Informed consent for early-phase clinical trials: therapeutic misestimation, unrealistic optimism and appreciation

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ABSTRACT

Unrealistic therapeutic beliefs are very common—the majority of patient-subjects (up to 94%) enrol in phase 1 trials seeking and expecting significant medical benefit, even though the likelihood of such benefit has historically proven very low. The high prevalence of therapeutic misestimation and unrealistic optimism in particular has stimulated debate about whether unrealistic therapeutic beliefs in early-phase clinical trials preclude adequate informed consent. We seek here to help resolve this controversy by showing that a crucial determination of when such therapeutic beliefs are ethically problematic turns on whether they are causally linked and instrumental to the motivation to participate in the trial. Thus, in practice, it is ethically incumbent on researchers to determine which understanding and beliefs lead to the participant's primary motivation for enrolling, not to simply assess understanding, beliefs and motivations independently. We further contend that assessing patient-subjects' appreciation as a component of informed consent—it is already an established component of decision-making capacity assessments—can help elucidate the link between understanding-beliefs and motivation; appreciation refers to an individual's understanding of the personal significance of both the medical facts and the experience of trial participation. Therefore, we recommend that: (1) in addition to the usual question, 'Why do you want to participate in this trial?', all potential participants should be asked the question: 'What are you giving up by participating in this trial?' and (2) researchers should consider the settings in which it may be possible and practical to obtain 'two-point consent'.

INTRODUCTION

Early-in-human clinical trials are changing. Traditionally, phase 1 oncology trials have tested *safety* prior to *efficacy* testing in subsequent phases.[1] More recent trials—such as those using immunotherapies or gene editing—may incorporate efficacy/effectiveness endpoints into phase 1.[2 3] As informed consent processes shift for mixed-phase trial designs, it is timely to address standing issues regarding adequate consent. Chief among these is the problem of *unrealistic therapeutic beliefs* harboured by desperate patient-subjects enrolling in early-phase trials.

Unrealistic therapeutic beliefs are very common—the majority of patient-subjects (up to 94%) enrol in phase 1 trials seeking and expecting significant medical benefit,[4] even though the likelihood of such benefit has historically proven very low.[5] Unrealistic therapeutic beliefs may present in the form of therapeutic misconception (TM), therapeutic misestimation (TMe) or unrealistic optimism (UO). TM involves mistakenly viewing the intervention as personal medical care rather than as a research study.[6] In TMe and UO, patient-subjects recognise that they are in a research study yet overestimate the likelihood that they will benefit medically; TMe refers to overestimating the likelihood and magnitude of benefit (and underestimating the risks) associated with any subject's trial participation[7] and UO consists of a trial participant overestimating medical benefit for themselves *relative to other participants*.[8] Importantly, research hype—such as when a new intervention is publicised as 'groundbreaking'—can further distort trial participant expectations.[9 10] Therefore, even if new, mixed-phase trials show modest improvements in the likelihood and magnitude of medical benefits, we can still expect that people will overestimate potential gains and TMe and UO will persist.

The high prevalence of TMe and UO in particular has stimulated debate about whether unrealistic therapeutic beliefs in early-phase clinical trials preclude adequate informed consent.[11] We seek here to help resolve this controversy by showing that a crucial determination of when such therapeutic beliefs interfere with adequate informed consent turns on whether these beliefs are causally linked and instrumental to the motivation to participate in the trial. We further contend that assessing patient-subjects' *appreciation* as a component of *informed consent*—it is already an established component of decision-making capacity (DMC) assessments—can help elucidate the link between understanding-beliefs and motivation; appreciation refers to an individual's understanding of the *personal significance* of both the medical facts and the experience of trial participation. A focus on appreciation in informed consent will help ensure a solid foundation for the development of appropriate standards for newer, mixed-phase trials as well as for traditional trials.

To illustrate the relevance of appreciation in early-phase trials, we first articulate the link between understanding-beliefs and motivation through an analysis of autonomy and agency. Then, based on our emphasis on agential decision making, we present a rationale for adding an assessment of appreciation to the informed consent process. Finally, we discuss how such assessments can be carried out in practice.

LINKING UNDERSTANDING-BELIEFS AND MOTIVATION

The debate about whether patient-subjects who believe they are very likely to have significant

medical benefits should be permitted to enrol in phase 1 trials remains unresolved. We suggest that articulation of the relationship between understanding-beliefs and motivation can provide some clarity.

