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Perspective

Ethics of Placebo Use in Palliative Care Research

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ABSTRACT

Placebo-controlled trials in palliative care raise ethical questions that do not reduce to the general placebo debate, because the population under study is often close to death, symptomatic, and under time pressure that standard risk-benefit frameworks do not fully anticipate.

This review examines the methodological case for placebo controls in symptom research, the population-specific objections raised by patient vulnerability and compressed prognosis, and empirical evidence on how dying patients and their families actually experience being asked to enroll in such trials.

It also considers the distinct evidentiary role of placebo and nocebo effects in symptom outcomes, including emerging evidence of inequitable nocebo harm linked to inconsistent disclosure practice.

We then survey the field's principal risk-minimization strategies: add-on designs against a background of standard care, time-limited exposure with pre-specified escape criteria, enriched-enrollment approaches, and staged informed-consent procedures.

We conclude that these procedural safeguards represent a reasonable working compromise rather than a resolution of the underlying ethical disagreement, and that continued attention to patients' and families' lived experience of these trials should guide future refinement more than further abstract argument.

Keywords: placebo; palliative care; research ethics; informed consent; clinical trial design

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INTRODUCTION

Placebo controls occupy an uneasy place in palliative care research. The methodological case for them is familiar from mainstream clinical trial design: without a placebo arm, it can be difficult to separate a drug's pharmacological effect from the substantial

contribution that expectation, attention, and the ritual of treatment itself make to symptom relief [1]. But palliative care trials rarely enroll the kind of participant a standard risk-benefit calculus was built around. Many are close to death, symptomatic, cognitively or emotionally taxed by their prognosis, and often already

receiving active treatment for pain, dyspnea, nausea, or delirium that a placebo arm would, by design, withhold or delay [2]. Asking whether placebo controls are ethical in this population is therefore not simply a restatement of the general placebo debate; it is a question about whether the standard justifications for placebo methodology survive contact with a population whose remaining time and tolerance for untreated suffering are both severely limited.

The regulatory and bioethics literature on placebo controls more broadly has settled, imperfectly, on the idea that a placebo arm is ethically acceptable when withholding effective treatment poses no serious risk of harm, when clinical equipoise genuinely exists, and when consent is properly informed [3]. Regulatory and scientific guidance developed for placebo use in oncology trials, a setting that shares much of palliative care's concern with seriously ill patients, has reached a broadly similar conclusion: placebo controls remain scientifically valuable but require correspondingly stronger procedural safeguards the sicker the trial population becomes [4]. Each of those conditions is harder to satisfy in palliative care than in, say, a trial of a new antihypertensive in otherwise healthy adults. This review examines the ethical architecture of placebo-controlled palliative care trials: the arguments for and against using placebos in this setting, what is known empirically about how dying patients and their families actually experience being asked to enroll in such trials, the special evidentiary role of placebo and nocebo effects in symptom research, and what alternative designs the field has proposed as a way of preserving methodological rigor without exposing a uniquely vulnerable population to unnecessary and unrelieved suffering.

THE CASE FOR PLACEBO CONTROLS IN PALLIATIVE CARE TRIALS

Proponents of placebo-controlled symptom trials in palliative care make an argument that is easy to dismiss as merely methodological but is not, in fact, ethically trivial. Symptom outcomes in this population, pain, nausea, breathlessness, fatigue, are notoriously susceptible to placebo response rates that can rival or approach those of the active intervention being tested, particularly in short trials with subjective endpoints [5]. If a new antiemetic or analgesic is tested only against an active comparator, and both arms show meaningful improvement, it becomes genuinely difficult to know whether the new agent has any real advantage or whether both groups simply improved because they were being closely monitored, reassured, and given something. A negative signal in that design is ambiguous in a way it would not be against placebo, and ambiguous evidence is itself an ethical cost: it can lead to ineffective treatments entering standard practice, or effective ones being abandoned, either of which harms future patients in the same position as the trial's own participants [6].

There is also a narrower version of the argument that applies specifically to conditions with no established effective treatment, or to add-on trials where all participants continue to receive standard background symptom management and the placebo arm receives that background care plus an inert addition rather than no care at all [7]. Framed this way, a placebo-controlled add-on design in palliative care is not withholding treatment from anyone; it is testing whether an additional intervention improves on a baseline of care every participant already receives. Much of the methodological literature treats this add-on structure as the ethically preferable default for placebo-controlled symptom trials precisely because it avoids the objection that a participant is left with untreated suffering [3].

