

Perspective

Ethical Considerations for Clinical Research in Persons with a Terminal Illness

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[Received January 22, 2026; Revised February 18, 2026; Accepted February 19, 2026]

ABSTRACT: Clinical research in persons with a terminal illness (PTI) can offer valuable scientific opportunities but raises the challenge of ensuring adequate protections for participants. Existing ethical frameworks provide limited, and sometimes conflicting guidance for navigating this tension. Given that enrolling only PTI (e.g., palliative care research) or PTI alongside participants without a terminal illness (many studies in geriatrics and other disciplines) is somewhat common, establishing the right balance is important. This paper—grounded in general research ethics requirements—thus proposes a framework based on the defining feature of PTI, namely, limited life expectancy. We explore how limited life expectancy and characteristics common (but not unique to) PTI (e.g., decisional impairment) can make it difficult for studies to meet one or more commonly recognized ethical requirements (e.g., social value, favorable risk-benefit ratio, fair participant selection, informed consent, and respect for participants and third parties). We suggest ways to address these challenges and offer considerations for IRBs when evaluating studies with adults with a terminal illness. This approach aims to balance protecting PTI and ensuring they can contribute to important research without undue restrictions.

Keywords: end-of-life research; palliative care research; research in dying patients; clinical research ethics; risk-benefit evaluations

INTRODUCTION

Clinical studies in persons with a terminal illness (PTI) – those enrolling only PTI (Table 1) or PTI alongside participants without a terminal illness – raise competing ethical considerations. This research is vital for improving care for PTI and can facilitate unique scientific opportunities, such as studying the dying process (Table 1). Furthermore, research participation is a meaningful experience for many PTI [1-3] and some – though not all – studies may offer potential clinical benefit. At the same time, this research raises the challenge of ensuring adequate protections for PTI [4-6].

Commentators differ in their views on whether PTI should be considered ‘vulnerable’ and what research protections are appropriate for PTI^a. Several commentators have noted that characteristics common in

PTI—such as decisional impairment and clinical dependence—can increase their vulnerability in research. Based on these concerns, which are shared by many families [7, 8], clinicians [8-10], and IRBs [10-12], some commentators have proposed that there are strong moral arguments against any research in PTI [13]. Others argue that this research should be permitted, but only when it offers a prospect of direct benefit to participants [14-16]^b, or it poses very low risks [4, 17-21]^c. Conversely, other commentators have argued against characterizing PTI as ‘vulnerable’ as a group [5, 6, 23-27]. Some have even argued that some research interventions may pose significantly lower risks in PTI than participants without a terminal illness and higher risks may be more acceptable in individuals with limited life expectancy. They conclude that PTI may be enrolled in studies that pose risks which would be excessive in other groups [22, 25] (see

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Supplementary Table 1 for a summary of previous commentators).

Table 1. Examples of completed, current, and proposed studies that limit inclusion to PTI. (italicized examples include only *proposed* research)

Category	Example(s)	Citation(s)
Investigating interventions for symptom management in PTI	Investigating interventions for pain in PTI.	[35, 100, 101] ^a
	Investigating interventions for dyspnea/shortness of breath in PTI.	[36, 102] ^b
	Investigating interventions for delirium in PTI.	[103, 104] ^b
Building an evidence base for standard end-of-life care practices	Evaluating clinical outcomes of/best practices for advance care planning in PTI.	[105-108] ^b
	Evaluating clinical outcomes of/best practices for artificial nutrition/hydration therapy in PTI.	[109-112] ^b
	Evaluating clinical outcomes/ethical acceptability of opioids for symptom control and sedation in PTI.	[113-115] ^b
	Evaluating symptoms in patients undergoing terminal wean to inform best practices for withdrawing life-sustaining treatment.	[116, 117] ^b
	Evaluating best practices for intravenous access in PTI.	[118, 119] ^b
	Evaluating the effects of deprescribing in PTI.	[120] ^b
Investigating the dying process	Monitoring physiological activity before and after withdrawal of life-sustaining treatment to guide optimal organ donation procedures.	[121-123] ^a
Ante- and post-mortem testing required	Comparing ante-mortem imaging results to autopsy findings to assess diagnostic accuracy.	[124, 125] ^b
	Investigating the HIV reservoir via ante-mortem blood draws and rapid autopsy.	[75, 76] ^a
Studies requiring ante-mortem enrollment for timely post-mortem procedures	Collecting tumor tissue through rapid autopsy.	[126, 127] ^c
Observing biomarkers, symptoms, and experiences of terminal illness	Evaluating prognostic indicators for life expectancy in PTI.	[128-133] ^a
	Observing symptoms of PTI.	[134-139] ^b
	Surveying PTI's experiences, preferences, and quality of life.	[94, 140-146] ^b
Interventions to improve organ donation	<i>Testing interventions to improve transplant outcomes (e.g., anticoagulants, nutritional support) in imminently dying organ donors.</i>	[147] ^d
Studies specifically including PTI—despite not scientifically necessary—because PTI face lower risks than other groups	Testing first-in-human systemic infusion of phage-displayed peptides in patients undergoing terminal wean patients.	[22, 148] ^b
	<i>Testing of HIV cure strategies (e.g., immune-based therapies, latency reversing agents) in PTI with HIV.</i>	[25, 149, 150] ^d