The primary purpose of informed consent in research is to respect participants as persons by respecting their autonomy (while for those with diminished DMC, respect for persons requires their *protection*).[12–14] [i] Here we consider philosophically what respect for autonomy requires. We can respect the autonomy of someone with the *capacity for autonomy* regardless of whether they actually choose to exercise autonomy—that is, whether they base their decisions on their core values and good reasoning. We do not require that people exercise autonomy in order to respect their choice because the point of respecting persons is to respect their mental freedom to exercise autonomy or not.[15 16] While respecting persons does not require that the research subject fully exercise autonomy, it does *minimally require* that they exercise *agency*.

Agency is a basic precondition for autonomy and requires that an individual's actions stem from some motivating reasons (however well thought out) that the individual can identify with. To view a person as exercising *agential control*—to act as an agent whose mental initiative and reasons are the source of their decisions—is central to respecting someone as a person, rather than viewing them as a 'wanton', a being who generates motives chaotically.[17]

Respecting agency may seem quite minimal but in fact it creates greater demands on informed consent than have thus far been recognised. In the case of respect for a research subject, we must assume that their beliefs about the trial have a controlling influence on their motivations rather than view them as merely subject to beliefs and motives that are unconnected. Their choice becomes coherent, and thus worthy of respect, insofar as it is clear how their understanding-beliefs are *causally linked* to their motivation to participate in the trial.

We think that this causal path from beliefs to motivation has been largely missed. For example, Kim and colleagues[18] conclude that although 60% of participants had a *primary therapeutic motivation* for enrolment, such motivation '[did] not seem to lower or dampen [their] perception of risk'. We agree that we should not assume that therapeutic motivation to enrol implies an issue with understanding or makes a person more likely to form incorrect beliefs. The problem, however, occurs when we look in the opposite direction: *if incorrect understanding-beliefs* ***lead to*** *acting on their therapeutic motivation by participating in the trial*, this is what makes their enrolment ethically troubling. Without consideration of the direction of causality—of whether *unrealistic* therapeutic beliefs are motivating the decision to participate or not—we are compartmentalising beliefs and motives in the way we would with a wanton.

That is, we agree with Kim and colleagues that many people will be motivated by the desire for a cure, and this desire need not be ethically problematic. What matters is the specific beliefs that then motivate them to act on that desire and enrol. If their decisive belief is that they have a very small chance of cure but are willing to take it, that is not a problem. However, if their decision to participate depends on believing they are very likely to be cured (an unrealistic therapeutic belief), then that is ethically problematic. Thus in practice, it is ethically incumbent on researchers to determine *which* understanding and beliefs *lead* to the participant's *primary reasons* for enrolling in a trial, not to simply assess understanding, beliefs and motivations independently. *An agent's decision to participate can only be respected in light of the specific beliefs it is based on*.

While we stress the formal necessity of identifying which among the beliefs a person holds are actually motivating them to participate, we understand that participants often hold complicated, ambiguous and conflicting beliefs about the trial as they face the difficult task of weighing potential and expectable upsides against potential and expectable downsides. It is still consistent with adequate informed consent for people to enrol for a complex amalgam of reasons—altruism, the wish to try a long shot,[19] the desire to become involved with more medical interventions or something else. We can acknowledge that people are emotionally and cognitively complex and not strictly logically consistent while still expecting them to be agents rather than random motive generators.[20]

Given the potential complexity and multiplicity of people's reasons and given that we cannot always know which causal pathway actual patients have travelled in deciding to participate, we need a less logic-based and more practical criterion to assess whether unrealistic therapeutic beliefs are undermining informed consent. We suggest this question to help determine whether someone is exercising agential control: have their unrealistic therapeutic beliefs prevented them from considering the *expectable personal downsides* of trial participation? Note that this approach adds the normative assumption that a subject should be acting on personal reasons (reasons they can identify with) and that their reasons should be tied to some kind of *realistic expectations* about their own likely experiences as a trial participant. Note that the normative assumption of realistic expectations remains a significantly lower standard than exercising autonomy while also allowing us to see the subject as an agent whose reasons are not out of touch with reality.

While informed consent does not require perfectly rational decision making and 'optimal understanding or appreciation',[14] Miller and Joffe[11] note that there is 'no consensus about what subjects must understand or appreciate in order to give ethically valid consent'. Here we are suggesting a concrete approach about which we perhaps can achieve consensus: a person should be able to demonstrate appreciation of *what they are giving up to participate in a trial (in addition to what they are seeking to gain)* to ensure that their decision to participate is based on their *own reasoning* about their personal future and that this reasoning is not unrealistic. For reasons we explain in the next section, we identify this as meeting the 'appreciation criterion' for informed consent.