VULNERABILITY, SUFFERING, AND THE LIMITS OF STANDARD JUSTIFICATIONS

The add-on defense is persuasive for genuinely mild or non-time-critical symptoms, but it strains when the symptom under study is itself severe, when standard background therapy is only partially effective, or when the trial window is long enough that a patient near the end of life spends a meaningful fraction of their remaining time in a placebo arm. Palliative care researchers have argued for decades that this population warrants ethical guidelines distinct from, and in some respects stricter than, those applied to research generally, precisely because prognosis compresses the time in which any harm from a placebo arm can be corrected [8]. A patient with weeks to live who is randomized to placebo for a distressing symptom cannot simply wait for the next study visit or the next protocol amendment; delayed relief is not a deferred cost recoverable later, it is suffering that occurred and cannot be given back.

This is compounded by the practical reality of consent in this population. Patients approached about a placebo-controlled symptom trial near the end of life are often fatigued, grieving an approaching loss, and under time pressure that a healthy trial volunteer does not face, all of which can complicate genuinely voluntary, unhurried decision-making [9]. Family members frequently participate in the decision in ways that formal consent procedures do not fully capture; a qualitative study of relatives of patients asked to join a double-blind, placebo-controlled trial for symptom control found that families experienced real ambivalence about the placebo design even when they ultimately supported the patient's decision to enroll, and that clinicians' framing of the trial substantially shaped how that ambivalence was resolved [10]. That finding matters because it complicates a common assumption in placebo ethics, that the person best positioned to judge whether a placebo arm is an acceptable risk is the patient alone, exercising ordinary autonomous consent; in practice the decision is often shared, time-pressured, and

shaped by how researchers present the trial's risks.

Access to experimental and compassionate-use treatment raises a related but distinct question: even outside formal placebo-controlled trials, terminally ill patients and advocates have pushed for expanded access to unproven interventions on the theory that a dying patient has comparatively little to lose from trying something unproven, an argument that sits in tension with the trial-integrity rationale for randomization and blinding in the first place [11]. Analyses of compassionate-use programs have found that the ethical justifications typically offered, autonomy, last-resort necessity, and beneficence, are individually weaker than they first appear and do not straightforwardly resolve the tension between individual access and the population-level need for rigorous, blinded, placebo-controlled evidence [12].

THE EVIDENTIARY WEIGHT OF PLACEBO AND NOCEBO EFFECTS

A separate strand of the literature treats placebo response not merely as a methodological nuisance to be controlled for, but as a clinically meaningful phenomenon in its own right, with implications for how palliative symptom trials should be designed and interpreted. Placebo effects in pain and symptom management appear to be driven by expectation, conditioning, and the therapeutic relationship itself, and are not simply statistical noise that cancels out between arms [1]. Expert consensus statements have argued that these mechanisms should be actively harnessed in clinical practice rather than merely subtracted out in trials, while also cautioning that the same mechanisms can produce harmful nocebo effects when patients are informed, as full disclosure sometimes requires, that they might receive an inert treatment [13]. A recent scoping review of placebo and nocebo responses concluded that trial design in symptom-focused fields still underestimates how much of the measured "placebo response" in a control arm reflects genuine physiological change rather than reporting bias, which complicates simple assumptions about what a placebo-controlled comparison is actually isolating [14]. Recent clinical-ethics commentary has likewise urged that placebo mechanisms be treated as a distinct ethical topic in their own right, not merely a design artifact to be neutralized, when clinicians and researchers decide how much to disclose about the possibility of an inert intervention [15].

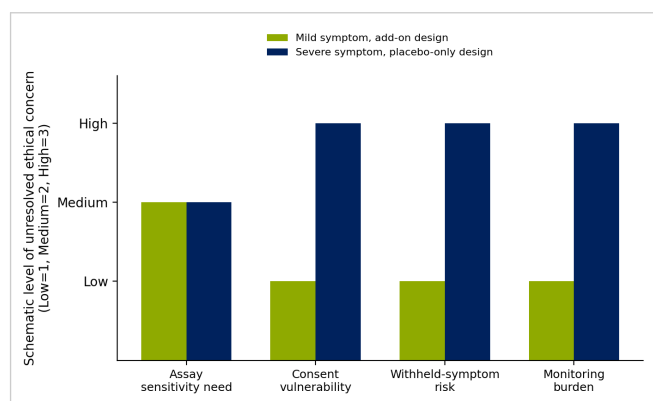
Nocebo effects also raise an equity concern specific to how placebo trials are explained to different populations. Work on health disparities in placebo and nocebo response has argued that poorly explained consent language, mismatched cultural expectations about disclosure, and differential trust in the research enterprise can produce disproportionate nocebo harm, and disproportionately weaker placebo benefit, among racial and ethnic minority patients, a dynamic with obvious relevance to palliative trials recruiting from