a. Cited studies are completed or currently enrolling participants.

b. Cited studies are completed.

c. Cited studies are currently enrolling participants.

d. Cited papers describe proposed research.

The restrictive proposals have the potential to unduly limit important studies in PTI [4, 13-18, 21], while proposals supporting higher-risk research may be insufficiently protective, especially for PTI who lack decision-making capacity [22]. Furthermore, the conflicting guidance makes it difficult to determine whether individual studies are ethically appropriate. We offer a new framework, grounded on the existing literature, that is comprehensive and consistent with

broader ethics frameworks (e.g., [28]), as well as offers some new insights into how to differentially evaluate risks and benefits for this population.

First, we argue that the defining feature of PTI—limited life expectancy—does not make research in PTI inherently unethical. Instead, it depends on whether specific studies in PTI satisfy recognized ethical requirements. We then explore how limited life expectancy and characteristics common (but not unique

to) PTI (e.g., decisional impairment) can make it difficult for studies to meet some ethical requirements (i.e., social value, favorable risk-benefit ratio, fair participant selection, informed consent, and respect for participants and third parties). We suggest ways to address these challenges in study design and offer considerations for IRBs when evaluating studies with adults with a terminal illness. We hope this paper helps investigators and IRBs balance protecting PTI and ensuring they can contribute to important research without undue restrictions. Our implications for studies that can reasonably anticipate enrolling PTI (e.g., studies of late-stage illness), may be relevant to many studies in geriatrics as well as other fields.

How PTI differ from other research populations and implications for research acceptability

In line with common eligibility criteria for hospice [29], we define ‘terminally ill’ as having an anticipated life expectancy of six months or less. However, ethical evaluation of research in PTI should account for significant uncertainty associated with predictions of life expectancy [10, 30, 31].

Terminal illness is frequently associated with characteristics that can influence the appropriateness of research participation, including decisional impairment, significant physical and clinical needs, and dependent healthcare relationships (Supplementary Box 1). Citing these characteristics, commentators have suggested that research in PTI should be subject to significantly greater restrictions than other populations [4, 13-21]. While these factors do raise concerns that some PTI may be less able to advocate for their interests, similar characteristics arise in research populations without a terminal illness (e.g., older adults and/or persons with serious but non-terminal disease). Furthermore, as these characteristics are not universally present in PTI, they do not justify treating *all* PTI differently. Rather, as some previous commentators have argued, investigators and IRBs should weigh these factors in accordance with their prevalence in the study population, with suggestions provided below [5, 6, 23-27].

What truly distinguishes PTI is their limited life expectancy (even if exact life expectancy is difficult to predict), which has important implications for ensuring ethical research. For example, having a limited life expectancy marks a period of personal and social significance and affects the risk-benefit profile of some studies, as outlined below. Therefore, studies that anticipate enrolling PTI need to factor in these considerations during study design and review. However, as a limited life expectancy alone does not impair PTI’s ability to protect their interests, it is difficult to justify

prohibiting all research in PTI, especially as doing so would likely undermine improvements in care for PTI [23, 24], some studies offer a chance of clinical benefits, and many PTI report wanting to participate in research [32, 33]. This raises the question of what safeguards are needed to ensure research in PTI is ethically appropriate.

