types of symptoms or signs of distress were recorded. No episodes of seizures were documented in any of the patients. Post-extubation stridor was auscultated in 5 patients. Three patients exhibited 4 or more types of symptoms or signs of distress, but exact symptoms were not specified and if it involved the group of</p>	Very Low

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		patients with terminal stage of cancer.	
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## RECOMMENDATIONS FROM OTHER GROUPS

GROUP OR AGENCY	RECOMMENDATION	STRENGTH OF RECOMMENDATION/CERTAINTY/QUALITY OF EVIDENCE
Downar et al., <sup>9</sup> Canada, 2016	<p>We SUGGEST that each ICU should develop and utilize protocols for withdrawal of mechanical ventilation and life- sustaining treatments.</p> <p>We RECOMMEND that the pace of withdrawal of life sustaining measures (LSM) be individualized for each patient. Typically, vasopressors and inotropes should be discontinued first, followed by mechanical ventilation and any artificial airway in a stepwise manner.</p> <p>We RECOMMEND that the sequence and process of withdrawal of mechanical ventilation must be individualized with comfort as the paramount goal. Mechanical ventilation should be withdrawn as quickly as possible, with the speed determined by the time it takes to achieve comfort at each step. Patients should not be routinely extubated to non- invasive mechanical ventilation.</p> <p>Pharmacologically paralysed patients should typically not be extubated or weaned to a spontaneous ventilator mode, continuous positive airway pressure or a T-piece.</p> <p>We SUGGEST that in most cases, the goal should be to extubate patients to room air. Extubation is preferable to leaving the patient intubated on minimal or no mechanical ventilatory support, but either option is acceptable.</p>	<p>Weak Recommendation</p> <p>Strong recommendation</p> <p>Strong</p> <p>Weak</p> <p>Weak</p>

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	<p>We SUGGEST that inhaled epinephrine should be used to treat post-extubation stridor in the conscious patient.</p> <p>We offer NO RECOMMENDATION about the routine use of anticholinergic medication (e.g. butylscopolamine) pre-extubation to prevent upper airway secretions, the routine use of furosemide to prevent congestive heart failure and the routine use of methylprednisolone to prevent post-extubation stridor.</p>	Weak
American College of Critical Care Medicine  Troug, et al, <sup>10</sup> 2008	<p><b>Preparing for withdrawal of life-sustaining measures ( mechanical ventilation )</b></p> <p>Recommends preparing family, preparing environment, and developing of a plan for withdrawal</p> <p><b>Discontinuation of life-sustaining treatment and monitoring</b></p> <p>Recommends discontinuation of physiologic monitoring. Suggests rapid discontinuation of most life-sustaining therapies other than oxygen or mechanical ventilation, which can be weaned.</p>	Weak
American Thoracic Society  Lanken, et al., <sup>11</sup> 2008	<p><b>Preparing for withdrawal of life-sustaining measures ( mechanical ventilation )</b></p>	Weak

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	<p>Recommends development of an individualized care plan for withdrawal of mechanical ventilation.</p> <p><i>Physicians should begin discussions regarding the decision to withdraw mechanical ventilation when patients or their surrogate(s) broach the issue, when health care providers believe that continued mechanical ventilation is no longer meeting the patient's goals, or it has become more burden- some than beneficial to the patient</i></p> <p><b>Discontinuation of life-sustaining treatment and monitoring</b></p> <p>Discusses terminal extubation and terminal weaning of mechanical ventilation.</p>	Weak
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## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

The cost of mechanical ventilation varies across hospitals. Below is a table containing a summary of the average cost of mechanically ventilated patient per day.

**Table 27. Cost of Mechanical ventilation<sup>12</sup>**

HOSPITAL	AVERAGE COST OF MECHANICALLY VENTILATED PATIENT PER DAY
Tertiary Provincial Private Hospital	Php 19,020 – P 30,000
Tertiary DOH retained Hospital	Php 11, 500
Tertiary Private Hospital in NCR	Php 40,000 – P120, 000

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## **PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY**

There is no data and evidence available in terms of patients' values, equity, and feasibility related to the practice of terminal extubation and its sequelae. The direct discussion of end-of-life planning with a patient with an imminent death is a sensitive and forbidden issue in Asian culture.

Decision making by next-of-kin was more prevalent than medical personnel or patients regarding end-of-life care in the country.<sup>3</sup> In terms of patients' preference, it was noted in a previous study that the preferences of patients with cancer regarding their end-of-life care were disregarded if there was a disagreement between patients and their families. The fact that a patient's right was overridden by a family's when the patient was unconscious and approaching end-of-life status, might partially explain why 10% of the patients with an advance care planning or documentation of verbal consent for Do not resuscitate (DNR) still received endotracheal tube intubation and artificial ventilation.<sup>4,13</sup> However, the decision to forgo life-sustaining treatment and withdrawal of mechanical ventilation should be judged in a patient's best interests.<sup>14</sup>

In terms of acceptance related to the practice of terminal extubation, lack of clarification can lead to a reluctance to accept the procedure causing anxiety and depression and other grief-related complications.<sup>8</sup> The need for a corroborative, clear and supportive communication with the healthcare team has to be emphasized as family members and other close relatives can feel guilty for the death of a loved one if there is very little or poor communication with the team. The study concluded that effective communication includes sharing the burden of decision making with family members. The shift from individual responsibility to patient-focused consensus often permits the family to understand, although reluctantly at first and with great sadness, that intensive care may involve letting go of life-sustaining interventions including withdrawal to mechanical ventilation.<sup>15</sup>

In recent years, compassionate extubation is now considered a shared decision in which patient and family members are included in the decision making process by the healthcare team but the ideal practice is to still include and address patient's desire and wishes. However, moral and legal limitations are noted to be major hindrances to the shared decision-making. Therefore, decision to perform the procedure of compassionate extubation should be made by the healthcare team and family based on their beliefs, values and expectations.<sup>16</sup>

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## 4.10 Palliative sedation and control of symptoms

**Question 10: Among actively dying adult cancer patients with severe intractable pain/restlessness/agitation, is palliative sedation effective in the control of symptoms?**

### RECOMMENDATION

Among actively dying adult cancer patients with severe intractable pain/restlessness/agitation, **we suggest to consider palliative sedation to supplement ongoing symptom control (management).** (*Weak recommendation, very low certainty of evidence*)

### Consensus Panel Considerations:

The consensus panel considered the following when formulating the recommendations:

- The panel emphasized that palliative sedation is not given alone but rather an add on to the palliative care management. According to the representative from the PAPO, giving palliative sedation is giving family and patient an option. Palliative sedation can be one of the options in dealing with severe, intractable symptoms including pain and anxiety the patient experiences in facing death.
- Due to the very low certainty of evidence, to safely use palliative sedation, different scales can be used to measure the level of restlessness or agitation (i.e. Richmond Agitation Sedation Scale). The patient has to reach a state wherein he/she is not restless or agitated.

### Key Findings

- A total of 19 studies are included in this evidence review; none were controlled trials. Only prospective or retrospective studies with a comparator group (with palliative sedation vs without palliative sedation) were included in this evidence summary.
- Results could not be pooled across the studies, due to the differing study designs and outcome measures; but most studies did not seem to show any effect of palliative sedation on control of symptoms or patient satisfaction. There was also no difference in time to death between the two groups (that is, palliative sedation

- did not seem to hasten death), or in the incidence of adverse events.
- The overall certainty of evidence was very low, so the evidence may still change with further research.

## Background

Toward the end-of-life, some symptoms such as pain, delirium, and dyspnea, can become distressing to patients and their carers, and refractory to standard therapy. In these situations, palliative sedation can become a therapeutic option. The European Association for Palliative Care (EAPC) defines palliative sedation as the monitored use of medications such as midazolam or phenobarbital to induce a state of decreased awareness and relieve the burden of intractable suffering. However, this practice may be associated with hesitation and controversy in the local healthcare setting. Hence a review of the evidence was undertaken to help ensure that it is ethically acceptable to patients, family, and healthcare providers.

Issues:

1. Manner of sedation: intermittent vs continuous
2. Level of sedation: mild vs intermediate vs deep; and how to titrate
3. Varying practices across countries and clinical settings (definition of “refractory;” expertise and composition of the team; terminal phase of illness or broader context of palliative care)

## Review Methods

A systematic search was done from the date of the last search (Dec 2014) of the most recent systematic review found on Medline, with a combined MeSH and free text search using the terms palliative sedation, pain, restlessness, and agitation.

We searched the Cochrane Database of Systematic Reviews and Medline for randomized controlled trials and studies of any design that compared palliative sedation against no palliative sedation. Outcomes of interest were quality of life, symptom control, patient satisfaction, and time to death. If any controlled trials were found, we planned to use the Cochrane Risk of Bias criteria.

## Results

### Characteristics of included studies

There were 19 studies for this evidence synthesis, which were included because they compared two groups of patients: one with palliative sedation and the other without palliative sedation. All were either retrospective cohort or prospective cohort studies, although only one (Maltoni 2009) attempted to match subjects based on age, gender, and Karnofsky performance status; none were controlled trials. A total of 8369 adults were included in these studies, of which 2231 received palliative sedation, and >95% had a diagnosis of cancer. The most common indications for palliative sedation were delirium and dyspnea; less common were anxiety, pain, and restlessness. The most common sedative agents used were benzodiazepines (midazolam, and, less commonly, lorazepam) and antipsychotic agents (haloperidol and chlorpromazine), given as intravenous infusions, either continuous or intermittently. The duration of sedation varied from 19 hours to 5 days, measured as either a mean or median.

**Table 28. Characteristics of Included Studies**

Author	Study design	Number (sedated /not sedated)	Indications for sedation	Sedative used	Mean sedation duration (days)
Alonso-Babarro 2010	retrospective cohort	29/236	delirium, dyspnea	midazolam	2.6
Bulli 2007	prospective cohort	136/939	-	Benzodiazepines	-
Caraceni 2012	retrospective cohort	83/46	dyspnea, delirium	Benzodiazepines	1.5 (median)
Chiu 2001	prospective cohort	70/206	delirium, dyspnea	haloperidol, midazolam	5 (median)
de Araujo 2022	retrospective cohort	92/814	delirium	-	-
Fainsinger 1998	retrospective cohort	23/53	delirium, dyspnea	midazolam	2.5
Kohara 2005	retrospective cohort	63/61	dyspnea, restlessness	midazolam	3.4

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Maltoni 2009	prospective cohort	267/251	uncontrolled symptoms	lorazepam, chlorpromazine	4
Maltoni 2012	prospective matched cohort	72/255	delirium	benzodiazepines	32.2 h
Muller-Busch 2003	retrospective cohort	80/468	pain, dyspnea	midazolam	2.5
Prado 2018	retrospective cohort	203/171	dyspnea, delirium	midazolam	36.9 h
Radha krishna 2012	retrospective cohort	68/170	anxiety, dyspnea	midazolam	-
Rietjens 2008	retrospective cohort	68/89	restlessness, dyspnea	midazolam	19 h
Schildman n 2018	retrospective cohort	149/43	delirium, dyspnea, pain	midazolam	2.3
Schur 2016	retrospective cohort	502/1912	delirium, dyspnea	midazolam	-
Stone 1997	retrospective cohort	30/85	delirium	midazolam	1.3
Sykes 2003	retrospective cohort	80/157	-	midazolam	-
Tan 2023	retrospective cohort	148/148	delirium, dyspnea, pain	chlorpromazine, midazolam	-
Vitetta	retrospective cohort	68/34	-	benzodiazepines	-

Midazolam; 19h to 3.4 d; only 1 study w matching (age, gender, reason for admission, KPS)

## Efficacy of Palliative Sedation

### Symptom Control

There were 5 studies that looked at symptom control, but these could not be pooled due to the different outcomes measured. For pain, for example, outcomes measured were pain score and pain prevalence at different time points before death, and usually with only one study per outcome. Most studies seemed to show that symptoms such as pain, delirium, or dyspnea were either inconclusive or were worse in the sedated group. The certainty of evidence was low for all 5 due mainly to the study design (retrospective cohort).

### GRADE Summary of Findings Tables

**Table 29. Sedated vs non-sedated actively dying adult cancer patients with intractable symptoms.**

CRITICAL OUTCOMES	BASIS (No. and type of studies, total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
<b>Pain Control</b>					
Pain 2 days before death	1 cohort 276	MD -0.39	-1.02, 0.24	Inconclusive	Very Low
Pain Prevalence 48-25 hours before death	1 cohort 157	RR 1.13	0.76, 1.67	Inconclusive	Low
Pain Prevalence 24-0 hours before death	1 cohort 157	RR 0.85	0.57, 1.28	Inconclusive	Low
Pain prevalence Last 48 hours	1 cohort 548	All patients had sufficient pain control in the last 48 hours of life in the sedated group		Benefit	Very Low
<b>Symptom Control</b>					
Dyspnea 2 days before death	1 cohort 276	MD -0.12	-0.87, 0.63	Inconclusive	Very Low

Dyspnea Prevalence 48-25hrs before death	1 cohort 157	RR 1.82	1.19, 2.79	Harm	Low
Dyspnea Prevalence 24-0 hrs before death	1 cohort 157	RR 1.55	1.01, 2.38	Harm	Low
Dyspnea Last 48 hours	1 Cohort 548	Burdensome dyspnea increased during the stay in the sedated group		Harm	Very Low
Delirium 2 days before death	1 Cohort 276	MD -0.66	-0.93, -0.39	Benefit	Very Low
Delirium 48-25 hrs before death	1 cohort 157	RR 1.33	0.55, 3.19	Inconclusive	Very Low
Delirium 24-0 hrs before death	1 cohort 157	RR 2.14	1.07, 4.31	Harm	Low
Delirium/ Agitation Day before death	1 cohort 192	58% vs 40%		Harm	Very Low
Delirium Last 48 hours	1 Cohort 548	Burdensome delirium increased during the stay in the sedated group		Harm	Very Low
Good symptom control Day of death Day prior to death 2 days prior to death	1 Cohort 76	61% vs 96% 35% vs 88% 38% vs 87%	p-value < 0.001	Harm	Very Low

## Quality of End-of-Life Care (Patient Experience)

There is 1 cohort study which comprises of 276 participants that investigated the satisfaction of the patients receiving palliative sedation. More than half (53%) of the participants were satisfied with their treatment.

