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ETHICS CASE

The Question of Clinical Equipoise and Patients' Best Interests

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Dr. Malone is a primary care doctor in the student health clinic at a large research institution, and one of her patients, 20-year-old Charlie, was just diagnosed with stage 4 non-small-cell lung cancer. The five-year observed survival rate is 1 percent and the current standard of care is chemotherapy. The Food and Drug Administration has just approved a promising new drug called MX320 for clinical trials. A medical school classmate of Dr. Malone's is the primary investigator of an active-controlled, double-blind, randomized clinical trial at a local hospital. Promising early-phase investigations suggest that patients receiving the new drug are improving and, based on this information, Dr. Malone thinks Charlie would probably be a good candidate for the drug.

There is no guarantee that Charlie would be randomized to the experimental arm of the trial, but Dr. Malone and Charlie are hopeful that he would improve. As a result, Charlie enrolls. After some weeks, he has shown no improvement, and, while it may be too early to tell, Dr. Malone begins to wonder whether he was in fact randomized to the control treatment arm. As Charlie's physician, Dr. Malone feels responsible for possibly giving him false hope. She is aware of another clinical trial from which Charlie might benefit and is unsure whether she should voice her suspicions to Charlie, which might prompt him to leave the study, or keep her concerns to herself.

Commentary

Dr. Malone's dilemma in this case centers on one of the most influential—and controversial—concepts in research ethics: clinical equipoise. In its canonical formulation, clinical equipoise stipulates that a randomized controlled trial (RCT) is only ethical insofar as there exists, at the outset, a state of genuine uncertainty in the community of medical experts about the relative therapeutic merits of every arm in the trial [1]. In other words, if clinical equipoise holds, then all arms are equally likely to be beneficial and all are consistent with competent medical care.

Background

This conception of clinical equipoise—as rooted in the uncertainty of the community of medical experts—emerged in response to an earlier (and perhaps more intuitive) conception, proposed by Charles Fried. Fried had argued that a physician-investigator could ethically enroll her patients in an RCT so long as she *individually* was in the state of equipoise—that is, she had no justified belief that one arm of the study was any better than the others. In other words, if she was perfectly indifferent about which treatment

arm was best, then she could enroll her patients in the trial and leave their assignments to chance [2].

However, critics were quick to point out that this state of individual equipoise—and therefore the ethical acceptability of enrolling research participants—was too fragile. A physician-investigator's beliefs might change suddenly in the midst of a trial—or before the trial began—perhaps in response to new emerging evidence, or even a "hunch" (similar to what Dr. Malone is experiencing) [3]. Yet whatever the reason for her change in belief, as soon as she was no longer indifferent, she would be ethically prohibited from encouraging future patients to enroll in the study. More to the case at hand, it would also obligate her to encourage any of her patients who were already enrolled in the study to withdraw.

In response to the fragility of individual equipoise, Benjamin Freedman proposed the concept of *clinical* equipoise. Under the principle of clinical equipoise, individual physicians may have beliefs about the superiority of one treatment over another in an RCT, but the trial is still ethical so long as there is no consensus in the community of medical experts. As Freedman put it:

> Instead of emphasizing the lack of evidence favoring one arm over another that is required by [individual] equipoise, clinical equipoise places the emphasis in informing the patient on the honest disagreement among expert clinicians. The fact that the investigator has a "treatment preference," if he or she does, could be disclosed; indeed, if the preference is a decided one, and based on something more than a hunch, it could be ethically mandatory to disclose it. At the same time, it would be emphasized that this preference is not shared by others [1].

Shifting the uncertainty about the better treatment from the individual to the medical community made for a far more robust epistemic threshold, one more accommodating to carrying out RCTs. If there is a state of clinical equipoise at the start of the trial, then a physician may ethically enroll her patients. Importantly, this remains an ethically justifiable action even if she has a suspicion that a patient of hers has been allocated to the supposed inferior arm, since the existence of clinical equipoise entails that the medical experts as a group *do not yet know* which arm is better.

The Story of Vemurafenib

A saga from oncology, which parallels Dr. Malone's dilemma, is worth mentioning. The *New York Times* published a story in 2010 describing the plight of two cousins who were enrolled in an RCT comparing dacarbazine, the marginally effective standard treatment, to a promising new drug, vemurafenib, for the treatment of BRAF-mutated metastatic melanoma [4]. One cousin received dacarbazine and succumbed to his cancer. The other received vemurafenib and, at least at the time of the article's writing, had survived.