Social value

Like all clinical research, research in PTI should be conducted only if it has sufficient social value (i.e., potential to improve human health or advance scientific knowledge) to justify its risks and use of limited resources [28, 34]. Research in PTI can yield significant—even unique—social value by allowing investigators to study the dying process, symptoms and biomarkers of terminal illness, and ante- and post-mortem testing, among others (Table 1). Moreover, this research is vital for developing treatments for PTI, providing an evidence base for fields such as palliative and geriatric care [35-38], as well as advancing knowledge to benefit populations with other disease etiologies than the research participants (e.g., recipients of organ donation) and/or populations with similar conditions who are not terminally ill (HIV cures; Table 1)^d.

Enrolling PTI in a research study can, however, also undermine its social value. For example, long-term outcomes may be impossible to capture in PTI, as they could manifest after the population’s anticipated life expectancy [25]. Furthermore, end-stage disease and comorbidities, along with low recruitment and high attrition in this research population may confound study outcomes and limit generalizability [8, 10, 25, 31, 39, 40]. Investigators should explore ways to address these concerns and enhance their study’s social value. For example, to mitigate recruitment/attrition issues, investigators might establish referral relationships [41-43], offer flexible scheduling [41, 42], and account for attrition when calculating sample size. Research institutions should evaluate a study’s relative social value to help determine funding and organizational priorities [28], especially as recruitment issues may necessitate prioritizing some studies over others.

A favorable risk-benefit profile

Previous ethics commentaries (Supplementary Table 1) lack sufficient discussion of how enrolling PTI may affect whether a study’s risks to participants are outweighed by the combination of potential benefits to participants and society—an ethical requirement of clinical research [28, 44, 45]. By applying general guidance for risk-benefit assessments, we identified important steps for minimizing

risks, enhancing potential benefits, and determining the acceptability of research in PTI.

PTI may face different risks and potential benefits than other research populations

Risk-benefit assessments involve an evaluation of the likelihood and magnitude of the anticipated risks and potential clinical benefits of the relevant research interventions [34, 45, 46]. Importantly, PTI may face different risks and potential benefits than other populations.

First, certain risks may be minimized or altogether absent for PTI, especially in studies that are not anticipated to improve participants' life expectancy. For example, delayed risks—especially those with a longer latency period than the top percentiles of the study population's anticipated life expectancy—may be unlikely to emerge before participants pass away (e.g., delayed risk of cancer from radiation exposure [47]) [25]. Likewise, prolonged or permanent side effects may affect PTI for significantly shorter periods than populations without a terminal illness (although the acute impact may be higher, as discussed below). Risks may also be reduced by PTI's circumstances. For instance, studies may be able to rely on routine clinical interventions in PTI to obtain research samples and data, thus eliminating the risks and burdens of added research procedures.

At the same time, comorbidities, frailty, and other characteristics frequently associated with PTI (Supplementary Box 1) may increase the likelihood of adverse events, and their severity were they to occur. For example, PTI with impaired clotting function—common at the end of life [48]—may face heightened risk of bleeding from invasive research procedures. Similarly, procedures posing small discomforts or inconveniences to other populations may be substantially more burdensome for some PTI due to physical and mental fatigue [5, 43, 49].

Second, the likelihood and magnitude of the potential clinical benefits may also differ in PTI. As with risks, PTI may benefit less from delayed-onset or permanent benefits given their limited life expectancy (unless the study may increase their life expectancy). An illustrative case is a potential study proposed by The Last Gift Study, which would involve testing potential HIV cure-related interventions in persons with HIV who have non-HIV-related terminal illnesses [25]. Here, PTI with HIV would experience a lower magnitude of potential benefit – if any – from HIV cure-related interventions than HIV populations without a terminal illness. Among some PTI, reduced physical function may also limit their therapeutic response to experimental interventions. By contrast, there may also be features associated with PTI that increase

potential clinical benefits: PTI with a higher baseline symptom burden than other populations may stand to benefit more from symptom-targeting interventions.

Finally, many studies that routinely enroll PTI (e.g., early-phase clinical trials) have the *potential* to prolong survival or—in rare cases—even cure participants [4, 17, 50, 51]. Such increases in participants' life expectancy may alter the likelihood and/or magnitude of other study outcomes — for example, by increasing the potential impact of long-term risks. However, some types of trials have a low likelihood of improving survival compared to standard care (e.g., cancer clinical trial participation appears not to be associated with a survival benefit [52, 53]). How to assess clinical trials with significant risks and a very low likelihood of a major benefit (e.g., 1% chance of cure) remains a challenge in this line of research [4, 17, 50, 51].