diverse hospice and hospital populations [16]. A 2025 cross-sectional survey of European healthcare professionals found considerable inconsistency in how clinicians themselves understand and discuss placebo and nocebo effects with patients, suggesting that the informed-consent process in placebo-controlled symptom trials may be less standardized in practice than trial protocols assume [17]. Table 1 summarizes how the principal ethical justifications for placebo-controlled palliative trials interact with the population-specific concerns that complicate each one, and Figure 1 sets out, schematically, how the balance of ethical concern shifts across three broadly different trial contexts.

Table 1. Principal ethical justifications offered for placebo-controlled palliative care trials, and the population-specific concerns that complicate each one.

Justification	Standard rationale	Palliative-specific complication
Assay sensitivity	Distinguishes drug effect from expectation/attention effects that inflate active-comparator-only trials	High placebo response rates for pain, nausea, and dyspnea make ambiguous negative results especially costly given limited remaining time
Add-on / background-care design	Placebo arm still receives standard symptom management, so no participant is left untreated	Only defensible when background care is genuinely adequate; strains when the studied symptom is severe or background therapy is only partly effective
Time-limited exposure with escape criteria	Bounds maximum possible harm from placebo assignment	Requires frequent, resource-intensive monitoring that many palliative trial sites are not funded to sustain
Informed consent	Patient autonomously weighs and accepts the risk of receiving placebo	Consent is frequently shared with family, made under time pressure and grief, and shaped by variable clinician disclosure practices

Figure 1. Schematic comparison of the relative level of unresolved ethical concern raised by placebo-controlled trial designs across three trial contexts (illustrative only, not derived from a single empirical study).



ALTERNATIVE DESIGNS AND RISK-MINIMIZATION STRATEGIES

Given these tensions, much of the recent methodological literature has focused less on whether placebo controls can ever be justified in palliative care and more on how trial design can minimize the harm a placebo arm imposes. Active-controlled and add-on designs, discussed above, remain the most widely endorsed compromise, but they are not universally applicable, particularly for first-in-class interventions with no accepted active comparator [3]. Enriched-enrollment designs, in which patients are first assessed on open-label active treatment and only placebo-responders or treatment-responders are subsequently randomized, have been proposed as a way to shorten the placebo-exposure window while preserving assay sensitivity, though this approach introduces its own selection biases into the resulting evidence [18].

Time-limited placebo exposure with pre-specified escape criteria, allowing a participant to exit to open-label active treatment if a symptom crosses a defined severity threshold, has become close to a standard requirement in palliative symptom trial protocols, precisely because it bounds the maximum harm any one participant can experience from randomization to placebo [9]. Reviews of palliative care research ethics more broadly have argued that the field needs procedural safeguards beyond what a general research ethics committee typically demands, including independent data safety monitoring with authority to halt a trial early on symptom-severity grounds, not only on grounds of serious adverse events, and closer, more frequent contact with participants than standard trial visit schedules require [19]. A related scoping review of compassionate symptom-control practice in palliative care has argued that ethical justification for any experimental or unproven intervention in this population needs to be assessed symptom-by-symptom and patient-by-patient rather than through a single blanket policy for or against placebo use [20].

Some of the strongest procedural recommendations concern consent itself rather than trial architecture. Palliative-specific guidance has called for staged consent processes, an initial conversation followed by a cooling-off period and a second confirmatory conversation, precisely because standard single-encounter consent may not reliably produce a genuinely considered decision under the time pressure and emotional load this population experiences [8]. Analyses of the broader informed-consent literature for placebo-controlled trials have likewise questioned whether the standard disclosure script, describing randomization probability and the possibility of receiving an inactive treatment, actually functions as intended when the person receiving it is simultaneously processing a terminal prognosis [21].

CONCLUSION

The ethics of placebo use in palliative care research cannot be settled by importing, unmodified, the justificatory framework built for placebo trials in healthier populations with more time to absorb both the risks of participation and the consequences of ambiguous results. The methodological case for placebo controls, cleaner separation of drug effect from expectation and attention, retains real force, and add-on designs against a background of standard care go a long way toward defusing the sharpest ethical objection, that a participant is left with untreated suffering. But the population's compressed timeline, the entanglement of family members in consent decisions that formal procedures do not fully capture, and emerging evidence that nocebo harm and disclosure quality vary systematically across patients mean that a placebo arm in this setting carries costs that a generic risk-benefit calculation is likely to understate. The field's own procedural innovations, time-limited exposure with escape criteria, enriched enrollment, staged consent, and independent monitoring keyed to symptom severity rather than only to serious adverse events, represent a reasonable working compromise, but they are safeguards layered onto a design that remains ethically contested rather than a resolution of the underlying disagreement. Continued attention to how actual patients and families experience these trials, not just to what trial protocols formally require, will matter more to getting this right than any further refinement of the abstract argument alone.