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**Table 30. Quality of End-of-Life Care Among Sedated Actively Dying Adult Cancer Patients with Intractable Symptoms**

CRITICAL OUTCOMES	BASIS (No and type of studies, total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Satisfaction with treatment	1 Cohort 276	Satisfied: 53%  Fair: 10%  Not satisfied: 4%  No data: 33%		Benefit	Very Low

### **Quality of End-of-Life Care (Family Experience)**

There is 1 cohort study that comprises of 276 participants that investigated the satisfaction of family members to the treatment received by their family member who is receiving palliative sedation. Majority (67%) were satisfied.

**Table 31. Quality of End-of-Life Care Among Family Members of Sedated Actively Dying Adult Cancer Patients with Intractable Symptoms**

CRITICAL OUTCOMES	BASIS (No and type of studies, total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Satisfaction with treatment	1 Cohort 276	Satisfied: 67%  Fair: 20%  Not satisfied: 4%  No data: 9%		Benefit	Very Low

## Family Goals of Care and Decision

One cohort study that comprised of 275 participants looked into the ethical acceptability of palliative sedation for which the majority (89%) said their family member who is at the actively dying state should be provided with palliative sedation.

**Table 32. Family Goals of Care and Decision of Sedated Actively Dying Adult Cancer Patients with Intractable Symptoms**

CRITICAL OUTCOMES	BASIS (No and type of studies, total participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Ethical acceptability	1 Cohort 276	Should provide sedation: 89% Might be right: 4.3% Unavailable: 7.1%		Benefit	Very Low

Another important outcome was patient satisfaction with treatment, with one identified study. Overall, the majority of patients and family members were satisfied with the treatment they received. However, the certainty of evidence was again low due mainly to cohort study design.

**Table 33. Survival time from admission to death (in days)**

Survival Time in patients on palliative sedation Patient or population: actively dying adult cancer patients. Setting: hospice or palliative care units Intervention: palliative sedation Comparison: no palliative sedation					
CLINICAL OUTCOME	BASIS	EFFECT SIZE	96% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Survival time admission to death	3 comparative studies 465	Mean difference 2.47 days	-0.15, 5.09	inconclusive	Low

There were no studies that compared the quality of life of actively dying cancer patients receiving or not receiving palliative sedation..

### Certainty of evidence

Although not among the critical outcomes originally planned to be included, several studies (18/19 of the studies included in this review) compared time to death between patients given palliative sedation and those not given palliative sedation; hence it was included for this evidence synthesis. However, this outcome was measured variably as mean, or median, and not all information was presented. The overall certainty of evidence was very low because all studies retrieved were either retrospective or prospective cohort studies, with no controlled trials. The best design available was a prospective cohort of consecutive cases with matching baseline characteristics (but not of symptom severity). Hence, the conclusions and interpretations can still change depending on the availability of new evidence.

### Safety outcomes

Only one study (Chiu 2001) reported on unintended adverse effects of sedation: none in the sedated group, though 4/70 appeared to have drug-induced delirium. No respiratory suppression.

Harrison (unpublished) observed 5 adverse events in 9 in the benzodiazepine group compared to 4 of 9 in the placebo group (RD 0.11; 95% CI -0.35, 0.57).

## RECOMMENDATIONS FROM OTHER GROUPS

GROUP	RECOMMENDATION	
German Guideline Program in Oncology Sep 2020	PS can be offered for symptom control in patients with incurable cancer and insufficiently manageable symptoms resulting in the desire to die.  PS shall be carried out by competent physicians and nurses experienced in palliative care.	expert consensus

## **ADDITIONAL CONSIDERATIONS**

### **COST**

The cost of palliative sedation using the most common agent (midazolam) is Php 90 for midazolam 5 mg/ml, 1 ml solution for injection; the usual dose for infusion is 5 mg/hr. Hence, the daily cost for a continuous infusion of midazolam would be about Php 2,160.

### **PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY**

There are no local studies on patients' or HCPs' values and preferences regarding palliative sedation (databases searched were HERDIN and WPRIM).

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## 5. Research Implications/Gaps

**Further research will be needed to enhance and strengthen the evidence base on palliative care.** Patients from countries with low socio-economic status, healthcare/resource disparities, and/or cultures different from those in current research are underrepresented. Data on the clinical features and outcome of withdrawal of life-sustaining treatment and artificial mechanical ventilation especially among patients with advanced cancer are very limited in Asian populations.

Other research gaps found include the following:

- Meta-analysis was not possible due to limited studies and different tools or methods in reporting the outcome.
- Some studies had a short duration of follow-up.
- Some studies were without controls.
- Studies have small sample sizes or are underpowered.
- A double-blind study was not possible due to different drug formations or dosing schedules

There were no studies or trials found on the effect of opioids on blood pressure and hastened death among actively dying hypotensive patients with cancer, the effect of spiritual care on patient autonomy in end-of-life decisions, peaceful or dignified death, or Quality of end-of-life care, as well as on the effectiveness of the 2-step ladder approach vs. WHO 3-step ladder approach on compliance to the regimen and healthcare provider's distress or anxiety. There are also no current direct studies on cancer patients in their last six months of life and the effects of enteral or parenteral nutrition in their comfort, symptom control, anxiety and distress, and perception of care and satisfaction.

A larger clinical trial is currently underway NCT04188418 to evaluate fentanyl buccal tablets and oral morphine against placebo for patients with advanced cancer who experience exertional dyspnea. There are 4 clinical trials (ClinicalTrials.gov Identifier: NCT05433090, NCT05444348, NCT05045040, NCT03387436) underway which will investigate the effects of advanced care practitioner-delivered ACP interventions on older patients), effects of compassionate communication and ACP to improve end-of-life care in the treatment of hematological disease with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), effect of additional collaborative ACP to improve the quality of life for palliative cancer patients and effectiveness of a facilitating program utilizing a mobile application for initiating ACP discussions between patients with advanced cancer and healthcare providers.

**Further studies are suggested to evaluate the effects, outcomes for terminal extubation considering our different culture, values and context of dying of family members. Further exploration of protocols and application of a terminal extubation process in palliative care management is suggested. As conducting randomized controlled trials can be quite challenging in end-of-life quality care studies, prospective multi-center studies may possibly be helpful.** Similarly, consideration for future studies may include the role of palliative care for patients with early-stage disease and specific pain and symptom outcome measures.

## 6. Dissemination and Implementation

The dissemination of the guideline will be done after clearance from the National Practice Guidelines Clearinghouse of the Department of Health. Dissemination platforms include the regular national forum of professional societies and the DOH-organized research forum.

The Steering Committee recommends the following dissemination indicators:

1. Number of guideline presentation
2. Number of attendees
3. Feedback of the participants on the presented guidelines

## 7. Applicability Issues

The Task Force accentuates some caveats of this CPG using equity, feasibility, and availability of some interventions included in this guideline that may influence the recommendations at a national level. It was highlighted that not all areas in the Philippines have palliative and hospice care specialists or anyone with training in palliative and hospice care. Accessibility to medications specifically opioids and different forms of nutrition are limited and often difficult in most areas of the country. At times these resources are costly.

This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances. **With the variety of ethnic groups, existing laws and practices across various settings in the country should be reviewed and considered.**

**Active efforts must be done to address the issues of cost, accessibility, feasibility and equity to facilitate the implementation of the guideline.**

## **8. Updating of the Guidelines**

**The CPG can be revised every three years to coincide with the turnover of new evidence on the topic.** The lead CPG Developers will designate a date by which it will be expected that the validity of the CPG should be reviewed. Updates or revisions will be indicated if there are identified gaps in the current knowledge on the subject, newly released evidence from large scale studies, approval of new interventions or therapies, changes in critical or important outcomes, changes in values placed on outcomes, changes in resources available for health care, or potential need for new advice.

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## 10. Appendices

### A. Members of the CPG Task Force

#### COI Review Committee

##### **Dr. Rowena Galarpe-Pedrajas**

Treasurer, Philippine Society of Palliative and Hospice Medicine (PSHPM).  
Manila City.

##### **Mr. Fefe Jaspe**

Jose B. Lingad Memorial General Hospital-Institutional Review Board.  
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##### **Dr. Al D. Biag, EdD**

Central Luzon Health Research and Development Consortium.  
Tarlac City.

#### Steering Committee

##### **Dr. Agnes Bausa-Claudio**

*Chair*

Clinical Associate Professor, University of the Philippines – Philippine General Hospital College of Medicine; Clinical Faculty, Palliative Care Service & Fellowship Training, FEU-NRMMF Department of Community & Family Medicine; Founding Board, Hospice Philippines, PalCare Hospice Foundation Inc.; Founding Board & Advisory Council, Philippine Society of Hospice & Palliative Medicine (PSHPM); Head, Palliative & Supportive Care Unit, Jose B. Lingad Memorial General Hospital; Consultant, The Medical City; Cardinal Santos Medical Center; Medical Director, ActivCare Home Health Solutions, Inc.; Head, Palliative & Supportive Care Unit (PASCU), Amang Rodriguez Memorial Medical Center (ARMMC).  
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*Co-chair*

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Hospice Council, Pain Society of the Philippines; Founding Board and Advisory Council, Philippine Society of Hospice and Palliative Medicine (PSHMP); Board of Director, The CHILDHaus; Founding Member and Secretary, Cancer Coalition Philippines, Philippine Society of Anaesthesiology.

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### Members

#### **Dr. Pauline Anne Peronilla-Cauton**

Medical Oncologist, Cardinal Santos Medical Center, Tri-City Medical Center, Amang Rodriguez Memorial Medical Center, Health Cube Clinics; Philippine College of Physicians, Marikina Valley Medical Society; Philippine Society of Medical Oncology, American Society of Clinical Oncology; European Society of Medical Oncology.

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#### **Mr. Teddy Dizon**

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### **Consensus Panel Meeting Facilitator**

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Contributing Author, Advance Care Planning in the Asia Pacific; and Former Secretary, Founding Board, and Advisory Council, Philippine Society of Hospice and Palliative Medicine (PSHPM).  
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Valenzuela City, Metro Manila.

**B. Summary of COI Declarations**

Name	Summary of Declared Conflicts of Interest	Assessment Recommendation
<b>Conflict Of Interest Reviewer</b>		
Dr. Rowena Fatima Galarpe-Pedrajas	Secondary COI (Non-financial)	Assessment B
Mr. Fede Jaspe	No identified COI	Assessment A
Dr. Al D. Biag, EdD	No identified COI	Assessment A
<b>Conflict Of Interest Reviewer</b>		
Dr. Agnes B. Bausa-Claudio	Primary COI (Financial and Non-financial COI)	Assessment C
Dr. Rachael Marie B. Rosario	Secondary COI (Non-financial)	Assessment B
Dr. Pauline Anne Peronilla-Cauton	Secondary COI (Non-financial)	Assessment B
Dr. Nicolle Lourdes B. Dela Cruz	Secondary COI (Non-financial)	Assessment B
Mr. Teddy S. Dizon	Secondary COI (Non-financial)	Assessment B
<b>Consensus Panel</b>		
Ms. Maria Fatima Garcia-Lorenzo	Secondary COI Non-financial)	Assessment B
Dr. Jane Eflynn L. Lardizabal-Bunyi	Secondary COI (Non-financial)	Assessment B
Dr. Maria Agnes Cubillas-Torres	Secondary COI (Non-financial)	Assessment B

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Dr. Maria Dolma Gudez Santos	Secondary COI (Non-financial)	Assessment B
Dr. Maximino De Guzman Bello III	Secondary COI (Non-financial)	Assessment B
Dr. Marianna Ramona Sy-Quia Sioson	Secondary COI (Non-financial)	Assessment B
Mr. Edmar San Jose Elcarte	Secondary COI (Non-financial)	Assessment B
Dr. Generoso Roberto	Secondary COI (Non-financial)	Assessment B
Ms. Maribel Tipan Felix	No identified COI	Assessment A
Dr. Raymundo F. Resurreccion	No identified COI	Assessment A
Dr. Manuel Francisco T. Roxas	Secondary COI (Non-financial)	Assessment B
Atty. Abdel Jamal R. Disangcopan	No identified COI	Assessment A
Dr. Mari Joanne A. Guerzon- Joson	Secondary COI (Non-financial)	Assessment B
Dr. Jose Emmanuel Martin Palo	Secondary COI (Non-financial)	Assessment B

#### **Consensus Panel Meeting Facilitator**

Dr. Joanna Michelle F. Sabal	Secondary COI (Non-financial)	Assessment B
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#### **Evidence Review Experts**

Dr. Divina Cristy Redondo-Samin	No identified COI	Assessment A
Ms. Anna Maria Vida P. Garcia	Secondary COI (Non-financial)	Assessment B
Dr. Jardine Santiago Sta. Ana	Secondary COI (Non-financial)	Assessment B
Dr. Nikko Theodore Valencia Raymundo	No identified COI	Assessment A
Dr. Paul Matthew D. Pasco	No identified COI	Assessment A
Dr. Rich Ericson C. King	Secondary COI (Non-financial)	Assessment B
Ms. Diane R. Tamayo	Secondary COI (Non-financial)	Assessment B
Dr. Mark Joseph de Villa Bitong	No identified COI	Assessment A
Dr. Eva I. Bautista	Secondary COI (Non-financial)	Assessment B

#### **External Reviewers**

Dr. Maria Fidelis C. Manalo	Secondary COI (Non-financial)	Assessment B
Dr. June Michael V. Razon	Secondary COI (Non-financial)	Assessment B

#### **Project Staff**

Dr. Criselda Isabel C. Ceniza	Secondary COI (Non-financial)	Assessment B
Dr. Michael Ian N. Sta. Maria	Secondary COI (Non-financial)	Assessment B
Mr. Lemuel T. Cacho	No identified COI	Assessment A
Dr. Marianne Joy Naria-Maritana	Secondary COI (Non-financial)	Assessment B
Dr. Ana Kristine V. Bermudez	Secondary COI (Non-financial)	Assessment B
Dr. Nenacia Ranali Nirena Palma Mendoza	Secondary COI (Non-financial)	Assessment B

Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: <https://ehospice.com/international-posts/integration-of-palliative-care-into-the-philippine-health-system/> along with this CPG.