Implications for study design and IRB review

Differences in risks and potential benefits for PTI may influence how investigators design studies to minimize risks and enhance potential benefits—an ethical requirement for research (45CFR46.111, 21CFR56.111) [28, 44-46]. Specifically, in accordance with data on the risks and potential benefits for the specific population of PTI, investigators should tailor strategies for optimizing the risk-benefit profile. This may include implementing additional safety measures, simplifying research procedures [42, 49, 54], and training researchers to manage PTI's physical and psychological needs [11, 42, 55, 56]. Importantly, these efforts should not jeopardize the study's social value, as without social value, it is difficult to justify *any* risks.

In line with general guidance [45], IRBs should evaluate the risks and potential clinical benefits for the specific population under study. Thus, IRBs reviewing research in PTI should consider the study population's anticipated life expectancy and associated circumstances/characteristics to accurately determine whether a study has a favorable risk-benefit profile. To facilitate this, investigators should provide IRBs with the population's relevant characteristics and data on how these may affect the study's risks and benefits. Reviewers with expertise in end-of-life care may help with interpreting complex and/or limited data [24, 42, 43, 57].

Evaluating differences in how PTI assess risks and benefits

Several experts in end-of-life care suggest that common changes in PTI's priorities from survival to symptom relief, dignity, relationships, and control can affect how PTI assess the importance of research risks and benefits

[4, 23-25, 43, 57]. For example, some propose that PTI may be more likely to perceive small increases in pain as a significant harm from research [58], while others argue that, given their limited life expectancy, PTI may be more willing to take on higher research risks without prospect of direct benefit [25]. Furthermore, PTI may be willing to accept higher risk for potential substantial (e.g., lifesaving) benefits [59]. Finally, although outside of the scope of traditional risk-benefit assessments, research participation may also offer psychosocial benefits (e.g., satisfaction with contributing to science); several authors have noted the importance of psychological benefits of research participation for PTI [43, 60]. Thus, several frameworks conclude that investigators and IRBs should consider data on how PTI may assess risks and benefits differently to determine a study's acceptability (Table S1, [23, 24, 43, 57]).

However, while some studies explored views of PTI on risks and benefits of participating in research, our targeted literature search revealed that very few *compare* views of PTI and persons without a terminal illness [1-3, 32, 33, 58, 61-67]. As such, we found that there is insufficient evidence on whether and how PTI assess risks/benefits differently from populations without a terminal illness to adjust risk-benefit assessments along the lines these commentators have proposed [1-3, 32, 33, 58, 61-67]. We echo calls for further investigation into this question [24, 25]. For now, IRBs should avoid non-evidence-based assumptions about PTI's risk/benefit perceptions, as this could unduly limit research opportunities or undermine research protections in ways that do not align with PTI's actual interests. There may be specific cases where IRBs have sufficient data to take into account, such as when investigators have performed in-depth study of their population's views (e.g., The Last Gift Study [25]). Moreover, studies should still factor in PTI's circumstances—and how they may affect the perceived importance of risks and benefits—during individual informed consent discussions.

Evaluating risk of death in research in PTI

Some commentators have suggested that the risk of death should be weighed differently in PTI (specifically, patients undergoing terminal wean [22]). In some cases, this seems intuitively plausible. Consider a highly socially valuable study which offers no potential for clinical benefit and poses a risk of death. For scientific purposes, the study could be conducted equally well in persons who are anticipated to die imminently due to the planned withdrawal of life support or in healthy adults with a life expectancy of 20 years or more. Given the significant difference between these two groups in the number of anticipated years of life lost if a participant were to die

from the study, some IRBs might judge the risk of death to have more limited weight in the terminal wean group. On that basis, they might even deem the study to be acceptable in patients undergoing terminal wean who can provide informed consent, but not acceptable in healthy adults.