APPRECIATION AS A CRITERION FOR INFORMED CONSENT

Appreciation is an established element of DMC and has been used in the clinical setting to refer to whether a patient can grasp how an intervention will foreseeably influence their own life, rather than merely restate medical risks and benefits (the usual focus of assessments of 'understanding').[21 22] The clinical context in which appreciation comes up as part of a DMC assessment is usually when a patient refuses a critical, recommended treatment.[16 23] In the research setting, Jansen and colleagues have suggested that cognitive biases (such as UO) may 'compromise the appreciation necessary for decision-making capacity' for

[i] While Miller & Wertheimer defend a 'fair transactional' model with emphasis on *beneficence*, we maintain that autonomy is the primary consideration of informed consent for research.[19]

enrolment in early-phase oncology trials.[24] While appreciation has only been evaluated in the context of questioning DMC, clinicians have observed many instances in which patients have substantial DMC yet their appreciation is questionable.

For example, a woman with hypomania who understood factually that she needed a pacemaker after being diagnosed with a life-threatening cardiac arrhythmia said, 'I know I have that diagnosis, but I feel so great that I can't see anything bad happening to me',[16] and patients with mild to moderate depression who are able to understand the risks and benefits of treatment (including the fact that medications can help them) often feel too negatively about their futures to imagine how they will actually feel better after treatment.[16 23] These patients have shown an ability to ultimately appreciate with further support. In other words, individuals can have the capacity to appreciate yet fail to apply that capacity to their present situation absent more intensive communication. While these are examples from clinical practice, we believe that assessing and seeking to improve appreciation should be a priority for enrolling patient-subjects in clinical trials.

Consider the following real, disguised example from a clinical trial shared with the first author by a team member. Mr A, an educated man in his 50s, has metastatic cancer unresponsive to existing treatments. He derives his greatest sense of well-being from his young grandchildren, with whom he spends time daily. Given his poor prognosis and desire to see his grandchildren grow up, he decides to participate in a phase 1 clinical trial involving an experimental bone marrow transplant. To participate, he needs to relocate to a research hospital far from his home for 3 months, during which time he will be severely immunocompromised, weak from the trial and isolated.

Once he is situated in the hospital room the evening before the bone marrow transplant, he becomes much less certain of a good outcome. He tells the nurse he is afraid of dying either from the trial or from his cancer, and he fears that he may never see his grandchildren again. As the nurse empathises, Mr A becomes tearful and his fear shifts to intense sadness as he begins to grieve about his illness and the time he will lose with his grandchildren over the next 3 months and perhaps forever. He becomes increasingly anxious and is given a valium-like drug. As it takes effect, his mind shifts away from the imminent transplant and prolonged isolation and he goes ahead with the trial.

Mr A's case illustrates the importance of appreciation for informed decision making. He most likely has the capacity to appreciate yet in fact did not exercise that capacity and failed to appreciate the personal significance of the expected separation from family. His decision to participate in the trial appears to reflect inflating the likelihood, and thus expected value, of being cured or put into long-term remission and having a long-term future with his grandchildren (extremely unlikely though extremely valued). Closely related to this, he also appears to be discounting the expected value of his current life, including spending time with his grandchildren over the next 3 months (highly likely and highly valued).

Mr A's delayed sadness suggests that his deliberation about participation was either incomplete before arriving at the hospital or was complete with the information he had at the time and now needed to recommence in light of new *material* information (how the experience of separation felt). It is also possible that he already appreciated the predictable outcome of being isolated from his grandchildren as a downside of trial participation and his decisional regret just retriggered an emotional process that he had already gone through. Which of these instances is the case matters for assessing the quality of his informed consent—when therapeutic beliefs lead to neglecting or discounting the personal costs of trial participation, we see it as an appreciation failure and erosion of informed consent.

As with many other patient-subjects, Mr A's cognitive bias towards expecting a cancer cure may have detracted from his paying attention to the *expected losses* that accompany trial participation, including the more certain, less dramatic and often non-medical losses from leaving home or otherwise sacrificing other critically important experiences to participate in a clinical trial. While some individuals may prefer participating in a phase 1 trial as a personally meaningful way to spend their final months, many would not and would more strongly choose other important life pursuits (eg, being with family, travelling or finishing a project). If they had appreciated the foreseeable trade-offs between alternatives, they might have chosen differently.

The most simple and immediate implementation of an appreciation criterion would be to ask potential participants the question: 'What are you giving up by entering this trial?' Additional questions to evaluate and support the appreciation process may include: 'What will your life be like during this trial?', 'What will your life be like after this trial concludes?' and 'If this trial does not give you significant medical benefit (cure or prolonged remission), will having participated still be acceptable to you?' We suggest that the ethical standard for enrolment involves the person appreciating the likely and *foreseeable outcomes* that are material to the person's own future, while of course they cannot fully appreciate *all* potential outcomes.