## C. SEARCH Strategy

### 1. Palliative Care and Improvement of Quality of Life and Symptom Control

DATABASE	No.	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
				Yield	Eligible
EBM Reviews - Cochrane Central Register of Controlled Trials <January 2023>; EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 15, 2023>; Embase <1974 to 2023 February 14>; Ovid MEDLINE(R) ALL <1946 to February 14, 2023>	1	exp neoplasm/	15 Feb 2023	9430881	
	2	(Cancer\$ or carcino\$ or neoplasm\$ or neoplas\$ or malignan\$ or tumo?r).ti,ab.	15 Feb 2023	9174775	
	3	adult/	15 Feb 2023	15112633	
	4	adult.ti,ab.	15 Feb 2023	2161087	
	5	(1 or 2) and (3 or 4)	15 Feb 2023	3388479	
	6	limit 5 to humans	15 Feb 2023	3305645	
	7	Palliative Care/ or Palliative Medicine/ or palliative therapy/ or exp cancer palliative therapy/	15 Feb 2023	205722	
	8	(palliat\$ adj3 (care or consult\$ or medicine or therap\$ or program\$ or proced\$ or surger\$ or treat\$ or chemo\$)).ti,ab.	15 Feb 2023	170285	
	9	7 or 8	15 Feb 2023	265270	
	10	6 and 9	15 Feb 2023	55029	
	11	clinical outcome/ or quality of life/ or quality of life assessment/ or health care quality/	15 Feb 2023	1548141	
	12	((pain or symptom) adj3 (intensity or burden or control or manage\$ or treat\$ or therap\$ or proced\$ or relief)).ti,ab.	15 Feb 2023	564271	
	13	((peace\$ or digni\$) adj3 death).ti,ab.	15 Feb 2023	2358	
	14	*Terminally ill/px	15 Feb 2023	1588	
	15	psychological assessment/ or psychological distress/ or psychological	15 Feb 2023	190099	

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	screening/ or			
	psychological treatment/ or mental stress/ or			
	Psycho-Oncology/			
16	Stress, Psychological/px	15 Feb 2023	33276	
17	(psychosocial adj3 (outcome\$ or factor\$ or aspect\$ or stud\$ or endpoint\$ or function\$ or assess\$ or screen\$)).ti,ab.	15 Feb 2023	101514	
18	Patients/ or Terminally ill patient/ or Family/ or Caregivers/ or Health care personnel/ or Patient Care Team/	15 Feb 2023	1902824	
19	Caregiver burden/	15 Feb 2023	11219	
20	health personnel attitude/ or health care personnel attitude/ or *professional-patient relationship/	15 Feb 2023	230086	
21	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	15 Feb 2023	4203389	
22	10 and 21	15 Feb 2023	17182	
23	((meta\$ or systematic) adj3 (analys\$ or review\$)).ti,ab.	15 Feb 2023	1184110	
24	22 and 23	15 Feb 2023	666	
25	limit 24 to yr="2017 – 2022"	15 Feb 2023	397	
26	remove duplicates from 25	15 Feb 2023	337	
27	((random\$ or clinical or control\$ or experiment\$ or interventional) adj3 (trial\$ or stud\$ or program\$)).ti,ab.	15 Feb 2023	5119408	
28	22 and 27	15 Feb 2023	2904	
29	remove duplicates from 28	15 Feb 2023	2188	

2. Adding opioids to the standard of care in the relief of dyspnea

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eli-gible
Medline	("analgesics, opioid"[MeSH Terms] OR ("papaveretum"[Title/Abstract] OR "morphine"[Title/Abstract] OR "fentanyl"[Title/Abstract] OR "hydromorphone"[Title/Abstract] OR "oxycodone"[Title/Abstract] OR "pentazocine"[Title/Abstract] OR "methadone"[Title/Abstract] OR "opioid**"[Title/Abstract] OR	January 25, 2023 8:00 PM	457	7

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	"opiate*"[Title/Abstract] OR "codeine"[Title/Abstract] OR "dextromoramide"[Title/Abstract] OR "OTFC"[Title/Abstract] OR "diamorphine"[Title/Abstract] OR "dihydrocodeine"[Title/Abstract] OR "dextropropoxyphene"[Title/Abstract] OR "meptazinol"[Title/Abstract] OR "sufentanil"[Title/Abstract] OR "alfentanil"[Title/Abstract] OR "remifentanil"[Title/Abstract] OR "nalbuphine"[Title/Abstract] OR "dipipanone"[Title/Abstract] OR "pethidine"[Title/Abstract] OR "tramadol"[Title/Abstract] OR "buprenorphine"[Title/Abstract])) AND ("dyspnea"[MeSH Terms] OR ("dyspnea"[Title/Abstract] OR "dyspnœa"[Title/Abstract] OR "breath*"[Title/Abstract])) AND ("neoplasms"[MeSH Terms] OR ("cancer"[Title/Abstract] OR "tumor"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "malignancy"[Title/Abstract]))			
CENTRAL	MeSH descriptor: [Analgesics, Opioid] explode all trees AND MeSH descriptor: [Dyspnea] explode all trees AND MeSH descriptor: [Neoplasms] explode all trees	January 25, 2023 8:00 PM	22	4
Google Scholar	allintitle: dyspnea AND cancer AND opioid OR morphine OR fentanyl OR hydromorphone OR oxycodone OR opiate	January 25, 2023 8:00 PM	59	7
ClinicalTrials.gov	Cancer AND opioid AND dyspnea	January 25, 2023 8:00 PM	15	3

### 3. Use of Opioids among actively dying hypotensive adult cancer patients

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields] OR ("morphine derivatives"[MeSH Terms] OR ("morphine"[All Fields] AND "derivatives"[All Fields]) OR "morphine derivatives"[All Fields] OR "morphines"[All Fields] OR "morphine"[MeSH Terms] OR "morphine"[All Fields] OR	January 29, 2023 6:34 PM	329	3

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	"morphin"[All Fields] OR "morphine s"[All Fields] OR "morphinic"[All Fields]) OR ("fentanyl"[MeSH Terms] OR "fentanyl"[All Fields] OR "fentanyls"[All Fields] OR "fentanyl s"[All Fields]) OR ("hydromorphone"[MeSH Terms] OR "hydromorphone"[All Fields]) OR ("oxycodone"[MeSH Terms] OR "oxycodone"[All Fields] OR "oxycodone s"[All Fields]) OR ("methadon"[All Fields] OR "methadone"[MeSH Terms] OR "methadone"[All Fields] OR "methadone s"[All Fields]) OR ("codeine"[MeSH Terms] OR "codeine"[All Fields] OR "codein s"[All Fields]) OR ("opiate alkaloids"[MeSH Terms] OR ("opiate alkaloids"[All Fields]) OR "opiate alkaloids"[All Fields] OR "opiate s"[All Fields]) OR ("nalbuphine"[MeSH Terms] OR "nalbuphine"[All Fields] OR "nalbuphin"[All Fields]) OR ("buprenorphin"[All Fields] OR "buprenorphine"[MeSH Terms] OR "buprenorphine"[All Fields] OR "buprenorphine s"[All Fields]) OR ("dextromoramide"[MeSH Terms] OR "dextromoramide"[All Fields])) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields])) OR ("cancer pain"[MeSH Terms] OR ("cancer"[All Fields] AND "pain"[All Fields]) OR "cancer pain"[All Fields])) AND ("antihypertensive agents"[Pharmacological Action] OR "antihypertensive agents"[MeSH Terms] OR ("antihypertensive"[All Fields] AND "agents"[All Fields]) OR "antihypertensive agents"[All Fields] OR "hypotensives"[All Fields] OR "hypotension"[MeSH Terms] OR "hypotension"[All Fields] OR "hypotensions"[All Fields] OR "hypotensive"[All Fields])) OR "effect on blood pressure"[All Fields]) AND (y_10[Filter]			
Medline	("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields])) OR ("cancer pain"[MeSH Terms] OR ("cancer"[All Fields] AND "pain"[All Fields]) OR "cancer pain"[All Fields])) AND ("antihypertensive agents"[Pharmacological Action] OR "antihypertensive agents"[MeSH Terms] OR ("antihypertensive"[All Fields] AND "agents"[All Fields]) OR "antihypertensive agents"[All Fields] OR "hypotensives"[All Fields] OR "hypotension"[MeSH Terms] OR "hypotension"[All Fields] OR "hypotensions"[All Fields] OR "hypotensive"[All Fields])) OR "effect on blood pressure"[All Fields]) AND (y_10[Filter]	March 25, 2023 11:07 AM	20	5

Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: [https://ehospice.com/international\\_posts/integration-of-palliative-care-into-the-philippine-health-system/](https://ehospice.com/international_posts/integration-of-palliative-care-into-the-philippine-health-system/) along with this CPG.

	Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND (("hasten"[All Fields] OR "hastened"[All Fields] OR "hastening"[All Fields] OR "hastens"[All Fields]) AND ("death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields])) AND ("terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields]) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]))			
Google Scholar	<b>allintitle: cancer AND opioid OR morphine OR fentanyl OR hydromorphone OR oxycodone OR opiate AND hypotension OR effect on blood pressure AND hastened death OR survival</b>	March 25, 2023 11:30 PM	164	1
ClinicalTrials. gov	<b>Cancer AND opioid AND hypotension AND survival AND hastened death</b>	January 25, 2023 8:00 PM	0	0

4. Effectivity of the 2-step ladder approach versus WHO 3-step ladder approach in achieving pain control

a. Search strategy and yield (as of Mar 1, 2023), (PubMed)

#	Query	Results
1	cancer	4,798,579
2	pain	989,182
3	#1 AND #2	132,342
4	Tramadol OR codeine OR dihydrocodeine OR "weak opioid" OR "WHO analgesic ladder" OR "WHO pain ladder" OR "three-step approach" OR "three-step pain ladder"	17,202
5	Morphine OR methadone OR fentanyl OR oxycodone OR buprenorphine OR tapentadol OR hydromorphone OR oxymorphone OR "strong opioid" OR "two step approach" OR "two step pain ladder"	121,516
6	#4 AND #5	10837
7	#3 AND #6	916
8	#3 AND 6 Filter: Humans	822

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## b. Search strategy and yield (as of Mar 2, 2023), (Cochrane Central)

#	Query	Results
#1	World Health Organization	15444
#2	two-step	1212
#3	three-step	427
#4	#2 AND #3	46
#5	#1 AND #4	5

## c. Search strategy and yield (as of Mar 2, 2023), (Herdin)

#	Query	Results
1	(Cancer AND Pain) AND ("World Health Organization") AND ((two-step) AND (three-step))	12

## d. Search strategy and yield (as of Mar 2, 2023), (Clintrials.gov)

#	Query	Results
1	World Health Organization   Cancer Pain   "two-step" AND "Three-step"	1

## 5. Effectivity of transdermal opioid patch vs subcutaneous opioid administration in symptom control

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	Search: (((transdermal fentanyl[Title/Abstract] OR transdermal buprenorphine[Title/Abstract] OR subcutaneous methadone[Title/Abstract] OR subcutaneous diamorphine OR subcutaneous oxycodone[Title/Abstract] OR subcutaneous fentanyl[Title/Abstract] OR subcutaneous buprenorphine[Title/Abstract] OR subcutaneous morphine[Title/Abstract] OR subcutaneous hydromorphone[Title/Abstract] OR	23-Feb-23	290	1

	subcutaneous sulfentanil[Title/Abstract] OR subcutaneous alfentanil[Title/Abstract]) ) NOT (oral[Title/Abstract])) AND (cancer*[Title/Abstract] OR carcin*[Title/Abstract] OR neoplas*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor[Title/Abstract])			
Europe PMC	Cancer AND (transdermal fentanyl OR transdermal buprenorphine OR subcutaneous fentanyl OR subcutaneous buprenorphine OR subcutaneous morphine OR subcutaneous hydromorphone OR subcutaneous sulfentanil OR subcutaneous alfentanill OR subcutaneous oxycodone OR subcutaneous methadone OR subcutaneous diamorphine) AND random*	23-Feb-23	69	0
Cochrane Central Register of Controlled Trials (CENTRAL)	5 Cochrane Reviews matching cancer in Title Abstract Keyword AND transdermal fentanyl OR transdermal buprenorphine OR subcutaneous fentanyl OR subcutaneous buprenorphine OR subcutaneous morphine OR subcutaneous hydromorphone OR subcutaneous sulfentanil OR subcutaneous alfentanill OR subcutaneous oxycodone OR subcutaneous methadone OR subcutaneous diamorphine in Abstract AND random* in Abstract - (Word variations have been searched)	23-Feb-23	5	0
ClinTrials.gov	108 Trials matching cancer in Title Abstract Keyword AND transdermal fentanyl OR transdermal buprenorphine OR subcutaneous fentanyl OR subcutaneous buprenorphine OR subcutaneous morphine OR subcutaneous hydromorphone OR subcutaneous sulfentanil OR subcutaneous alfentanill OR subcutaneous oxycodone OR subcutaneous methadone OR subcutaneous diamorphine in Abstract AND random* in Abstract - (Word variations have been searched)	23-Feb-23	108	0

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medRxiv.org (and bioRxiv.org)	"cancer AND (transdermal buprenorphine OR transdermal fentanyl)"	23-Feb-23	46	0
Cross-referencing			6	1

## 6. Psychosocial and Spiritual Care

### a. Psychosocial Care

Database	Search Strategy	Date and Time	Yield
Pubmed	((("spiritual"[All Fields] OR "spiritualism"[MeSH Terms] OR "spiritualism"[All Fields] OR "spirituality"[MeSH Terms] OR "spirituality"[All Fields] OR "spiritualities"[All Fields] OR "spirituality s"[All Fields] OR "spiritually"[All Fields] OR "spirituals"[All Fields] OR ("spiritual"[All Fields] OR "spiritualism"[MeSH Terms] OR "spiritualism"[All Fields] OR "spirituality"[MeSH Terms] OR "spirituality"[All Fields] OR "spiritualities"[All Fields] OR "spirituality s"[All Fields] OR "spiritually"[All Fields] OR "spirituals"[All Fields]) OR "spiritual intervention"[All Fields] OR "spiritual therapy"[All Fields] OR "spiritual care"[All Fields] OR ("religion"[MeSH Terms] OR "religion"[All Fields] OR "religions"[All Fields] OR "religion s"[All Fields] OR "religiosity"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] AND ("Comfort care"[All Fields] OR "end-of-life care"[All Fields] OR "end-of-life care"[All Fields] OR "palliative care"[All Fields])) AND ((guideline[Filter] OR meta-analysis[Filter] OR practiceguideline[Filter] OR systematicreview[Filter]) AND (humans[Filter])))	June 3, 2023 4:07:15	76
Pubmed	(((((((((((cancer) OR (sarcoma)) OR (leukemia)) OR (lymphoma)) OR (multiple myeloma)) OR (melanoma)) OR (germ cell tumor))		