The authors were divided on whether IRBs should weigh the 'badness' of death differently in individual cases. Some believe they should. Others felt that doing so raises the potential for a significant slippery slope that could lead to abuses. IRBs which agree with the former view should assign more limited weight to a risk of death in PTI only when the difference in anticipated life expectancy is highly significant; if the difference is modest or uncertain, they should regard the risk of death as equally weighty across all groups. Moreover, they should include additional safeguards in the study as appropriate. These might include formal capacity assessments for all potential participants, a more robust informed consent process to ensure potential participants understand the risks, and consultation with community representatives.

Developing general principles for when it can be appropriate to judge the risk of death to have more limited weight in PTI will have to await further conceptual and empirical analysis of several important questions. First, death has profound normative significance, regardless of terminal illness. This raises the question of how a relative reduction in harm from death in PTI compares to the absolute harm from death itself. Second, any general principles for weighing the risk of death differently should consider what likelihood and magnitude of life expectancy lost is consistent with limits on research risks. Third, it will be important to consider what level of prognostic certainty is needed to deem differences in life expectancy for PTI less weighty in comparison to other groups. Fourth, it will be important to assess whether it is appropriate to evaluate the risk of death differently in other populations based on differences in life expectancy. For example, does this approach support giving less weight to a risk of death in healthy 70-year-olds compared to healthy 30-year-olds? Or to a risk of death in Chad, where life expectancy is 56, compared to Hong Kong, where it is 86? These examples illustrate that such an approach—applied across all circumstances—may lead to some problematic judgments. Finally, it will be important to recognize that research-related deaths have the potential to undermine public trust in research and identify ways to address this possibility (e.g., by ensuring that the principles are consistent with societal and community values).

Limits on acceptable risks for PTI with and without capacity in net risk research

Many studies in PTI offer limited or no potential clinical benefits to participants (Table 1). In these cases, the ‘net’ risks to participants are justified solely by the study’s social value. Previous commentators have argued for limits on how much net risk all [68-70] or certain vulnerable populations (e.g., children [71]) may be exposed to, independent of the magnitude of the study’s social value, with some proposing stricter limits for PTI than other populations [4, 17, 18]. However, as outlined above, the difference between PTI and other populations—their limited life expectancy—does not limit their ability to protect their interests. Accordingly, PTI should not face stricter or more permissive risk limits based on their terminal illness alone. Rather, net risk studies in PTI should use general guidance for limits on acceptable risks.

For adults with decision-making capacity, it remains controversial whether there is any limit on net risks independent of social value [72, 73] and what this limit is [69, 70, 74]. While resolving these debates is beyond this paper’s scope, it is widely agreed that research posing greater than a minor increase over minimal risk can be permissible in adults who can provide informed consent—whether they have a terminal illness or not. For example, studies involving large blood draws [75, 76] or invasive biopsies [7, 77] without prospect of direct benefit may be acceptable in PTI who provide informed consent. Net-risk research should only include PTI without capacity to provide informed consent if necessary to achieve the study’s goals [4, 16, 56]^e. Furthermore, aligning with previous recommendations [34, 79-81], we propose that in net-risk research, adults without consent capacity should face no greater than a minor increase over minimal net risk, as they are less able to advocate for their interests. ^f ‘Minimal risk’ is defined as risks no greater than those ordinarily encountered by the average adult in daily life or during the performance of routine physical or psychological examinations (45CFR46.102), guidance on what a ‘minor increase’ means is limited [34, 71]. As an additional protection for studies involving a minor increase over minimal risk, investigators should require positive evidence that the study aligns with the person’s values (e.g., prior indication of a desire to help others). However, if PTI lose capacity after providing informed consent to enroll, they should generally be allowed to continue participation—even if it involves greater than a minor increase over minimal risk—as they already indicated the study aligns with their values. Exceptions to this include if the participant dissents to continuing participation or there is reason to think they would have changed their mind (e.g., major clinical change). Legally

authorized representatives (LARs) may also withdraw the participant at any time (for more information on LARs, please see section ‘Informed Consent’).

Fair participant selection

Studies may limit inclusion to PTI if necessary to meet their scientific goals (e.g., studies of the dying process) [28]. There may also be cases where limiting inclusion to PTI is not scientifically necessary, but robust evidence indicates PTI would face significantly lower risks than other populations, such as studies posing significant long-term risks [25]. General guidance supports limiting inclusion to groups facing substantially lower risks while meeting the study’s goals [28]—for example, limiting inclusion to persons who are not pregnant in studies with risk of endangering pregnancy. However, doing so is more controversial for PTI [4, 16-20] because—as discussed above—terminal illness is associated with several factors (e.g., decisional impairment, clinical dependence) that may increase PTI’s vulnerability in research.

