



Bioethics

ISSN: 2989-5448 (Online)

Publisher: Tomorrow's Research Publications (TRP)

An International Peer-Reviewed Open Access Journal

Commentary

Therapeutic Misconception in Early-Phase Oncology Trials: Ethical Implications

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ABSTRACT

Patients enrolling in phase I oncology trials frequently report expecting personal therapeutic benefit from a study designed primarily to establish safe dosing, a gap between trial design and participant belief that bioethicists call the therapeutic misconception.

This commentary examines how the misconception has been defined and distinguished from adjacent constructs such as therapeutic misestimation and dispositional optimism, and why three decades of consent-form reform have produced only modest gains in participant understanding.

It then considers how the rise of targeted agents, immunotherapy, and biomarker-selected enrollment has measurably improved response rates in early-phase trials, complicating the assumption that any expressed hope of benefit reflects confusion rather than an accurate read of improved prospects.

We argue that responsibility for managing the misconception cannot rest on consent documents alone, since much of the relevant communication happens in the physician-researcher relationship and is shaped by the scarcity of alternatives facing patients with treatment-refractory cancer.

We conclude that consent processes calibrated to agent-specific evidence, combined with communication training addressing how trials are described in conversation, offer a more defensible path forward than continued reliance on document revision alone.

Keywords: therapeutic misconception; informed consent; phase I trials; oncology; research ethics

Citation: Lefevre I, Greco P and Colombo C (2023) Therapeutic Misconception in Early-Phase Oncology Trials: Ethical Implications. *Bioethics*. 1(2):01-05.

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Article History: Received 15 June 2023 | Accepted 18 September 2023 | Published 07 December 2023

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INTRODUCTION

A patient enrolling in a phase I oncology trial is, by the logic of the study design, primarily contributing to a

dose-finding exercise rather than receiving a treatment selected for its likely benefit to them. Yet study after study has found that a large share of these patients believe, and often say directly, that they are enrolling

because the treatment is expected to help their cancer [1]. This gap between what a trial is designed to do and what a participant believes it will do for them is what bioethicists call the therapeutic misconception, and it has proven remarkably durable across three decades of consent reform, plain-language forms, and dedicated communication training [2].

The stakes are higher in oncology than in most other areas of early-phase research because the population enrolling has, in most cases, exhausted standard treatment options and is confronting a life-threatening illness. That context does not create the therapeutic misconception on its own, but it supplies powerful psychological reasons for a patient to interpret enrollment as a treatment decision rather than a research decision, and for a family to encourage that interpretation [3]. This review examines how the concept has been defined and measured, why efforts to fix it through better consent documents have had limited success, how the therapeutic landscape itself has complicated the picture, and what more recent scholarship suggests about where responsibility for managing the misconception actually lies.

DEFINING AND MEASURING THE MISCONCEPTION

The term therapeutic misconception was coined to describe a specific error: treating research procedures as if they were individualized clinical care, calibrated to the participant's own medical needs, when in fact they follow a fixed protocol designed to answer a scientific question [4]. This is a narrower claim than simple optimism about outcomes. A patient can accurately understand that a phase I trial is a dose-escalation study testing toxicity, and still hope, reasonably, that it helps them; that combination is not a misconception, it is realistic hope. The misconception proper occurs when a patient fails to grasp that the study's design does not aim at, and is not structured to reliably produce, benefit to them specifically.

Distinguishing this from adjacent phenomena, and from the ordinary optimism that any seriously ill patient might reasonably feel about a new treatment option, has occupied much of the empirical literature [5]. Researchers have proposed separating therapeutic misconception (misunderstanding the purpose of the research), therapeutic misestimation (overestimating personal probability of benefit even while understanding the research's aggregate purpose), and therapeutic optimism (a general hopeful disposition that colors how risk information is processed) [1]. A 2016 study of dispositional optimism in early-phase oncology participants found that people who scored high on general optimism measures also reported higher expected benefit from trial participation, independent of what the consent form or oncologist actually told them, suggesting that some of what looks like a comprehension failure is really a stable personality trait interacting with hopeful framing [6].

More recent work has pushed back on how these constructs are measured in practice, arguing that some validated instruments conflate genuine misunderstanding of trial design with ordinary hope for a good outcome, and that studies reporting very high rates of "therapeutic misconception" may be over-counting patients who actually understand the trial correctly but still hope it helps them [7].

Table 1. Three related but distinct constructs used in the therapeutic misconception literature, what each describes, and whether it is correctable through better disclosure.

