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Early phase clinical trials: communicating the uncertainties of ‘magnitude of benefit’ and ‘likelihood of benefit’

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Miller and Joffe present one of the most cogent summaries to date of the ethics issues at stake in Phase 1 cancer trials. Specifically, they suggest that direct medical benefit from participating in Phase 1 trials is possible, but the likelihood of such benefit occurring cannot at present be quantified. Further, they clarify that while the primary purpose of Phase 1 trials generally is to determine the safety profile and/or appropriate dosing for a therapeutic agent, this primary purpose in no way negates the possibility that participation could also offer some direct clinical benefit to an enrolled patient. Their paper is an important contribution to the literature in terms of unpacking the debates that have existed about ethics and Phase 1 cancer trials. It also contributes by separating the ethics *issues* raised through the conduct of these trials – e.g., whether patients adequately understand such trials and whether oncologists present information about trials in a thorough and accurate way – from whether, as designed, the trials themselves are *ethical*. In this commentary, I will only build on their discussion and focus on two particular points – magnitude of benefit, and communication about benefit.

Miller and Joffe focus much of their argument on whether it is reasonable to conclude that therapeutic benefit is possible for an individual patient, and whether it is ethically acceptable for either a patient or oncologist to acknowledge and act upon this possibility. They point out that, logically, clinical benefit can result only if changes observed in a trial (such as tumor shrinkage or disease stabilization) are causally related to the investigational intervention, and, significantly, if the changes observed are associated with *clinical improvement* (e.g., longer life or better quality). In examining existing data, they conclude data are too varied or of inadequate quality to determine whether or how *likely* such clinical improvement is. Nonetheless, their analysis leads them to conclude that clinical benefit indeed is possible as a result of Phase 1 trial participation.

While raised in passing in their commentary, largely missing from their analysis, however, is the third step: *magnitude* of benefit. That is, even if one could demonstrate that a trial *does* generally causally result in tumor shrinkage and, further, the tumor shrinkage observed was generally associated with longer life, is that enough? Can oncologists and patients simply talk about the increased life span that seems to sometimes be associated with the drug, or is it also relevant whether increased life span means a few more days, a few more months, a few more years, or a cure? In considering the *ethics*, issues at stake in Phase 1 trials, patients’ understanding, and oncologists’ presentations of information, one might want the trajectory to have three parts [1]: Do the investigational drugs used in Phase 1 trials *cause*

changes in tumors or other markers [2]? Do those changes seem to be clinically relevant? And [3] what is the nature of the benefit (pain relief? increased life span?) and *for how long*?

Let me be clear. Saying magnitude of benefit should also systematically be included in an analysis of Phase 1 trial benefit is *not* to suggest that lines can or should be drawn about how much benefit or what length of response is meaningful. The answer is in the eye of the beholder and healthy people are in no position to declare what amount of additional life should be of value to those who are dying.

At the same time, since data suggest that oncologists tend to speak in generalities rather than specifics [1], and that patients, to some degree, fill in their own ‘narratives’ about what the specifics might be [2], the lack of mention of magnitude – especially when hopes are high – has the potential to lead to extraordinary misestimations of what level of magnitude is normative. For example, Miller and Joffe cite a study that found that advanced cancer patients would try a treatment that offered a 1% chance of complete cure. Miller and Joffe presumably include this citation in order to demonstrate that patients are willing to join trials when the likelihood of benefit is very low. Nonetheless, it illustrates the importance of magnitude. Even with existing data, one might claim that the question itself examines a wholly unrealistic scenario (1% chance of complete cure). By contrast, it would be interesting to ask patients their willingness to join a study that offered a 1% chance of 1–2 additional months of survival. Again, many patients may decide to join such a trial, and, for the sake of future patients, one hopes they will. Nonetheless, underscoring in ethics analyses and in consent discussions with patients that the likelihood of benefit may be very small without *also* describing that the magnitude may be very small makes analyses and discussions incomplete. Sadly, even with incomplete data, given the populations eligible for these trials, if dramatic improvements in magnitude of benefit were frequently seen across Phase 1 oncology trials – e.g., if patients routinely lived even 6–12 months longer than expected – then such improvements likely would have been documented even absent formal control groups.

The second point has to do with communication. Miller and Joffe conclude ‘it is vital that clinical investigators communicate meaningfully to patients about risks, benefits, and uncertainties.’ This conclusion is important and must continue to be emphasized. Nonetheless, a challenge is posed from the sizeable literature suggesting that patients’ understanding may not be accurate even after quality disclosure. Further, engaging in *dialogue* with patients about risks, benefits, and uncertainties may be more promising, and deserves further empirical evaluation [3]. Research suggests that asking patients a few questions to learn what their beliefs and understandings are may be useful [4]. For example, asking patients what they think a Phase 1 study is about, which benefits they think are possible and which benefits they think are likely is an intervention to both *assess* what patients are thinking and also to *improve* understanding. Arguably, the clearer the data are that many patient-subjects carry misunderstandings about a trial, and the greater concerns – if any – we have, morally, about the nature of their misunderstandings, the greater the obligation we as a research community have to identify mechanisms to increase that understanding. As Miller and Joffe assert, optimism is fine and may actually be therapeutic. The problem comes if we as a research community knowingly enroll patients who fundamentally misunderstand the nature of these trials. Given our reliance on having them join in order to further our scientific purposes, moving forward with enrollment in such a context risks being viewed as conflicted and ethically suspect. Fortunately, however, such fundamental misunderstandings may be relatively uncommon. At least one study suggests that survey data showing that many patients expect cure or long-term benefit from Phase 1 trial participation may not accurately reflect patients’ understanding. Indeed, more extended

qualitative discussions with patients reveal more tempered expectations of personal benefit [5].

The ethics literature has devoted sizeable attention to questions of ethics and Phase 1 cancer trials. Miller and Joffe make an important contribution to the literature by suggesting that both the ‘benefit skeptics’ and the ‘benefit enthusiasts’ are in error and that the potential for benefit in these trials certainly exists, but data are not available to ‘support any definitive estimate of a clinical benefit rate’. Their analysis might be further refined by devoting the sophisticated level of attention they have given to likelihood of benefit also to questions of magnitude. Even more importantly, the literature reviews describing likelihood of response [6-8] would also benefit by providing attention to the nature and magnitude of benefit, not only to the likelihood of changes being observed.

Cancer research is critical to determining which new therapies are useful, and progress in this area cannot occur without the willingness of very ill patients to be part of the enterprise. It is our duty to help frame the issues as carefully as possible for patients, engage them in discussion, and continue to collect data on what types, how much, and how often benefit results for current and future patients, and whether both patients’ and oncologists’ beliefs about those benefits are in keeping with emerging data.

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