We argue that it can be appropriate to limit inclusion to PTI with capacity to provide informed consent when they face significantly lower risks than individuals without a terminal illness, provided the study can still meet its objectives. In such cases, PTI with capacity can decide for themselves if the research aligns with their interests and values. Such studies should generally exclude PTI without capacity to provide informed consent unless their enrollment is needed to ensure the study’s social value *and* the net risks they face are no greater than a minor increase over minimal. Finally, several commentators express concern that studies might specifically include PTI out of convenience, ease of access, or the perception that they are ‘dying anyway’ [17, 18, 22]. It should be emphasized that these are never appropriate justifications for including PTI (or any group) in research.

Informed Consent

Informed consent involves a decisionally capable individual making a voluntary decision to enroll in research after being adequately informed [44, 82]. Informing potential participants about research opportunities—rather than refraining from doing so because of assumed preferences—allows them to decide for themselves whether participation aligns with their interests and values [28, 82]. While general recommendations for informed consent should apply to research in PTI [28, 34, 44], a few notable considerations may arise.

First, many PTI lack capacity to make decisions in medical contexts [83-85]. As argued above, PTI without capacity to provide informed consent should only be included in net-risk research if including them is necessary to achieve the study's goals. When having capacity has especially significant consequences for potential participants (e.g., high-risk studies or studies limited to participants with capacity), investigators should use a validated tool to formally assess decision-making capacity in all potential participants. Studies should also plan for potential fluctuations or permanent loss of participants' decision-making capacity when nearing death [4, 20, 84, 86] by establishing protections in their protocol for patients that lose capacity (e.g., by establishing criteria for when continued enrollment is clinically, scientifically, or ethically not appropriate, and creating safeguards for enrolled patients without capacity). When possible, investigators should time informed consent discussions such that participants have capacity to make their own research decisions—for example, by obtaining advance consent [49, 79]. Participants with capacity may be encouraged to complete advance directives and discuss research-related preferences with their designated LAR to support their LAR in future decision-making [26].

Second, research specifically including PTI based on their terminal condition raises the question of whether—and how—to inform potential participants about their prognosis [55, 87], especially as this information may be distressing and preference-sensitive [88, 89]. If potential participants require information about their terminal condition to understand the study and how participation may affect them, they should be informed of their prognosis. For example, if a study exclusively enrolled patients with terminal cancer with a limited life expectancy to compare pre- and post-mortem tumor biology, participants would need to know their prognosis to evaluate the study's key components, including its procedures and overall objectives. In such cases, PTI should only be approached about potential study enrollment if they have already been informed by their clinical team about their prognosis. Following this, researchers and study materials should use sensitive language, focusing on population-level prognostic information relevant to the study.

Third, previous commentators suggest that PTI may be especially susceptible to therapeutic misconception (i.e., failing to understand how research differs from clinical care [90]) or therapeutic misestimation (i.e., underestimating risks and/or overestimating benefits [91]). For example, early-phase clinical trials raise special concern that PTI's desperation for treatments will influence their ability to appreciate a study's low likelihood of direct clinical benefit [4, 17, 50, 51]. To

address this, potential participants should be informed in precise and understandable language about the difference between research and clinical care, the likelihood/magnitude of risks and potential benefits (if any), and alternatives to research participation [92]. Importantly, investigators should aim to distinguish between failure to appreciate a study's risk-benefit profile and personal optimism about the study's outcomes, as the latter is not inherently problematic [91].

Finally, informed consent should include information about how the study may affect participants' end-of-life needs and circumstances, including specific risks to PTI and impacts on the dying process (e.g., time with family, funeral arrangements, post-mortem appearance) [16, 19, 22].

Respect for participants

Respecting participants includes allowing withdrawal from research without penalty^g, protecting privacy, communicating clinically relevant information, monitoring welfare, and recognizing participants' contributions [28]. However, research in PTI poses additional challenges, as evidence suggests clinicians and researchers are concerned that approaching PTI about research and imposing research burdens fails to respect their clinical and psychosocial circumstances [7, 9, 10]—a concern shared by several commentators [13, 17, 18].