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	OR (blastoma)) OR (neuroendocrine tumor)) OR (carcinoid tumor)) AND (((((((spiritual care) OR (spirituality)) OR (existential care)) OR (psychospiritual)) OR (spiritual)) OR (religion)) OR (religious)) OR (religiosity)) OR (existential))) AND (((("Psychosocial Intervention"[Mesh]) OR (psychosocial care)) OR (psychosocial support)) OR (psychosocial therapy))) AND ((((((((((((randomized controlled trial[Publication Type]) OR (randomized controlled trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[sh])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) OR (pretest-posttest study)) OR (pretesting)) OR (pre-post tests)) OR (quasi-experimental design)) OR (quasi-experimental study)) OR (quasi-experimental study design)) OR (repeated measurement)) OR (repeated measures)) OR (time series)) OR (cohort)) OR (case-control)) OR (cohort study)) OR (case-control study)) OR (observational study)) NOT ((animals[mh]) NOT ((animals[mh]) AND (humans[mh]))))		
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## 6.2 Psychosocial Care

Database	Search Strategy	Date and Time	Yield
Pubmed	((("psychosocial"[All Fields] OR "psychosocially"[All Fields] OR ("psychotherapie"[All Fields] OR "psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields] OR "psychotherapies"[All Fields] OR "psychotherapy s"[All Fields]) OR "psycho*"[All Fields] OR "behavioral therapy"[All Fields] OR "cognitive behavior"[All Fields] OR "cognitive behaviour"[All Fields] OR "behavior*"[All Fields] OR "behaviour*"[All Fields] OR "cognitive therapy"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR	June 3, 2023 4:00:41	491

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"neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("Comfort care"[All Fields] OR "end-of-life care"[All Fields] OR "palliative care"[All Fields])) AND ((guideline[Filter] OR meta-analysis[Filter] OR practiceguideline[Filter] OR systematicreview[Filter]) AND (humans[Filter]))		
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## 7. Advance Care Planning and Satisfaction and Perception with Care

DATABASE	SEARCH STRATEGY/SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
NCCN	Palliative	February 6, 2023. 2245H	34	0
Cochrane	cancer and "advance care planning."	February 6, 2023. 2315H	3	0
Pubmed	("advance care planning"[All Fields] AND ((("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult s"[All Fields]))) AND ((y_5[Filter]) AND (meta- analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	February 27, 2023. 2122H	58	0

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Pubmed	<p>Search: ("advance care planning" OR "advance directives" OR "living will" OR "goals of care" OR "anticipatory care" OR "healthcare directive" OR "healthcare decisions at the end-of-life" AND (y_10[Filter])) AND (cancer) AND (y_10[Filter])) AND (satisfaction)</p> <p>Filters:</p>	March 14, 2023. 1800H	157	4
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## 8. Parenteral and Enteral Nutrition in the last six months of life

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	"hydrational"[All Fields] OR "hydrations"[All Fields])))) AND ("terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields]) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) OR ((("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("time"[MeSH Terms] OR "time"[All Fields])) OR ("comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR "comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields]) OR ("anxiety"[MeSH Terms] OR "anxiety"[All Fields] OR "anxieties"[All Fields] OR "anxiety s"[All Fields]) OR ("distress"[All Fields] OR "distressed"[All Fields] OR "distresses"[All Fields] OR "distressful"[All Fields] OR "distressing"[All Fields]) OR ("percept"[All Fields] OR "perceptibility"[All Fields] OR "perceptible"[All Fields] OR "perception"[MeSH Terms] OR "perception"[All Fields] OR "perceptions"[All Fields] OR "perceptional"[All Fields] OR "perceptive"[All Fields] OR "perceptiveness"[All Fields] OR "percepts"[All Fields]) OR ("personal satisfaction"[MeSH Terms] OR ("personal"[All Fields] AND "satisfaction"[All Fields]) OR "personal satisfaction"[All Fields] OR "satisfaction"[All Fields] OR "satisfactions"[All Fields] OR "satisfaction s"[All Fields]) OR ("benefit"[All Fields] OR "benefited"[All Fields] OR "benefiting"[All Fields] OR "benefits"[All Fields] OR "benefitted"[All Fields] OR "benefitting"[All Fields]))) AND ((y_5[Filter]) AND (systematicreview[Filter]))	
22	#5 AND #11 AND #21  ((("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR ("death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All Fields] AND "life"[All Fields]) OR "end-of-life"[All Fields]) OR ("terminally ill"[MeSH Terms] OR ("terminally"[All Fields] AND "ill"[All Fields]) OR "terminally ill"[All Fields]) OR ("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields]) OR "palliative care"[All Fields])) AND ("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutrition s"[All Fields])	16,897

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	"nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritional"s"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields] OR ("enteral nutrition"[MeSH Terms] OR ("enteral"[All Fields] AND "nutrition"[All Fields]) OR "enteral nutrition"[All Fields]) OR ("parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields]) OR ("artificial"[All Fields] OR "artificially"[All Fields]) AND ("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritional"s"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields] OR "nutritive"[All Fields])) OR ("artificial"[All Fields] OR "artificially"[All Fields]) AND ("hydratation"[All Fields] OR "hydrate"[All Fields] OR "hydrated"[All Fields] OR "hydrates"[All Fields] OR "hydrating"[All Fields] OR "hydration"[All Fields] OR "hydrational"[All Fields] OR "hydrations"[All Fields])) AND ("terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields]) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) AND "care"[All Fields] OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields] OR ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("time"[MeSH Terms] OR "time"[All Fields])) OR ("comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR "comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields]) OR ("anxiety"[MeSH Terms] OR "anxiety"[All Fields] OR "anxieties"[All Fields] OR "anxiety s"[All Fields]) OR ("distress"[All Fields] OR "distressed"[All Fields] OR "distresses"[All Fields] OR "distressful"[All Fields] OR "distressing"[All Fields]) OR ("percept"[All Fields] OR "perceptibility"[All Fields] OR "perceptible"[All Fields] OR "perception"[MeSH Terms] OR "perception"[All Fields] OR "perceptions"[All Fields] OR "perceptional"[All Fields] OR "perceptive"[All Fields] OR "perceptiveness"[All Fields] OR "percepts"[All Fields]) OR ("personal satisfaction"[MeSH Terms] OR ("personal"[All Fields] AND "satisfaction"[All Fields]) OR "personal satisfaction"[All Fields] OR	
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	"satisfaction"[All Fields] OR "satisfactions"[All Fields] OR "satisfaction s"[All Fields] OR ("benefit"[All Fields] OR "benefited"[All Fields] OR "benefiting"[All Fields] OR "benefits"[All Fields] OR "benefitted"[All Fields] OR "benefitting"[All Fields]))	
21	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20  "terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields]) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields] OR ((("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("time"[MeSH Terms] OR "time"[All Fields])) OR ("comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR "comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields]) OR ("anxiety"[MeSH Terms] OR "anxiety"[All Fields] OR "anxieties"[All Fields] OR "anxiety s"[All Fields]) OR ("distress"[All Fields] OR "distressed"[All Fields] OR "distresses"[All Fields] OR "distressful"[All Fields] OR "distressing"[All Fields]) OR ("percept"[All Fields] OR "perceptibility"[All Fields] OR "perceptible"[All Fields] OR "perception"[MeSH Terms] OR "perception"[All Fields] OR "perceptions"[All Fields] OR "perceptional"[All Fields] OR "perceptive"[All Fields] OR "perceptiveness"[All Fields] OR "percepts"[All Fields]) OR ("personal satisfaction"[MeSH Terms] OR ("personal"[All Fields] AND "satisfaction"[All Fields]) OR "personal satisfaction"[All Fields] OR "satisfaction"[All Fields] OR "satisfactions"[All Fields] OR "satisfaction s"[All Fields]) OR ("benefit"[All Fields] OR "benefited"[All Fields] OR "benefiting"[All Fields] OR "benefits"[All Fields] OR "benefitted"[All Fields] OR "benefitting"[All Fields]))	3,187,643
20	Benefit  "benefit"[All Fields] OR "benefited"[All Fields] OR "benefiting"[All Fields] OR "benefits"[All Fields] OR "benefitted"[All Fields] OR "benefitting"[All Fields]	887,911
19	Satisfaction "personal satisfaction"[MeSH Terms] OR ("personal"[All Fields] AND "satisfaction"[All Fields]) OR "personal satisfaction"[All Fields] OR "satisfaction"[All Fields] OR "satisfactions"[All Fields] OR "satisfaction s"[All Fields]	248,917
18	Perception  "percept"[All Fields] OR "perceptibility"[All Fields] OR "perceptible"[All Fields] OR "perception"[MeSH Terms] OR	730,599

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	"perception"[All Fields] OR "perceptions"[All Fields] OR "perceptual"[All Fields] OR "perceptive"[All Fields] OR "perceptiveness"[All Fields] OR "percepts"[All Fields]	
17	Distress  "distress"[All Fields] OR "distressed"[All Fields] OR "distresses"[All Fields] OR "distressful"[All Fields] OR "distressing"[All Fields]	179,745
16	Anxiety  "anxiety"[MeSH Terms] OR "anxiety"[All Fields] OR "anxieties"[All Fields] OR "anxiety s"[All Fields]	310,180
15	Comfort  "comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR "comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields]	60,328
14	Survival time  ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("time"[MeSH Terms] OR "time"[All Fields])	602,605
13	Quality of life  "quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]	520,652
12	End-of-life care  "terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields]) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields])	101,571
11	#6 OR #7 OR #8 OR #9 OR #10  "nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritional s"[All Fields] OR "nutritive"[All Fields] OR ("enteral nutrition"[MeSH Terms] OR ("enteral"[All Fields] AND "nutrition"[All Fields])) OR "enteral nutrition"[All Fields] OR ("parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields])) OR "parenteral nutrition"[All Fields] OR ("artificial"[All Fields] OR "artificially"[All Fields]) AND ("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields])) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms]	765,401

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	OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritional"[All Fields] OR "nutritive"[All Fields])) OR ((("artificial"[All Fields] OR "artificially"[All Fields]) AND ("hydratation"[All Fields] OR "hydrate"[All Fields] OR "hydrated"[All Fields] OR "hydrates"[All Fields] OR "hydrating"[All Fields] OR "hydration"[All Fields] OR "hydrational"[All Fields] OR "hydrations"[All Fields]))	
10	Artificial hydration  ("artificial"[All Fields] OR "artificially"[All Fields]) AND ("hydratation"[All Fields] OR "hydrate"[All Fields] OR "hydrated"[All Fields] OR "hydrates"[All Fields] OR "hydrating"[All Fields] OR "hydration"[All Fields] OR "hydrational"[All Fields] OR "hydrations"[All Fields])	1,967
9	Artificial nutrition  ("artificial"[All Fields] OR "artificially"[All Fields]) AND ("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[AllFields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritional s"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields])	10,117
8	Parenteral nutrition  "parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields]	35,998
7	Enteral nutrition  "enteral nutrition"[MeSH Terms] OR ("enteral"[All Fields] AND "nutrition"[All Fields]) OR "enteral nutrition"[All Fields]	31,470
6	Nutrition  "nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritional s"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields]	763,963
5	#1 OR #2 OR #3 OR #4  ((("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR ("death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All	2,993,077

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	Fields] AND "life"[All Fields]) OR "end-of-life"[All Fields]) OR ("terminally ill"[MeSH Terms] OR ("terminally"[All Fields] AND "ill"[All Fields]) OR "terminally ill"[All Fields]) OR ("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields]) OR "palliative care"[All Fields])	
4	Palliative care "palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields]) OR "palliative care"[All Fields]	98,532
3	Terminally ill "terminally ill"[MeSH Terms] OR ("terminally"[All Fields] AND "ill"[All Fields]) OR "terminally ill"[All Fields]	11,260
2	End-of-life "death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All Fields] AND "life"[All Fields]) OR "end-of-life"[All Fields]	1,119,244
1	Cancer patients  ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])	1,959,915

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	((("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR ("death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All Fields] AND "life"[All Fields]) OR "end-of-life"[All Fields]) OR ("terminally ill"[MeSH Terms] OR ("terminally"[All Fields] AND "ill"[All Fields]) OR "terminally ill"[All Fields]) OR ("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields])) OR	Januar y 20, 2023 1830H	393	4 SR; 2 CPG