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Conflict of Interest

The authors declare no conflicts of interest relevant to this work.

Author Contributions

Chiara Makela conceived the review, drafted the initial manuscript, and coordinated revisions. Vaclav Rossi carried out the literature synthesis on trial design and alternative methodologies and critically revised the manuscript. Pieter Radcliffe contributed the analysis of vulnerability, consent, and equity considerations and approved the final version for submission. All authors read and approved the final manuscript.

Ethics Statement

As a literature review synthesizing previously published, publicly available research and policy analysis, this article did not involve new data collection from human participants and did not require institutional ethics committee approval.

Data Availability

No new data were generated or analyzed for this review. All sources discussed are cited in the reference list and are publicly available through their respective publishers.

REFERENCES

- Colloca L, Grillon C (2014) Placebo and nocebo effects in randomized controlled trials: the implications for research and practice. *Journal of Pain and Symptom Management*, DOI:[10.1016/j.jpainsymman.2013.08.021](https://doi.org/10.1016/j.jpainsymman.2013.08.021).
- Bruera E (1994) Ethical issues in palliative care research. *Journal of Palliative Care*.
- Temple R, Ellenberg SS (2000) Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Annals of Internal Medicine*.
- Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials (2008) *Cancer*, PMID:18227527.
- Hardy JR (1997) Placebo-controlled trials in palliative care: the argument for. *Palliative Medicine*, DOI:[10.1177/026921639701100514](https://doi.org/10.1177/026921639701100514).
- Ethical use of placebo controls in research (2023) *AMA Code of Medical Ethics*.
- Miller FG, Brody H (2000) Are placebo-controlled clinical trials ethical or needed when alternative treatment exists? *Annals of Internal Medicine*.
- Kirk TW, et al. Are special ethical guidelines needed for palliative care research? (2000) *Journal of Pain and Symptom Management*.
- Casarett D, Karlawish J (2003) Maximizing benefits and minimizing risks in palliative care research that involves patients near the end of life. *Journal of Pain and Symptom Management*.
- van Esch HJ, Stoppelenburg A, van Zuylen L, van der Rijt CCD, van der Heide A (2022) When a dying patient is asked to participate in a double-blind, placebo-controlled clinical trial on symptom control: the decision-making process and experiences of relatives. *Palliative Medicine*, DOI:[10.1177/02692163221127557](https://doi.org/10.1177/02692163221127557).
- Should dying patients have the right to access experimental treatments? (2015) *The Conversation*.
- An analysis of common ethical justifications for compassionate use programs for experimental drugs (2016) *BMC Medical Ethics*, PMID:27842495.
- Evers AWM, et al. (2018) Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychotherapy and Psychosomatics*, PMID:29895014.
- A scoping review of placebo and nocebo responses and effects: insights for clinical trials and practice (2025) *Health Psychology Review*, DOI:[10.1080/17437199.2025.2471792](https://doi.org/10.1080/17437199.2025.2471792).
- Ethical considerations with using placebo treatments and effects in clinical practice (2025) PMID:41161965.
- What do placebo and nocebo effects have to do with health equity? The hidden toll of nocebo effects on racial and ethnic minority patients in clinical care (2021) *Frontiers in Psychology*.
- Placebo and nocebo in clinical practice: an online cross-sectional survey of healthcare professionals from European countries on views, practices and training needs (2025) *PLOS ONE*, DOI:[10.1371/journal.pone.0338905](https://doi.org/10.1371/journal.pone.0338905).
- de Grazia S, et al. Placebo -- to be or not to be? Are there really alternatives to placebo-controlled trials? *European Neuropsychopharmacology*.
- Recognition and resolution of ethical barriers to palliative care research (2018) in *Textbook of Palliative Care*, Springer.
- On the compassionate use of drugs in palliative care for symptom control: ethical justifications for its use: a scoping review (2023) *Journal of Pain and Symptom Management Reports*, DOI:[10.1016/j.jpsr.2023.100032](https://doi.org/10.1016/j.jpsr.2023.100032).
- Informed consent for placebo-controlled trials: do ethics and science conflict? (2023) *Perspectives in Biology and Medicine*, PMC9841466.