Investigators should carefully consider participants' end-of-life circumstances when developing strategies for respecting participants through all phases of research. For example, consent and research procedures should be timed to minimize interference with meaningful end-of-life moments and avoid intruding on physically or emotionally distressing periods when feasible [19, 42, 93]. Researchers should engage sensitively with PTI, with specialized knowledge of how to respond to their physical, emotional, and social needs [25]. To support this approach, end-of-life research teams should be trained in end-of-life communication, managing emotional distress, and respect for diverse beliefs about death and dying [6, 42, 55, 93]. Finally, by prospectively engaging with the study population, investigators may tailor these strategies to the specific needs and circumstances of their participants [34].

Respect for third parties

The end of life frequently involves close engagement from PTI's loved ones and/or caregivers, whose interests can be impacted by research—for example, by increasing their distress or caregiving burden, or reducing time with the person who is dying [5, 19, 20, 49, 94]. Investigators should consider the interests of relevant third parties

during study design and mitigate negative impacts where feasible [49]. Furthermore, if studies significantly affect these third parties, participants may be encouraged to share this information with them or invite them to join the informed consent discussion. Finally, several disease communities (e.g., HIV, cancer) have long-standing engagements with research involving PTI. Engagement with the study population, as recommended earlier, may not only facilitate study design but also help signal respect for the community.

Additionally, conducting research with participants at the end of life may place significant emotional and psychological burdens on researchers and research teams [7, 10, 20, 42, 95]. Researchers may also face moral distress^h when navigating ethical challenges noted in this paper [96], such as instances where the interests of participants and their loved ones diverge. Investigators should anticipate and monitor burdens for research teams. Further investigation is needed to evaluate strategies for

reducing psychological and moral distress in end-of-life research teams [97-99].

Conclusion

Though research in PTI can have significant social value, may offer a prospect of clinical benefits, and be a meaningful experience for participants, it raises concerns about what risks are acceptable and whether additional protections are needed. This paper has sought to help investigators and IRBs navigate these competing ethical concerns by examining how PTI differ from other populations and the influence of these differences on social value, risk-benefit assessments, and some of the other commonly recognized ethical considerations in research (Box 1). Our goal is to propose appropriate protections while not overly limiting opportunities for PTI to participate in valuable research.

Box 1. Summary of ethical considerations for research in PTI.

Overview

PTI are distinguished from other research populations by their limited life expectancy, which can have implications for social value, risk-benefit assessments, and participants' personal/social circumstances. Other characteristics associated with PTI (e.g., decisional impairment, clinical needs) should be considered based on their relevance to the specific population and the study in question.

Social Value

1. Research in PTI can offer important—even unique—social value.
2. Enrolling PTI may also limit a study's social value due to:
 - Inability to assess long-term outcomes given limited life expectancy.
 - Population-specific characteristics (recruitment issues, comorbidities) that may confound findings and reduce generalizability.
3. Investigators should explore opportunities to address limitations to social value when enrolling PTI, and IRBs should consider these limitations when evaluating whether a study has sufficient social value.

Risk-benefit assessment

1. PTI may face different risks and potential benefits than populations without a terminal illness, due to:
 - Reduced likelihood/magnitude of delayed/permanent outcomes given limited life expectancy.
 - Population-specific characteristics and circumstances (e.g., physical impairment) that may increase or decrease risks and potential benefits.
2. Investigators and IRBs should consider population-specific risks and potential benefits when designing strategies to minimize risks and enhance potential benefits and determining whether a study has a favorable risk-benefit profile.
3. Further empirical and conceptual analysis is needed to explore:
 - Whether PTI perceive risks and benefits differently than populations without a terminal illness—and, if so, how to incorporate such differences into IRB review.
 - Whether risk of death should be evaluated differently in research in PTI.
4. PTI should face the same limits on acceptable net risk as non-terminal populations with and without decision-making capacity.

Fair participant selection

1. Studies can be justified in limiting inclusion to PTI if:
 - Necessary to achieve the study's scientific goals or
 - The study's scientific goals can be met by limiting inclusion to PTI with capacity, and PTI with capacity face significantly lower risks than other groups

Informed Consent

1. Studies should only enroll PTI without capacity to provide informed consent if necessary to achieve the study's goals; such studies should have prospect of direct benefit or pose no greater than a minor increase over minimal risk.
2. Investigators should plan for how capacity will be assessed and what to do if participants lose capacity while enrolled.
3. If prognosis awareness is necessary to understand the study, PTI should only be approached about study participation if their clinical team has already informed them about their prognosis.