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	<p>"palliative care"[All Fields]))</p> <p>AND ("nutrition s"[All Fields]</p> <p>OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR</p> <p>"nutrition"[All Fields] OR</p> <p>"nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR</p> <p>"nutritional"[All Fields] OR</p> <p>"nutritional s"[All Fields] OR</p> <p>"nutritions"[All Fields] OR</p> <p>"nutritive"[All Fields] OR</p> <p>("enteral nutrition"[MeSH Terms] OR ("enteral"[All Fields] AND "nutrition"[All Fields]) OR "enteral nutrition"[All Fields]) OR</p> <p>("parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields]) OR</p> <p>((("artificial"[All Fields] OR</p> <p>"artificially"[All Fields]) AND</p> <p>("nutrition s"[All Fields] OR</p> <p>"nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR</p> <p>"nutrition"[All Fields] OR</p> <p>"nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR</p> <p>"nutritional"[All Fields] OR</p> <p>"nutritional s"[All Fields] OR</p> <p>"nutritions"[All Fields] OR</p> <p>"nutritive"[All Fields])) OR</p> <p>((("artificial"[All Fields] OR</p> <p>"artificially"[All Fields]) AND</p> <p>("hydratation"[All Fields] OR</p> <p>"hydrate"[All Fields] OR</p> <p>"hydrated"[All Fields] OR</p> <p>"hydrates"[All Fields]</p> <p>OR "hydrating"[All Fields] OR</p> <p>"hydration"[All Fields] OR</p> <p>"hydrational"[All Fields] OR</p>		
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	"hydrations"[All Fields])))) AND ("terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields]) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) OR (("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) AND ("time"[MeSH Terms] OR ("time"[All Fields]))) OR ("comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR "comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields]) OR ("anxiety"[MeSH Terms] OR "anxiety"[All Fields] OR "anxieties"[All Fields] OR "anxiety s"[All Fields]) OR ("distress"[All Fields] OR "distressed"[All Fields] OR "distresses"[All Fields] OR "distressful"[All Fields] OR "distressing"[All Fields]) OR ("percept"[All Fields] OR "perceptibility"[All Fields] OR "perceptible"[All Fields]) OR		
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	"perception"[MeSH Terms] OR "perception"[All Fields] OR "perceptions"[All Fields] OR "perceptual"[All Fields] OR "perceptive"[All Fields] OR "perceptiveness"[All Fields] OR "percepts"[All Fields]) OR ("personal satisfaction"[MeSH Terms] OR ("personal"[All Fields] AND "satisfaction"[All Fields]) OR "personal satisfaction"[All Fields] OR "satisfaction"[All Fields] OR "satisfactions"[All Fields] OR "satisfaction s"[All Fields]) OR ("benefit"[All Fields] OR "benefited"[All Fields] OR "benefiting"[All Fields] OR "benefits"[All Fields] OR "benefitted"[All Fields] OR "benefitting"[All Fields])) AND (y_5[Filter]) AND (systematicreview[Filter]))			
Cochrane	Enteral nutrition; Parenteral nutrition; End-of-life; Cancer patients; Quality of life; Survival; Benefit	January 27, 2023; 1140H	570	4 indiv studies

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Google Scholar	Enteral nutrition; Parenteral nutrition; End-of-life; Cancer patients; Quality of life; Survival; Benefit; Perception	February 16, 2023; 1200H	1318	4 SR; 4 CPC; 17 indiv studies
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## 9. Terminal extubation and quality of end-of-life care

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Pubmed	(advanced cancer) AND (((end-of-life) OR (end-of-life care)) AND (intensive care unit))  ("advance"[All Fields] OR "advanced"[All Fields] OR "advancement"[All Fields] OR "advancements"[All Fields] OR "advances"[All Fields] OR "advancing"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ((("death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All Fields] AND "life"[All Fields]) OR "end-of-life"[All Fields] OR ("terminal care"[MeSH Terms] OR ("terminal"[All Fields] AND "care"[All Fields])) OR "terminal care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]) OR "end-of-life care"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] OR ("end"[All Fields] AND "life"[All Fields] AND "care"[All Fields]))) AND (("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR ("intensive"[All Fields] AND	February 12, 2023 9:00 PM	466	4

Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: [https://ehospice.com/international\\_posts/integration-of-palliative-care-into-the-philippine-health-system/](https://ehospice.com/international_posts/integration-of-palliative-care-into-the-philippine-health-system/) along with this CPG.

	"care"[All Fields] AND "unit"[All Fields]) OR "intensive care unit"[All Fields])			
Google Scholar	Terminal/Palliative extubation AND advanced cancer in end-of-life care	March 6, 2023 8:00AM	24	8
Cochrane Central	Terminal illness-late stage AND advanced cancer	March 27, 2023 6:00 AM	7	0
National Cancer Care Network	Terminal extubation and advanced cancer		1	0
American Thoracic Society	Terminal Extubation		2	1
Society of Critical Care Medicine	Terminal extubation AND Cancer		0	0
American Society of Critical Care-Nurses	Terminal/palliative Extubation and Cancer		0	0
Canadian Critical Care Society	Terminal/palliative Extubation and Advanced Cancer		1	1
Canadian Association of Critical Care Nurses	Terminal/palliative extubation		1	1
Intensive Care Society	Terminal/palliative extubation		1	0

## 10. Palliative sedation and control of symptoms

A systematic search was done last 2 July 2023 from the date of the last search (Dec 2014) of the most recent systematic review found on Medline, with a combined MeSH and free text search using the terms palliative sedation, cancer pain, restlessness, and agitation.

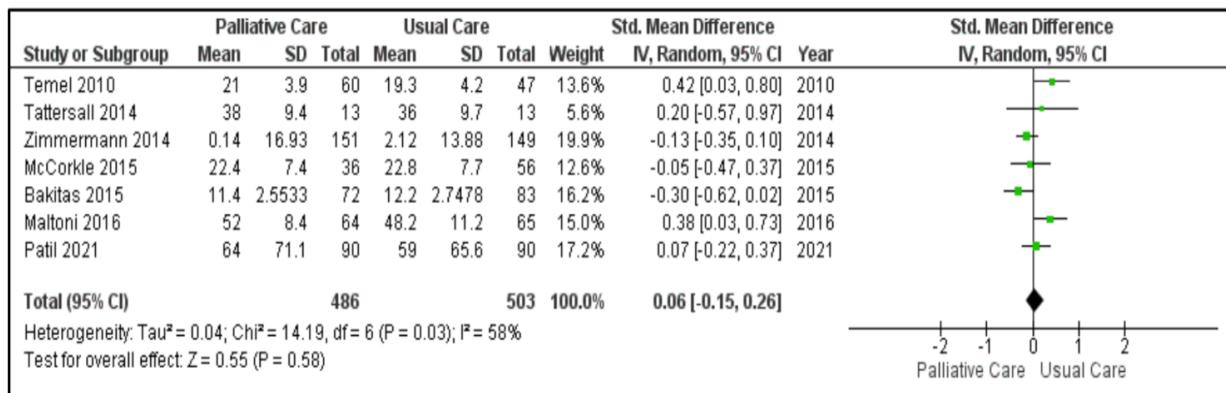
Pubmed search strategy: ("cancer pain"[MeSH Terms] OR ("cancer"[All Fields] AND "pain"[All Fields]) OR "cancer pain"[All Fields]) AND ("palliative"[All Fields] OR "palliatively"[All Fields] OR "palliatives"[All Fields]) AND ("sedate"[All Fields] OR "sedated"[All Fields] OR "sedating"[All Fields] OR "sedation"[All Fields] OR "sedations"[All Fields])

Number of hits: 311; number excluded: 292; number included: 19

We searched the Cochrane Database of Systematic Reviews and Medline for randomized controlled trials and studies of any design that compared palliative sedation against no palliative sedation. Outcomes of interest were quality of life, symptom control, patient satisfaction, and time to death. If any controlled trials were found, we planned to use the Cochrane Risk of Bias criteria.

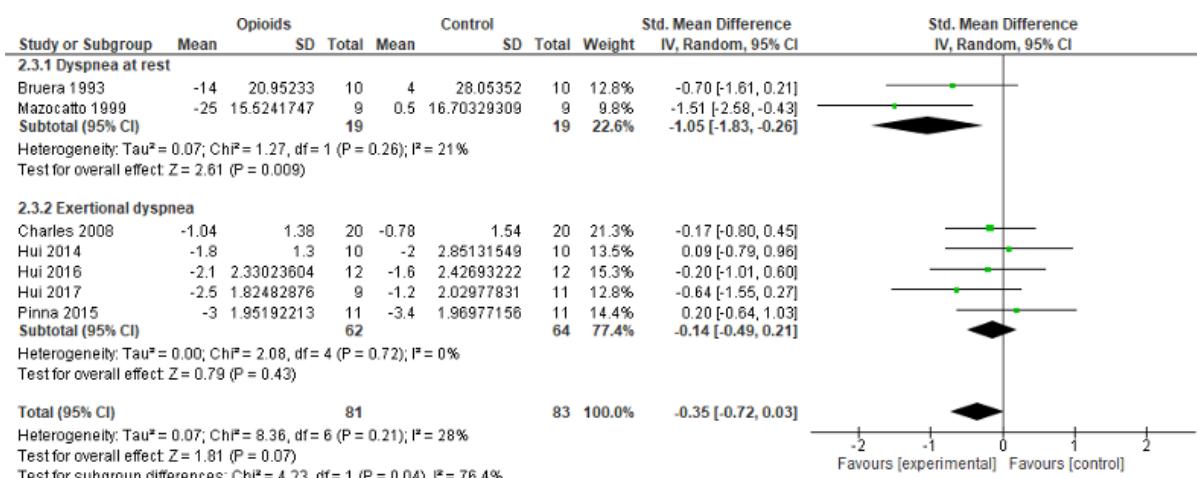
## D.Forest Plots

### 1. Palliative Care and Improvement of Quality of Life and Symptom Control

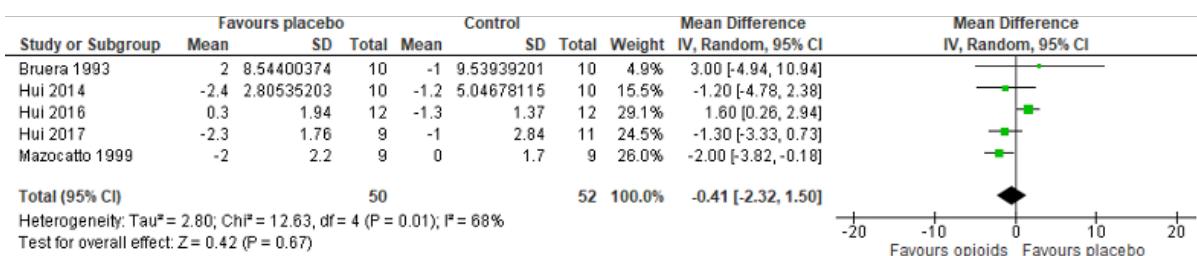


### 2. Adding opioids to the standard of care in the relief of dyspnea

#### a. Opioids versus placebo among patients with cancer - breathlessness

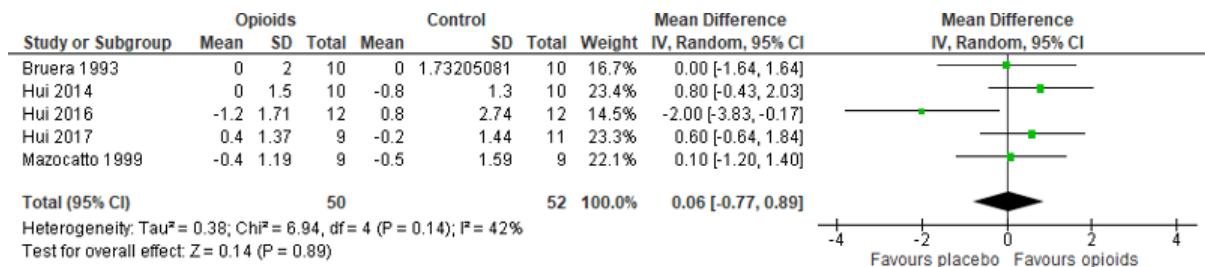


#### b. Opioids versus placebo among patients with cancer – respiratory rate

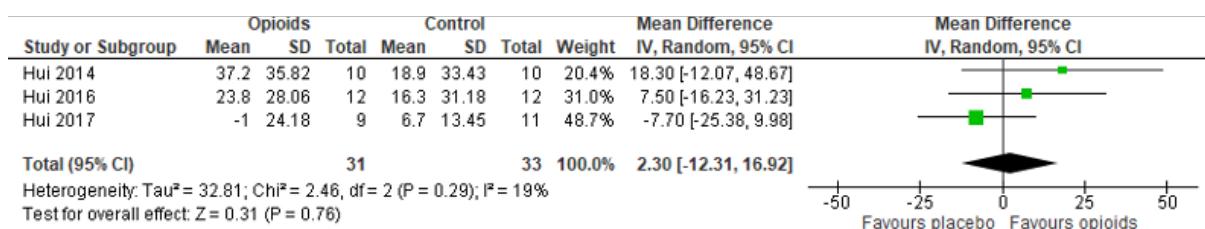


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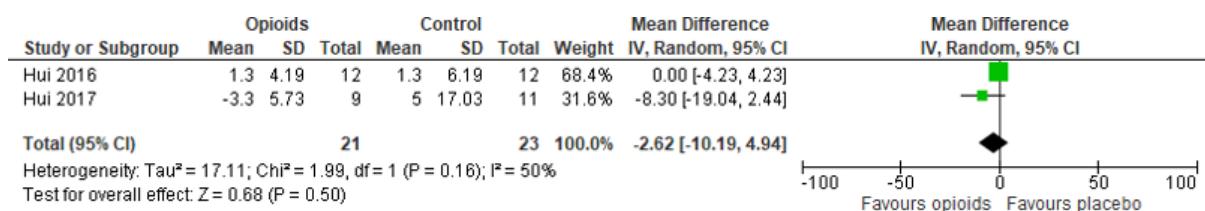
c. Opioids versus placebo among patients with cancer – oxygen saturation



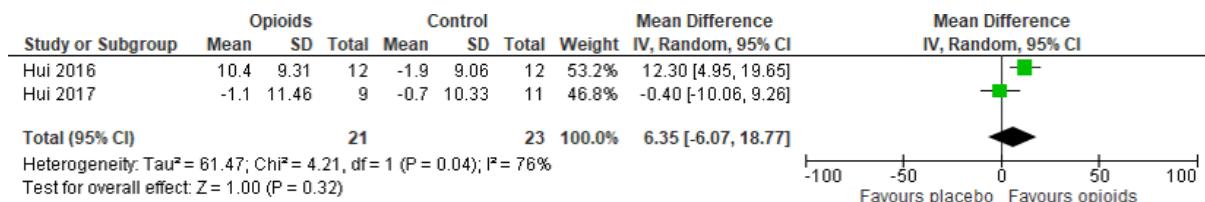
d. Opioids versus placebo among patients with cancer – walking distance