To make this account of the need for appreciation concrete, a therapeutic motivation for enrolment in a phase 1 trial that is substantially based on a wish to try a long shot (with significant appreciation for the personal costs of enrolment) is indicative of adequately informed consent. In contrast, a decision to enrol that is substantially based on unrealistic therapeutic beliefs and/or a deflated perception of personal costs or sacrifices (and potential benefits of alternatives) is problematic, even if the participant correctly answers questions about the study protocol and aims. For example, if Mr A accurately repeated the medical facts of the trial but responded that he was not giving anything up by participating, it would be clear that he had not emotionally considered the obvious fact of separation from his family when making his decision to participate in the trial and hence failed to appreciate the personal consequences.

PRACTICAL RECOMMENDATIONS FOR APPRECIATION IN INFORMED CONSENT

We now describe practical steps to integrate appreciation into the informed consent process so as to respect participant autonomy by viewing their decisions as agential (with understanding-beliefs connected to motivation). Our first recommendation is that in addition to the usual question 'Why do you want to participate in this trial?', all potential participants should be asked the question: 'What are you giving up by participating in this trial?'. This focus on appreciation in informed consent will direct investigators' attention to possible failures of appreciation that now go undetected. Additionally, it will also demonstrate the severity of each failure (ie, does it suggest an *incapacity* to appreciate or merely that the person has not been adequately helped to appreciate?); it is important to remember that in many instances, a person's demonstrated lack of appreciation is not a permanent condition. The arguments of this paper lead us to see that adding the simple question 'What are you giving up?' is ethically required for adequate informed consent.

Our second recommendation is to consider the settings in which it may be possible and practical to obtain 'two-point consent'. Consider how the ideal standard for appreciating what it will be like to participate in research would be to actually go through the experience. But short of a time machine, this is not possible. Therefore, the closer the research participant can get to having some form of personal experience (ideally within the same location, time and context) to supplement the other material information regarding participation, the more effectively they should be able to appreciate what the personal meaning of the experience will be for them and the more informed their decision making will be. In the case of Mr A, he could have benefited from a second consent process once he relocated for the trial (perhaps the night before it began) to ensure that he had in fact appreciated the realities of trial participation. A second consent would also have recognised that even if he had previously appreciated (given all available information) he could have more completely appreciated the material conditions of his participation—the administration of a sedative was thus ethically problematic in its own right as it served to interrupt his rekindled appreciation/deliberation regarding participation. While people already have the right to opt out of a study at any time, we suggest that eliciting a second consent when possible will improve informed consent for these reasons.

Others have made suggestions about the appropriate setting for informed consent. For example, Lidz and colleagues[25] suggest that patient-subjects should go through the consent process outside the treatment environment given that 'Everything about a medical setting will evoke participants' expectations of personal care'. While this recognises the importance of context in decision making, we suggest *two independent consent processes* (one outside the treatment setting and one in the study environment at the commencement of the study (or shortly after)). This approach looks for consistency in understanding and appreciation *over time* instead of relying on a moment of perceived adequacy. If consistency across time points is lacking (even within the same conversation), that is a strong indication that consent is inadequate or volatile. Additionally, if this inconsistency proves unresponsive to intervention, there may be an underlying problem with DMC that would need to be addressed for the person to be included in the trial.

We recognise that research funding is limited, and this expansion in personnel time might be considered unduly burdensome. To find out if this use of resources is warranted, our hope would be that the National Institutes of Health (NIH) or other funding sources could fund studies to implement and evaluate the impact of the two-point consent model.

CONCLUSION

As we shift towards more mixed-phase trials (incorporating expectations of efficacy in safe dosage trials), it is crucial to address long-standing, unresolved problems with informed consent. Importantly, we have shown that careful attention to appreciation (a lacking and much needed component of informed consent) can help identify when unrealistic therapeutic beliefs, such as those that accompany TMe and UO, undermine informed consent and when they do not. Our emphasis on foreseeable personal costs may prove especially helpful for newer, mixed-phase trials in which mispredictions of benefit may be exacerbated by research hype.

It is manipulative (and thus unethical) to enrol participants if we believe them to be acting without agential control (ie, to ignore a clear causal link between a subject's belief that a phase 1 trial will be curative and their therapeutic motivation to enrol). A standard that ignores this link permits investigators to cherry-pick among participant's statements to permit their inclusion. If we intend to respect participants and enrol them ethically, we must view their actions as based on their reasons, and we must notice when they have failed to consider the personal costs as well as benefits of trial participation.

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