4.	Information provided during informed consent should be tailored to the end-of-life context, including specific risks to PTI and impacts on the dying process.
Respect for Participants	
1.	Investigators should design studies to minimize intrusion in meaningful end-of-life moments and/or periods emotional/physical distress.
2.	Researchers should sensitively engage with PTI, supported by training in end-of-life communication, managing emotional distress, and respect for diverse beliefs about death and dying.
Third Parties	
1.	Investigators should carefully consider the interests of family, caregivers, and friends (e.g., caregiving burden) and minimize negative impacts when feasible.
2.	Investigators should carefully consider psychological burdens and moral distress in research teams and explore strategies for reducing them.

Importantly, several of this paper's recommendations rely on data about differences between PTI and other research populations. As this research continues, investigators are likely to learn more about how enrolling PTI may alter a study's social value, risk-benefit profile, and appropriate strategies for respectful engagement with participants. These findings should be published and shared across research institutions with the goal of developing evidence-based practices and safeguards. Guidelines for research in PTI should adapt to this growing evidence base.

Notes

^aWe conducted a targeted search for existing ethical frameworks on research in PTI in Embase, Scopus, CINAHL, PubMed, APA Psych Net, and Google Scholar. In a series of iterative searches, we used combinations of search terms for PTI ("terminally ill," "terminal," "end-of-life," "end of life," "dying," "life-limiting," "hospice," "palliative," "end-stage"), ethical considerations ("ethic*," "ethical considerations," "ethical framework," "ethical guidance," "ethical challenges," "guidelines," "recommendations,") and research ("research," "clinical trials," "study," "studies," "investigation"). Papers that significantly discussed ethical considerations for research with PTI were included. Overall, we aimed to provide a comprehensive representation of the existing literature, though it may not be exhaustive.

^bSeveral frameworks suggest that research in PTI should always 'aim to' benefit participants, though recognizing that this is not always feasible. [15, 16].

^cMurphy et al., 2023; 2023 [19, 20] as well as Pentz et al., 2003 [22] pertain to PTI imminently withdrawing from life-sustaining measures.

^dSeveral previous commentators have proposed that the social value should accrue to a particular population that research participants are part of, such as other PTI [4, 19] or those with the same life-limiting disease [17, 22]. Indeed, general research ethics guidance suggests that ensuring research targets conditions that affect the participant group can be an appropriate special protection

for vulnerable populations [34]. However, as the morally relevant group is unclear and consenting PTI should be allowed to decide for themselves whether to enroll in research that benefits a particular group, such restrictions on social value seem difficult to justify.

^eHere, we are more demanding than some general guidelines, which allow research that is minimal risk in participants without the capacity to consent [34], as fair burden sharing suggests that the burdens of burdensome research should be borne by those best placed to bear them [28, 78] and this will typically not be the case for PTI, being in a period of personal and social significance.

^fSome guidelines also allow enrollment of persons without the capacity to provide informed consent in minimal risk studies that could enroll patients with capacity, if the research interventions or procedures without a prospect of benefit have been previously tested in people with the capacity to consent[34].

^gIn some studies, withdrawal may not be practically feasible (e.g., after an irreversible intervention is already delivered and safety monitoring is required); this should be carefully considered and communicated to IRBs and potential research participants.

^hMoral distress is defined as negative 'self-directed emotions or attitudes that arise in response to one's perceived involvement in a situation that one perceives to be morally undesirable'[96].

Disclosures

The authors report no conflicts of interest.

Acknowledgements

This research was supported by the Intramural Research Program of the National Institutes of Health (NIH; ZIA CL010537-13, 1ZIDHG200347, CL090125-01). The contributions of the NIH authors are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

We thank Dr. Irene Cortese and Elizabeth Bartrum for insightful early discussions. We also thank Dr. Yael Schencker and Dr. Charles Weijer for providing their expertise and offering feedback on the presented version of the paper during the NIH Ethics Grand Rounds in April 2025.

Supplementary Materials

The Supplementary data are available online at: www.aginganddisease.org/EN/10.14336/AD.2026.0099.

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