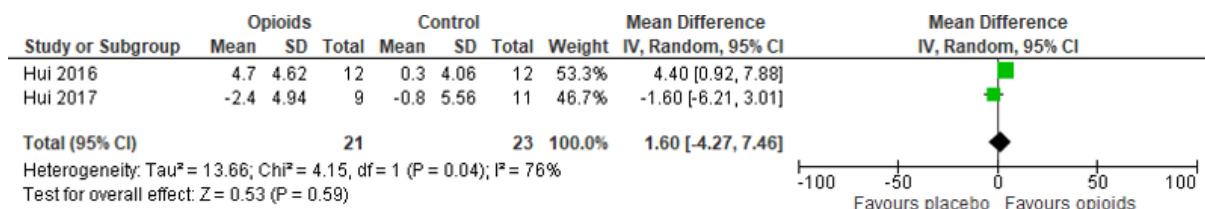
e. Opioids versus placebo among patients with cancer – heart rate



f. Opioids versus placebo among patients with cancer – systolic blood pressure

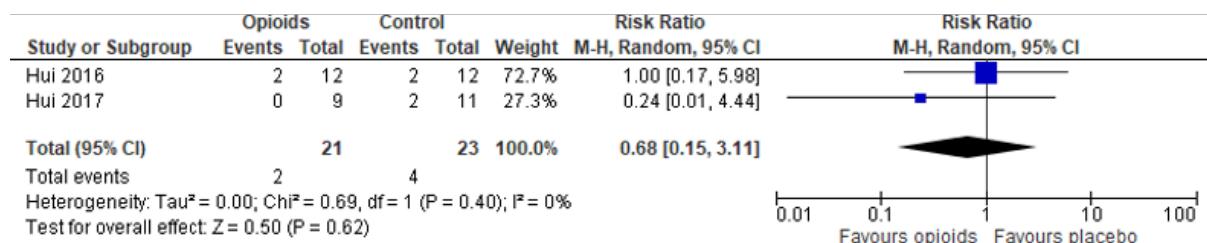


g. Opioids versus placebo among patients with cancer – diastolic blood pressure

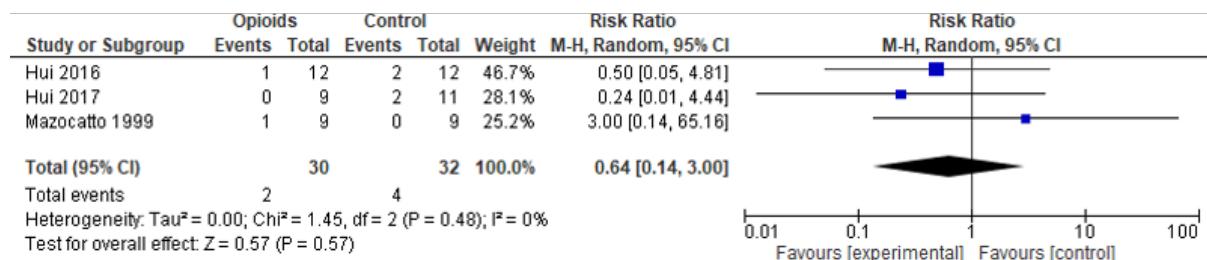


Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: <https://ehospice.com/international-posts/integration-of-palliative-care-into-the-philippine-health-system/> along with this CPG.

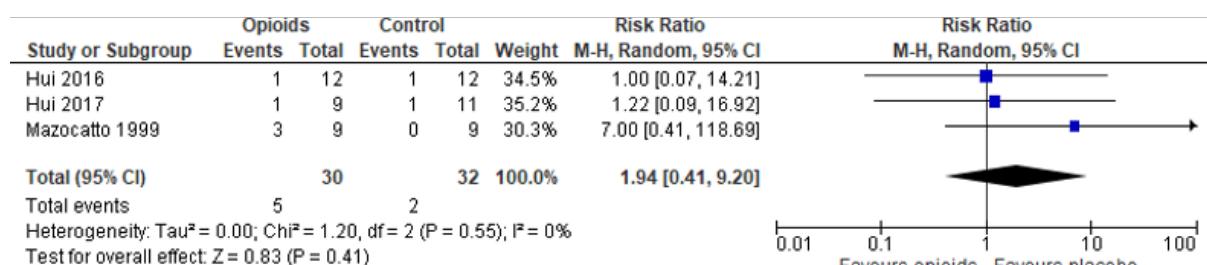
h. Opioids versus placebo among patients with cancer – dizziness



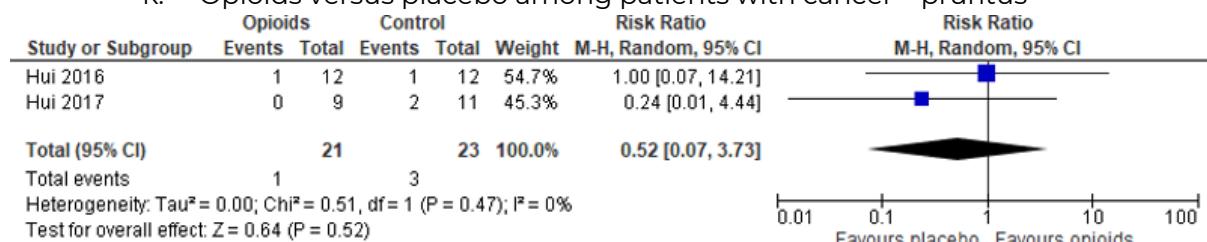
i. Opioids versus placebo among patients with cancer – drowsiness



j. Opioids versus placebo among patients with cancer – nausea



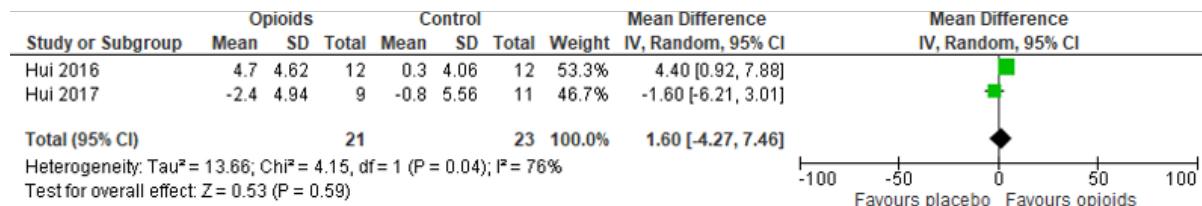
k. Opioids versus placebo among patients with cancer – pruritus



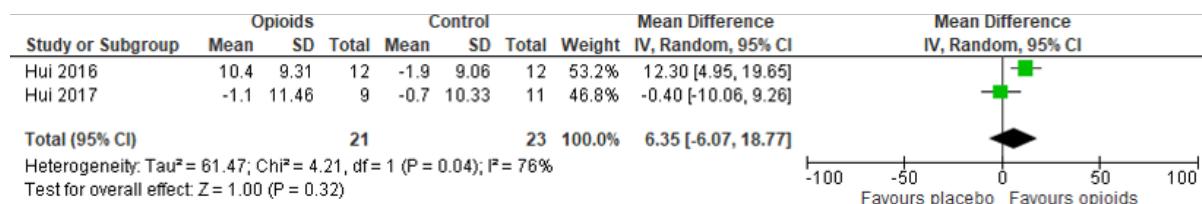
Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: <https://ehospice.com/international-posts/integration-of-palliative-care-into-the-philippine-health-system/> along with this CPG.

### 3. Use of Opioids among actively dying hypotensive adult cancer patients

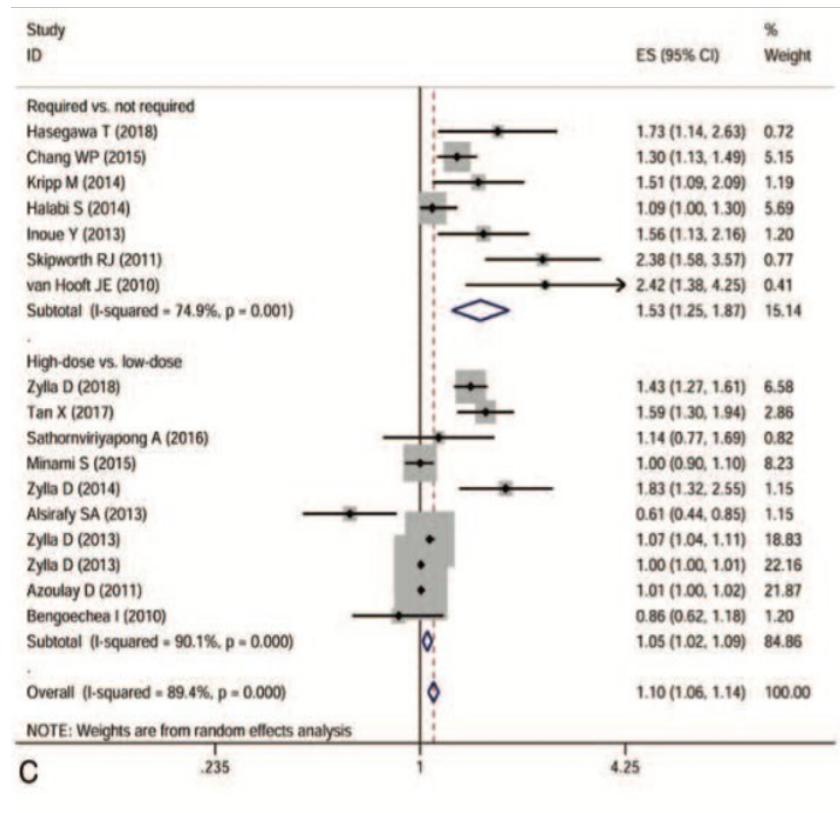
- a. Opioids vs. No Opioids in patients with advanced cancer – change is Systolic Blood Pressure (SBP)



- b. Opioids vs. No Opioids in patients with advanced cancer – change is Systolic Blood Pressure (SBP)



- c. Opioid required/High dose opioid use vs. No opioid required/Low dose opioid use for Cancer Patients and its effect on Overall Survival



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4. Effectivity of the 2-step ladder approach versus WHO 3-step ladder approach in achieving pain control

None

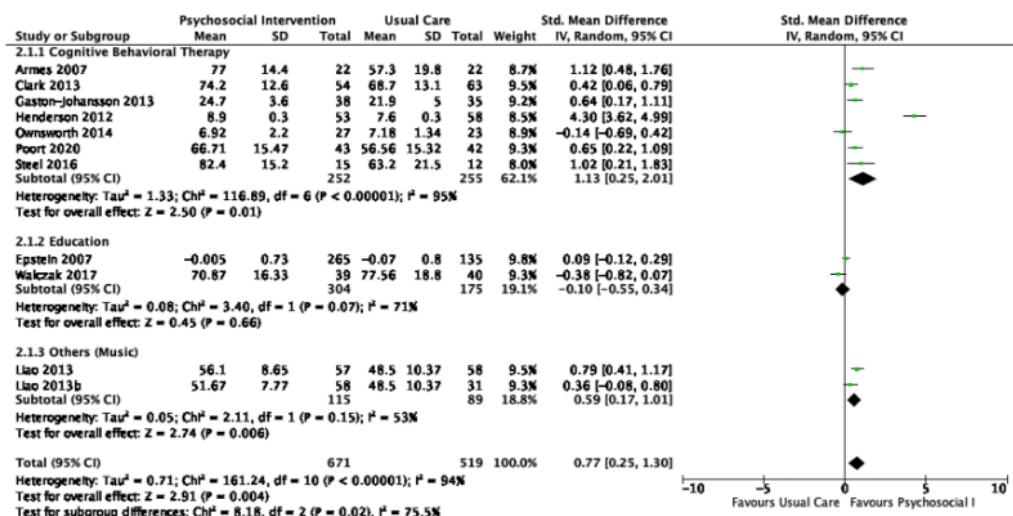
5. Effectivity of transdermal opioid patch vs subcutaneous opioid administration in symptom control

None

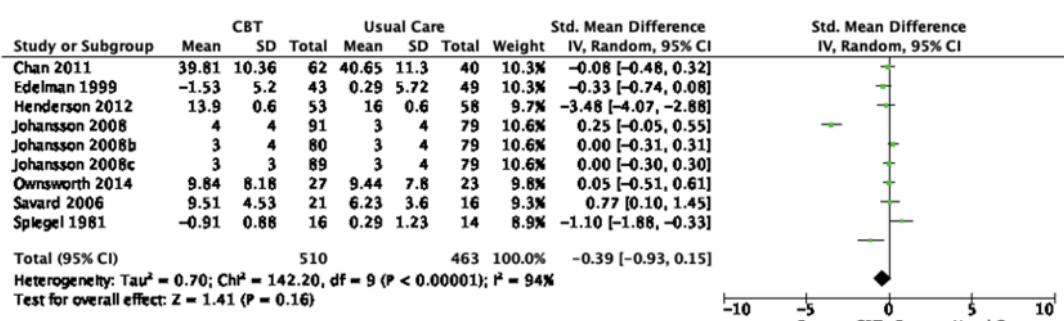
6. Psychosocial and Spiritual Care

6.1 Psychosocial Care

a. Psychosocial Intervention vs Usual Care. Quality of Life

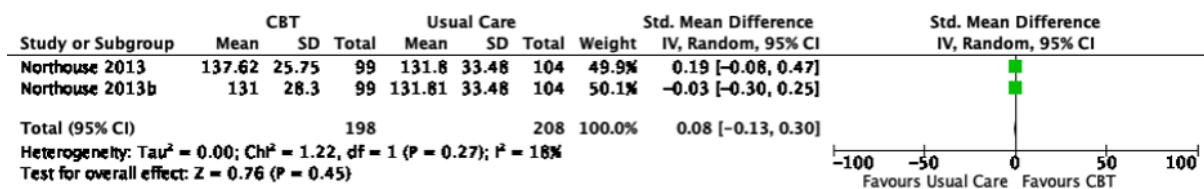


b. Psychosocial Intervention vs Usual Care. Anxiety

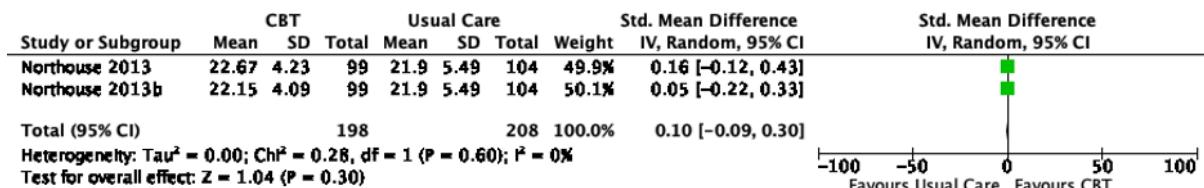


Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: [https://ehospice.com/international\\_posts/integration-of-palliative-care-into-the-philippine-health-system/](https://ehospice.com/international_posts/integration-of-palliative-care-into-the-philippine-health-system/) along with this CPG.