Construct	What the patient misunderstands or overestimates	Underlying mechanism	Correctable through disclosure?
Therapeutic misconception	Believes the trial is designed to benefit them individually rather than to answer a scientific question	Conflation of research protocol with individualized clinical care	Largely yes, in principle, with clearer explanation of trial purpose
Therapeutic misestimation	Overestimates their own personal probability of benefit even while understanding the study's aggregate purpose	Difficulty reasoning about small probabilities under emotional strain	Only partially; numeric literacy and framing effects persist
Therapeutic optimism	Holds a generally hopeful outlook that colors how risk and benefit information is processed	Stable dispositional trait, not a factual error	Not applicable; hope itself is not a comprehension failure to correct

Table 1 lays out how these three related constructs differ along the dimensions that matter for informed consent: what exactly the patient misunderstands or overestimates, and what intervention, if any, could plausibly correct it. The distinctions are not merely semantic. A misconception about trial purpose is, in principle, correctable through clearer explanation; a misestimation of personal benefit probability may persist even after correct explanation, because probabilistic reasoning about small numbers is difficult under emotional strain; and a general optimistic disposition is not, strictly speaking, an error to correct at all.

THE LIMITS OF CONSENT-FORM REFORM

The dominant institutional response to concerns about the therapeutic misconception has been to revise consent documents: adding explicit statements that the primary purpose is to establish safe dosing, clarifying historical response rates for phase I agents, and requiring teach-back procedures where participants restate the purpose of the study in their own words [8]. The results of this approach have been

mixed at best. A randomized trial of enhanced versus standard informed consent for early-phase oncology participants, registered to test whether a structured, plain-language consent process improves patient understanding relative to usual practice, was designed specifically because prior form-based interventions had shown only modest and inconsistent gains [9,10].

Part of the difficulty is that the misconception is not principally a reading-comprehension problem. Interview studies of oncologists conducting phase I consent conversations have found that physicians themselves often blend scientific and therapeutic language when explaining a trial, describing dose-escalation cohorts in terms of "trying" a new treatment and referring to prior patients' outcomes in ways that invite a participant to infer personal benefit, even when the oncologist does not intend to mislead [11]. Bioethicists writing on this problem have argued that the misconception is partly produced, not merely tolerated, by the therapeutic relationship itself: an oncologist who has cared for a patient through prior treatment failures is not well positioned to present the next option in coldly non-therapeutic terms, and patients read the ongoing relationship, correctly, as evidence that their doctor is still trying to help them [12]. This account reframes the problem as inherent to the physician-researcher dual role in oncology, not simply a failure of disclosure that a better paragraph in a consent form can fix.

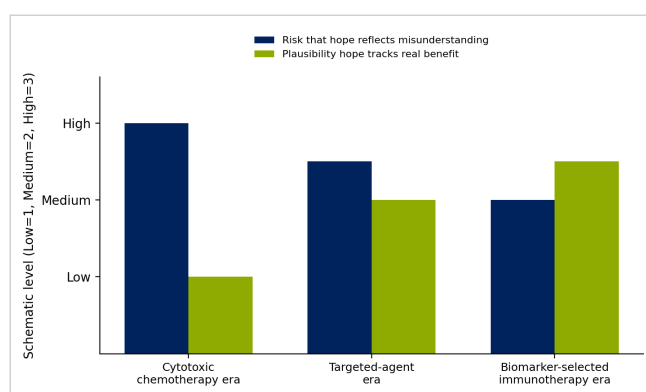
A separate strand of criticism has questioned whether the entire framing of the misconception as a comprehension deficit is itself too narrow. Some scholars argue that patients enrolling in phase I trials frequently make an entirely rational decision under genuine uncertainty: given the absence of any better standard option, a trial offering close monitoring, novel agents, and a nonzero chance of benefit can be a reasonable choice even without a therapeutic misconception at all, and treating every expression of hope for benefit as evidence of confusion risks pathologizing ordinary decision-making under scarcity [13]. Voices writing from a patient-advocacy perspective have made a related point about "false hopes," arguing that bioethics discourse sometimes treats hope itself as the problem to be corrected, when the deeper issue is a healthcare and research system that offers few alternatives to patients with advanced, treatment-refractory cancer [14].

A CHANGING THERAPEUTIC LANDSCAPE

Much of the empirical and ethical literature on therapeutic misconception was developed at a time when phase I oncology trials had low objective response rates, often in the low single digits, making optimism about direct benefit statistically difficult to justify. That landscape has shifted. A systematic review and meta-analysis of phase I trials of targeted single-agent anticancer therapies found that response rates and overall benefit measures have risen

meaningfully compared with the cytotoxic-chemotherapy era, driven by molecularly targeted agents and, more recently, immunotherapies tested with biomarker-informed enrollment [15]. Popular reporting on this same shift described response rates in phase I cancer trials as having nearly doubled over roughly the past two decades [16], and single-institution analyses of more recent trial cohorts have described meaningfully improved outcomes for patients enrolled in contemporary early-phase programs compared with historical cohorts [17].

Figure 1. Schematic comparison across three broad eras of early-phase oncology trial design of the risk that patient hope reflects genuine misunderstanding of trial purpose versus the plausibility that such hope tracks a real prospect of benefit (illustrative, not derived from a single empirical study).



This complicates the ethical analysis considerably. If early-phase oncology increasingly does offer a realistic, if still modest, chance of direct benefit for some biomarker-selected patients, then a participant's expectation of personal benefit is less obviously a misconception and more plausibly an accurate, if optimistic, read of a genuinely improved situation [18]. Expansion cohort designs, now common in the immunotherapy era, further blur the traditional phase I/phase II boundary by enrolling larger numbers of patients at a therapeutic dose specifically to characterize activity signals, a structural change that a recent systematic review found has outpaced updates to how consent documents describe the trial's purpose to participants [19]. Biomarker enrichment strategies, which select patients more likely to respond before enrollment, add a further wrinkle: they can make an individual's elevated probability of benefit both real and something the older therapeutic-misconception framework was not built to accommodate [20]. None of this eliminates the misconception as a phenomenon, since it can still occur even where response rates are meaningfully higher, but it means that a blanket assumption that any hope of benefit in a phase I trial reflects confusion is no longer defensible on its own terms, and consent processes need to be specific about the actual, agent-level evidence rather than reciting historical phase I statistics as if they still applied uniformly [21].

Figure 1 presents a schematic comparison, not derived from a single study, of how the balance between the therapeutic-misconception risk and the plausibility of genuine expected benefit has likely shifted across three broad eras of early-phase oncology trial design. The intended point is qualitative: the risk that a patient's hope reflects a true misunderstanding of trial purpose has probably not disappeared, but the plausibility that some of that hope tracks real, if modest, prospects of benefit has grown as trial designs have become more selective and molecularly informed.

WHOSE RESPONSIBILITY IS IT?

A recurring question in this literature is where responsibility for managing the therapeutic misconception should sit: with the consent document, the investigator, the institutional review process, or the broader clinical culture that surrounds a cancer diagnosis. Ethics-focused reviews of phase I oncology consent have generally converged on a layered answer, holding that no single fix, whether a better form or a scripted disclosure, is sufficient on its own, and that institutional oversight needs to evaluate the whole consent process, including how oncologists actually speak with patients, rather than auditing documents alone [21]. Communication-training interventions aimed specifically at oncologists conducting these conversations have shown that how a physician frames dose-escalation cohorts and prior-patient outcomes measurably affects how participants describe the purpose of the trial afterward, suggesting the conversation itself, not just the written form, is a legitimate and modifiable point of intervention [22].

There is also a case that some responsibility properly rests upstream of any individual consent encounter, at the level of how a healthcare system structures options for patients who have exhausted standard care. Where a phase I trial is functionally the only remaining option being offered, patients face something closer to a Hobson's choice than a genuine decision among alternatives, and framing their hope for benefit as an individual comprehension failure may obscure a more structural problem about the scarcity of late-line treatment options [23]. Others have cautioned against overcorrecting toward institutional or systemic explanations in a way that erases patient agency altogether, and have argued instead for consent processes that explicitly separate the scientific purpose of a trial from a patient's independent hope, allowing both to be stated honestly rather than treating the second as a symptom to be eliminated [24].

CONCLUSION

The therapeutic misconception in early-phase oncology trials has resisted three decades of definitional refinement, consent-form redesign, and communication training not because these efforts have

been poorly executed, but because the phenomenon sits at the intersection of a genuinely difficult research design, a therapeutic relationship that predates the research encounter, and a patient population facing few alternatives. The rise in phase I response rates driven by targeted and immune therapies has made the picture more complicated rather than simpler, since some patient optimism that once reflected a clear misunderstanding may now track a real, if still modest, prospect of benefit. What the recent literature converges on is not a single corrective but a layered one: consent processes calibrated to the actual evidence for the specific agent under study, communication training that addresses how oncologists talk about dose-escalation cohorts rather than only what the form says, and an honest acknowledgment that some of what looks like confusion is simply hope operating exactly as it does everywhere else in serious illness.

DECLARATIONS

Acknowledgements

The authors are grateful to colleagues in their respective departments of philosophy and bioethics for helpful conversations that sharpened the arguments developed in this review.

Funding

This review received no external funding.

Conflict of Interest

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

Author Contributions

Ingrid Lefevre conceived the review, conducted the literature synthesis on definitional and measurement issues, and drafted the initial manuscript. Pierre Greco contributed the sections on consent-form reform and the changing therapeutic landscape and critically revised the manuscript for intellectual content. Chiara Colombo contributed the section on responsibility and accountability, coordinated reference verification, 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.

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