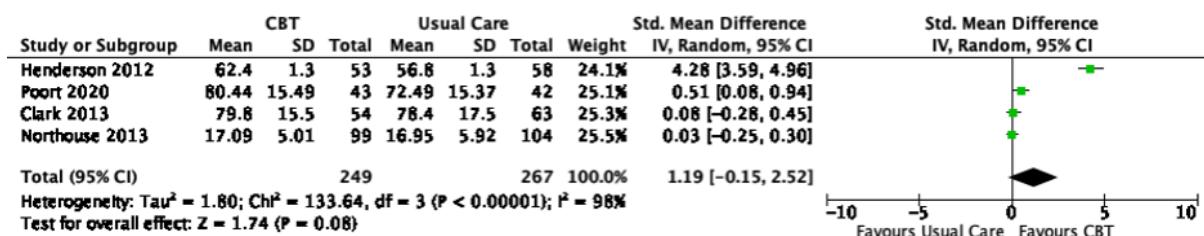
c. Psychosocial Intervention vs Usual Care. Autonomy



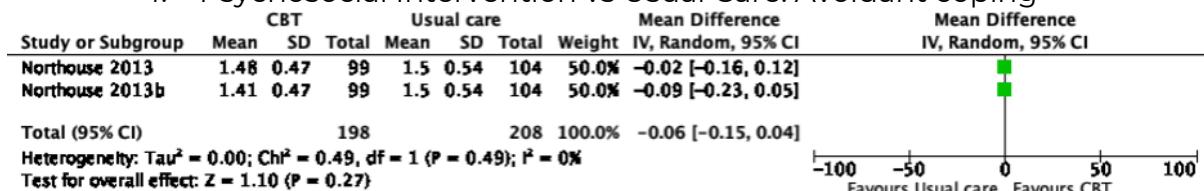
d. Psychosocial Intervention vs Usual Care. Quality of Relationship



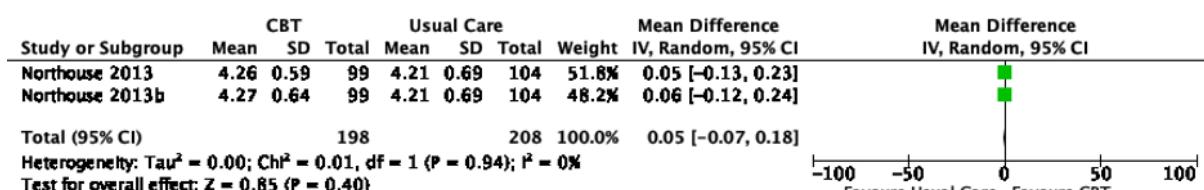
e. Psychosocial Intervention vs Usual Care. Active Behavioral Coping



f. Psychosocial Intervention vs Usual Care. Avoidant coping



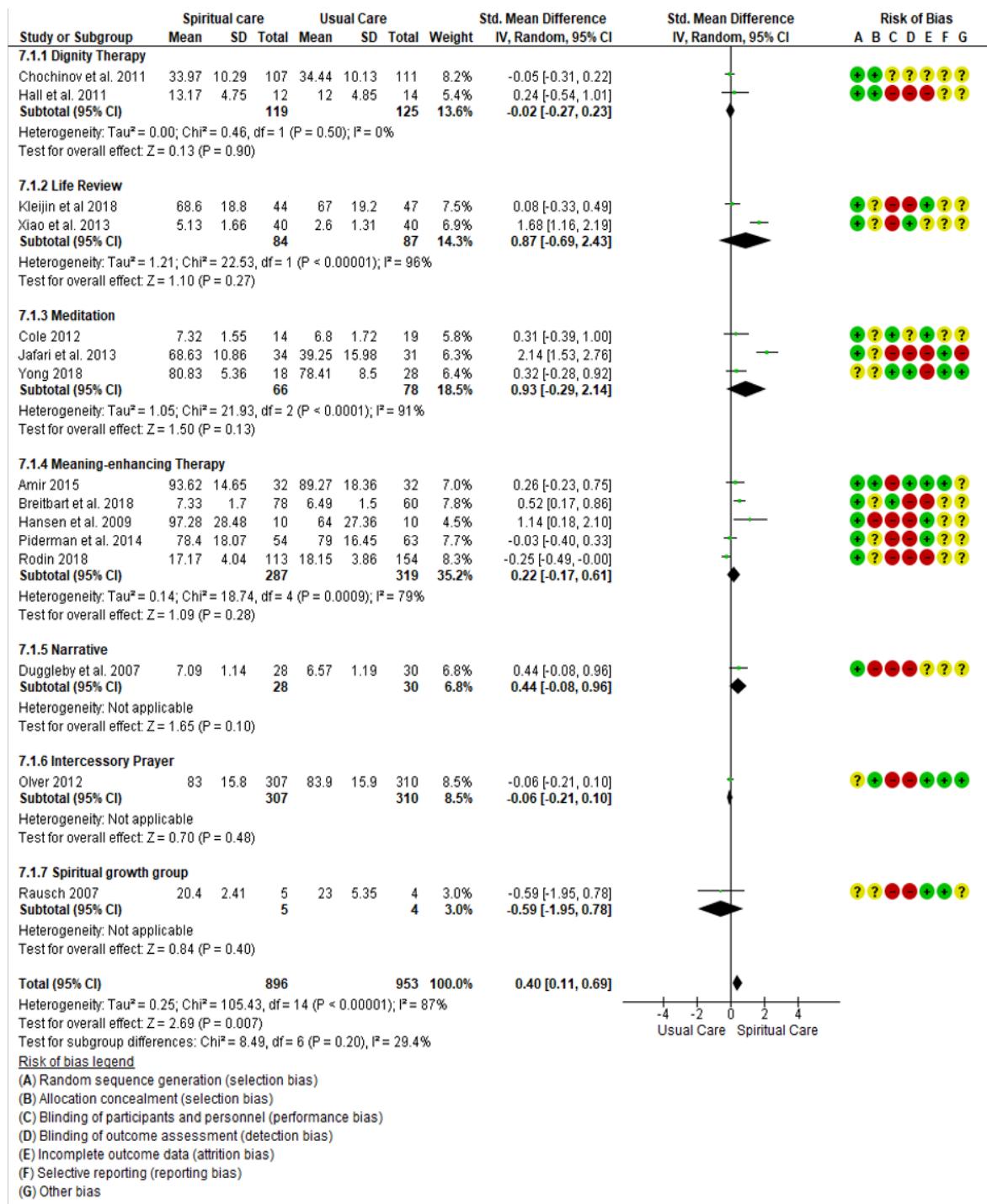
g. Psychosocial Intervention vs Usual Care. Dyadic support



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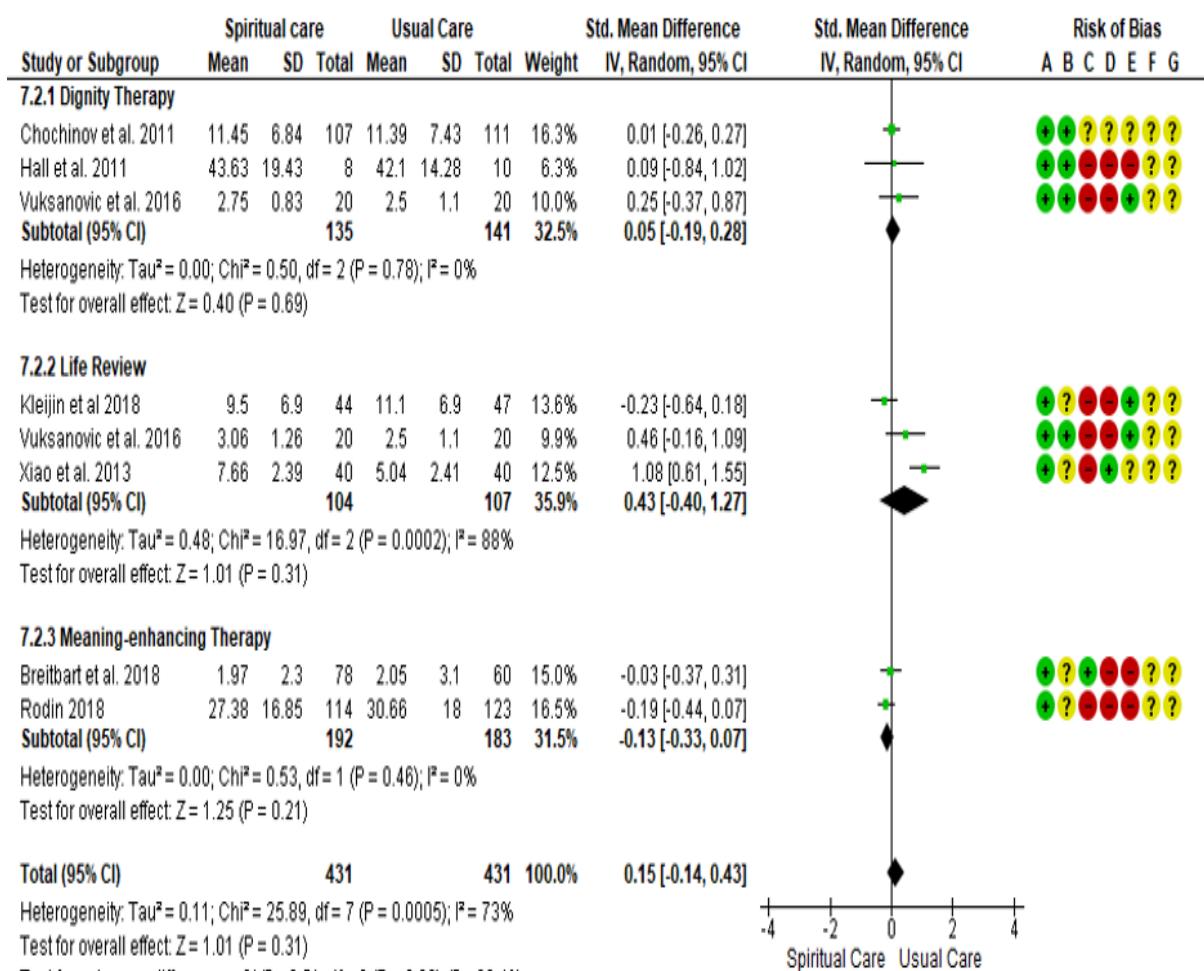
## 6.2 Forest Plots and Risk of Bias and Assessment for Spiritual Care

### a. Spiritual Care vs Usual Care: Outcome. Quality of Life



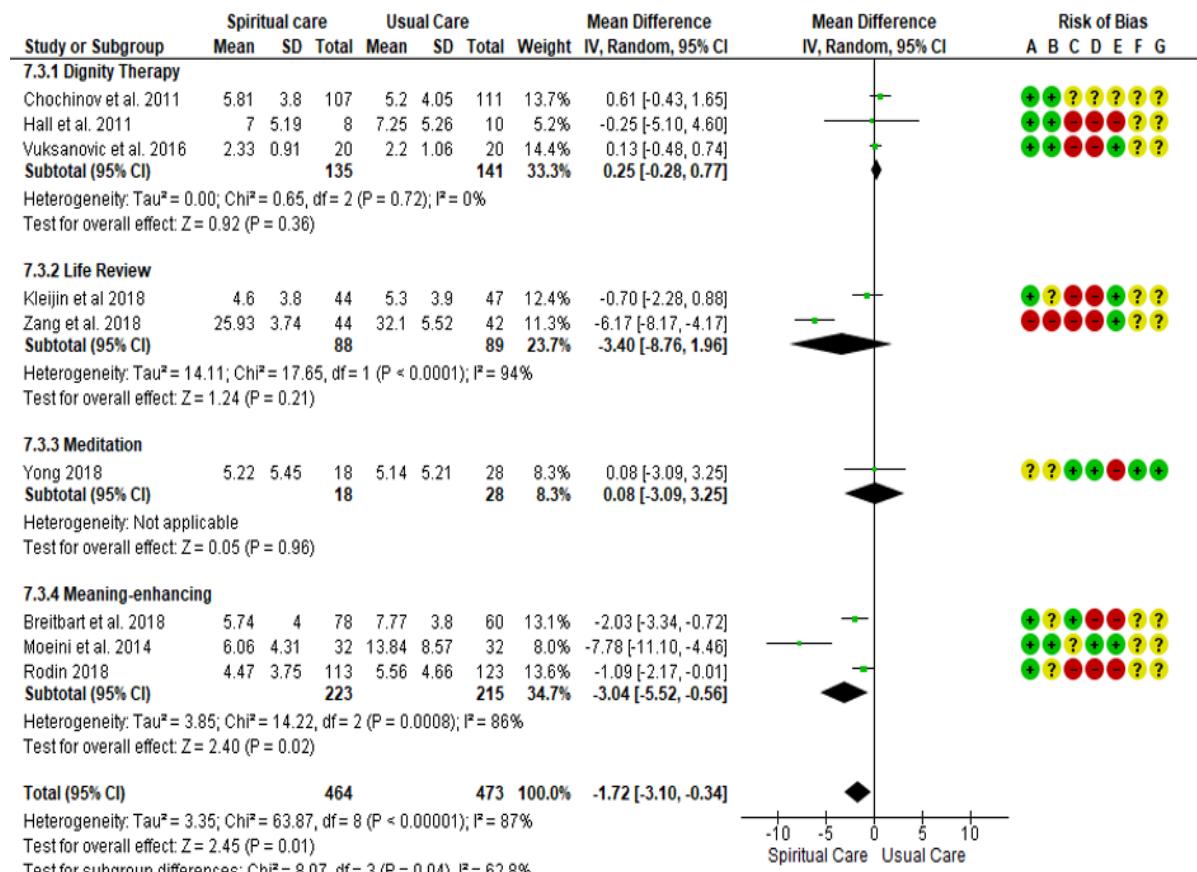
Readers of this CPG should understand concepts and practices of palliative and end-of-life care. Kindly read the DOH-MOPS for National Palliative and Hospice Care Program available at: <https://ehospice.com/international-posts/integration-of-palliative-care-into-the-philippine-health-system/> along with this CPG.

b. Spiritual Care vs Usual Care: Outcome. Patient Distress



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### c. Spiritual Care vs Usual Care: Outcome: Patient Anxiety



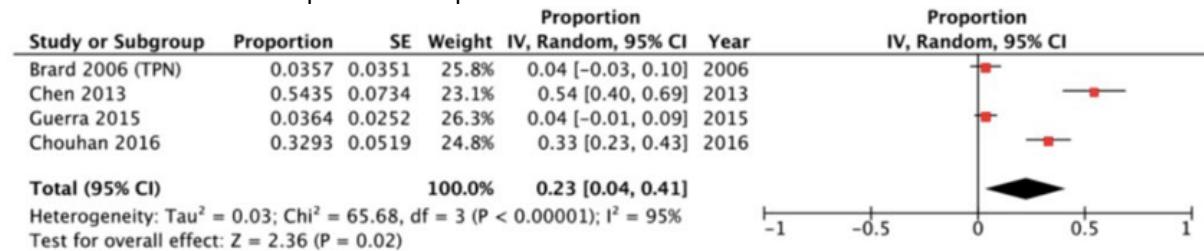
## 7. Advance Care Planning and Satisfaction and Perception with Care

None

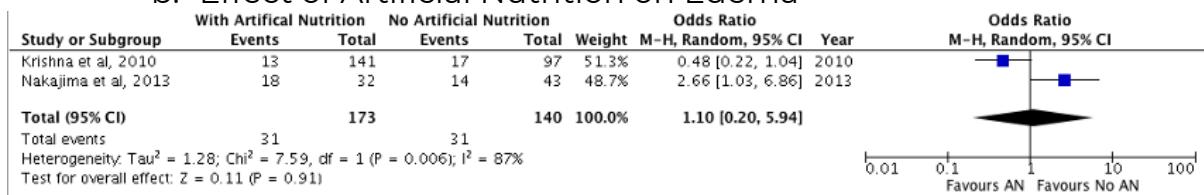
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## 8. Parenteral and Enteral Nutrition in the last six months of life

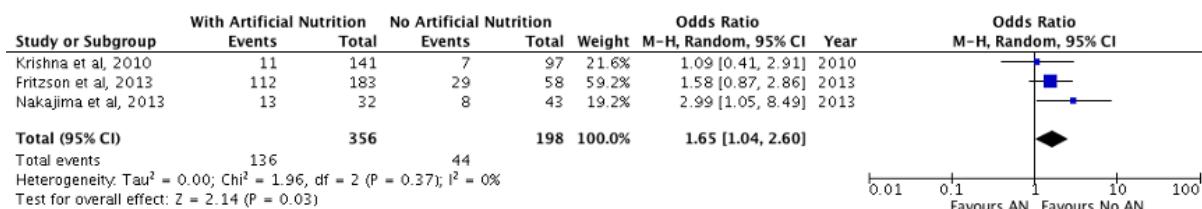
### a. Proportion of Patients on Total Parenteral Nutrition who developed Complications



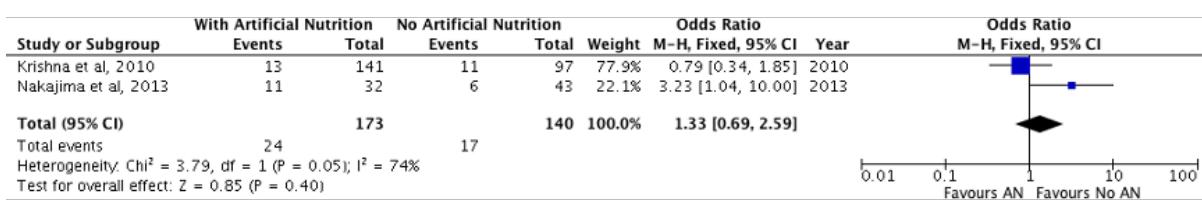
### b. Effect of Artificial Nutrition on Edema



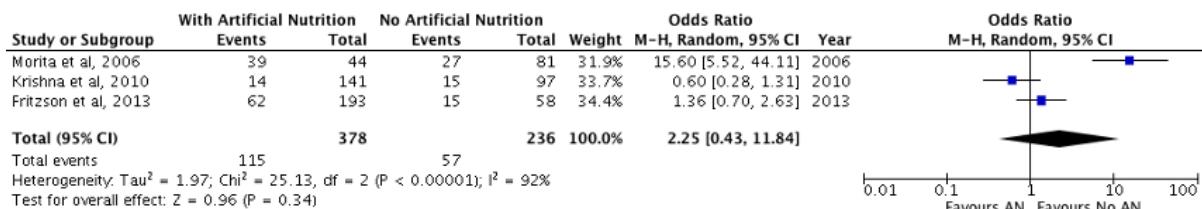
### c. Effect of Artificial Nutrition on Respiratory Secretions



### d. Effect of Artificial Nutrition on Ascites



### e. Effect of Artificial Nutrition on Nausea and Vomiting



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9. Terminal extubation and quality of end-of-life care  
None

10. Palliative sedation and control of symptoms  
None

## AGREE Reporting Checklist (Self Evaluation)

Fillable forms may be downloaded here: <http://www.agreetrust.org/resource-centre/agree-reporting-checklist/>

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
<b>1. OBJECTIVES</b> <i>Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.</i>	<input checked="" type="checkbox"/> Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) <input checked="" type="checkbox"/> Expected benefit(s) or outcome(s) <input checked="" type="checkbox"/> Target(s) (e.g., patient population, society)	
<b>2. QUESTIONS</b> <i>Report the health question(s) covered by the guideline, particularly for the key recommendations.</i>	<input checked="" type="checkbox"/> Target population <input checked="" type="checkbox"/> Intervention(s) or exposure(s) <input checked="" type="checkbox"/> Comparisons (if appropriate) <input checked="" type="checkbox"/> Outcome(s) <input checked="" type="checkbox"/> Health care setting or context	See relevant sections
<b>3. POPULATION</b> <i>Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.</i>	<input checked="" type="checkbox"/> Target population, sex and age <input checked="" type="checkbox"/> Clinical condition (if relevant) <input type="checkbox"/> Severity/stage of disease (if relevant) <input type="checkbox"/> Comorbidities (if relevant) <input checked="" type="checkbox"/> Excluded populations (if relevant)	
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
<b>4. GROUP MEMBERSHIP</b> <i>Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.</i>	<input checked="" type="checkbox"/> Name of participant <input checked="" type="checkbox"/> Discipline/content expertise (e.g., neurosurgeon, methodologist) <input checked="" type="checkbox"/> Institution (e.g., St. Peter's hospital) <input checked="" type="checkbox"/> Geographical location (e.g., Seattle, WA) <input checked="" type="checkbox"/> A description of the member's role in the guideline development group	

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<p><b>5. TARGET POPULATION PREFERENCES AND VIEWS</b></p> <p><i>Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)</li> <li><input checked="" type="checkbox"/> Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups)</li> <li><input checked="" type="checkbox"/> Outcomes/information gathered on patient/public information</li> <li><input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations</li> </ul>	
<p><b>6. TARGET USERS</b></p> <p><i>Report the target (or intended) users of the guideline.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators)</li> <li><input checked="" type="checkbox"/> How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)</li> </ul>	2
<b>DOMAIN 3: RIGOUR OF DEVELOPMENT</b>		
<p><b>7. SEARCH METHODS</b></p> <p><i>Report details of the strategy used to search for evidence.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL)</li> <li><input checked="" type="checkbox"/> Time periods searched (e.g., January 1, 2004 to March 31, 2008)</li> <li><input checked="" type="checkbox"/> Search terms used (e.g., text words, indexing terms, subheadings)</li> <li><input checked="" type="checkbox"/> Full search strategy included (e.g., possibly located in appendix)</li> </ul>	8, 287
<p><b>8. EVIDENCE SELECTION CRITERIA</b></p> <p><i>Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Target population (patient, public, etc.) characteristics</li> <li><input checked="" type="checkbox"/> Study design</li> <li><input checked="" type="checkbox"/> Comparisons (if relevant)</li> <li><input checked="" type="checkbox"/> Outcomes</li> <li><input checked="" type="checkbox"/> Language (if relevant)</li> <li><input type="checkbox"/> Context (if relevant)</li> </ul>	8
<p><b>9. STRENGTHS &amp; LIMITATIONS OF THE EVIDENCE</b></p> <p><i>Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Study design(s) included in body of evidence</li> <li><input checked="" type="checkbox"/> Study methodology limitations (sampling, blinding, allocation concealment, analytical methods)</li> </ul>	8

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<p>evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.</p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Appropriateness/relevance of primary and secondary outcomes considered</li> <li><input checked="" type="checkbox"/> Consistency of results across studies</li> <li><input checked="" type="checkbox"/> Direction of results across studies</li> <li><input checked="" type="checkbox"/> Magnitude of benefit versus magnitude of harm</li> <li><input checked="" type="checkbox"/> Applicability to practice context</li> </ul>	
<p><b>10. FORMULATION OF RECOMMENDATIONS</b> <i>Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered)</li> <li><input checked="" type="checkbox"/> Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures)</li> <li><input checked="" type="checkbox"/> How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)</li> </ul>	9-15
<p><b>11. CONSIDERATION OF BENEFITS AND HARMS</b> <i>Report the health benefits, side effects, and risks that were considered when formulating the recommendations.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Supporting data and report of benefits</li> <li><input checked="" type="checkbox"/> Supporting data and report of harms/side effects/risks</li> <li><input checked="" type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks</li> <li><input checked="" type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks</li> </ul>	9
<p><b>12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE</b> <i>Describe the explicit link between the recommendations and the evidence on which they are based.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations</li> <li><input checked="" type="checkbox"/> Link between each recommendation and key evidence (text description and/or reference list)</li> <li><input checked="" type="checkbox"/> Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline</li> </ul>	See relevant sections
<p><b>13. EXTERNAL REVIEW</b> <i>Report the methodology used to conduct the external review.</i></p>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence)</li> <li><input checked="" type="checkbox"/> Methods taken to undertake the external review (e.g., rating scale, open-ended questions)</li> <li><input checked="" type="checkbox"/> Description of the external reviewers (e.g., number, type of reviewers, affiliations)</li> </ul>	16

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	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Outcomes/information gathered from the external review (e.g., summary of key findings)</li> <li><input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)</li> </ul>	
<b>14. UPDATING PROCEDURE</b> <i>Describe the procedure for updating the guideline.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> A statement that the guideline will be updated</li> <li><input checked="" type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur</li> <li><input checked="" type="checkbox"/> Methodology for the updating procedure</li> </ul>	17
<b>DOMAIN 4: CLARITY OF PRESENTATION</b>		
<b>15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS</b> <i>Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> A statement of the recommended action</li> <li><input checked="" type="checkbox"/> Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects)</li> <li><input checked="" type="checkbox"/> Relevant population (e.g., patients, public)</li> <li><input checked="" type="checkbox"/> Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)</li> <li><input checked="" type="checkbox"/> If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline</li> </ul>	See relevant sections
<b>16. MANAGEMENT OPTIONS</b> <i>Describe the different options for managing the condition or health issue.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Description of management options</li> <li><input checked="" type="checkbox"/> Population or clinical situation most appropriate to each option</li> </ul>	See relevant sections
<b>17. IDENTIFIABLE KEY RECOMMENDATIONS</b> <i>Present the key recommendations so that they are easy to identify.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms</li> <li><input checked="" type="checkbox"/> Specific recommendations grouped together in one section</li> </ul>	See relevant sections and Executive Summary (ix)
<b>DOMAIN 5: APPLICABILITY</b>		
<b>18. FACILITATORS AND BARRIERS TO APPLICATION</b> <i>Describe the facilitators and barriers to the guideline's application.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Types of facilitators and barriers that were considered</li> <li><input checked="" type="checkbox"/> Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback</li> </ul>	225

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	<p>from key stakeholders, pilot testing of guidelines before widespread implementation)</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography)</li> <li><input checked="" type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations</li> </ul>	
<b>19. IMPLEMENTATION ADVICE/TOOLS</b> <i>Provide advice and/or tools on how the recommendations can be applied in practice.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Additional materials to support the implementation of the guideline in practice. For example: <ul style="list-style-type: none"> <li>○ Guideline summary documents</li> <li>○ Links to check lists, algorithms</li> <li>○ Links to how-to manuals</li> <li>○ Solutions linked to barrier analysis (see Item 18)</li> <li>○ Tools to capitalize on guideline facilitators (see Item 18)</li> <li>○ Outcome of pilot test and lessons learned</li> </ul> </li> </ul>	222-223
<b>20. RESOURCE IMPLICATIONS</b> <i>Describe any potential resource implications of applying the recommendations.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs)</li> <li><input checked="" type="checkbox"/> Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.)</li> <li><input checked="" type="checkbox"/> Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course)</li> <li><input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations</li> </ul>	223 and other relevant sections
<b>21. MONITORING/ AUDITING CRITERIA</b> <i>Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.</i>	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations</li> <li><input checked="" type="checkbox"/> Criteria for assessing impact of implementing the recommendations</li> <li><input checked="" type="checkbox"/> Advice on the frequency and interval of measurement</li> <li><input checked="" type="checkbox"/> Operational definitions of how the criteria should be measured</li> </ul>	16, 260

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DOMAIN 6: EDITORIAL INDEPENDENCE		
<b>22. FUNDING BODY</b> <i>Report the funding body's influence on the content of the guideline.</i>	<input checked="" type="checkbox"/> The name of the funding body or source of funding (or explicit statement of no funding) <input checked="" type="checkbox"/> A statement that the funding body did not influence the content of the guideline	17
<b>23. COMPETING INTERESTS</b> <i>Provide an explicit statement that all group members have declared whether they have any competing interests.</i>	<input checked="" type="checkbox"/> Types of competing interests considered <input checked="" type="checkbox"/> Methods by which potential competing interests were sought <input checked="" type="checkbox"/> A description of the competing interests <input checked="" type="checkbox"/> How the competing interests influenced the guideline process and development of recommendations	17-18, 239

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