As the author of the *Times* story noted, there was considerable disagreement about the ethical acceptability of this RCT. Vemurafenib had achieved an 81 percent response rate in early-phase melanoma trials for patients with the requisite BRAF-mutated tumors [5]. Therefore, some physicians argued, RCTs were unethical because vemurafenib was clearly superior to the standard of care for this patient population [4]. Proponents of the RCTs argued that, despite the dramatic response rate in the early-phase studies, clinical equipoise could not be overturned on the basis of a surrogate endpoint (i.e., tumor response rate) alone. Therefore, an RCT employing clinical endpoints was still needed to definitively determine which treatment was superior [4].

This controversy points to a subtle but important dimension of clinical equipoise: a given case—the treatments and procedures that clinical equipoise either allows or prohibits—is based on the state of scientific knowledge at the outset of the clinical trial. If, at the outset of the trial, sufficiently robust evidence exists to rule out the possibility that the two treatments are clinically equivalent, then the trial is unethical. However, if this robust evidence does not exist, then the trial can still be ethical.

Given that high response rates in early-phase oncology trials can regress in subsequent studies, it is reasonable to think that clinical equipoise had not yet been overturned in the case of vemurafenib. And, as it turned out, the observed response rates with vemurafenib did regress considerably over the course of testing: from 81 percent in phase 1, to 53 percent in phase 2, to 48 percent in phase 3 [6]. There are also legitimate concerns that promising results on surrogate endpoints (such as response rate) or sometimes even clinical endpoints do not straightforwardly support conclusions of superior clinical effectiveness [7]. These additional dimensions of uncertainty and variability in clinical development must be factored into judgments of clinical equipoise. In retrospect, it appears that the vemurafenib skeptics may have been right to insist on RCTs: the drug is certainly efficacious, but we now know that it is not overwhelmingly more beneficial than other drugs for the treatment of BRAF-mutated metastatic melanoma.

Hope and Uncertainty

Returning now to Dr. Malone's case, if clinical equipoise held for Charlie's RCT, then every arm in that study was consistent with competent care, which means that the fact that he is not seeing immediate benefit does not mean that he is being disadvantaged. To illustrate, let's assume that preliminary testing with MX320 suggests that it has a mean response rate of 40 percent. However, since this is based on preliminary data, there should be considerable uncertainty around the 40 percent estimate. This uncertainty can be represented formally with wide 95 percent confidence intervals, ranging from 15 to 65 percent, say. In other words, we are very confident that the true response rate of MX320 lies somewhere between 15 percent and 65 percent.

Let's also assume that the standard treatment is known to have a mean response rate of 25 percent. Since there is typically much more evidence about the standard treatment, there will also be less uncertainty around this estimate (e.g., 95 percent confidence interval ranges from 15 to 35 percent). We can thus establish that there ought to be a state of clinical equipoise: since the confidence intervals of our average effect estimates for these two treatments overlap, there is legitimate scientific uncertainty about which is better. Furthermore, since the interval for MX320 does not fall below the interval for standard treatment, then both are consistent with competent medical care.

If we assume the RCT is using an equal allocation ratio, then there was a 50 percent chance that Charlie would get assigned to the MX320 arm. Once Dr. Malone observes that he is not responding to therapy, it is now a slightly better bet that he is in the control arm. But this is still far from certain. Charlie may be a late responder, or the new drug may just not be effective for him. A valid RCT requires that, until the study is complete, we do not know the arm of the trial in which Charlie is enrolled. Additionally, the existence of clinical equipoise explains why it is ethically acceptable to let Charlie continue in the study.

Clinical equipoise should also alleviate some of the guilt that Dr. Malone is experiencing. Clinical trials necessarily involve uncertainty about the effectiveness of new agents. Indeed, this is why we do research—to reduce uncertainty. Moreover, it is a necessary scientific feature of RCTs that some patient-subjects are exposed to what is later discovered to be an inferior treatment. Yet, this does not mean that the hope of an effective treatment that Dr. Malone offered to Charlie was false. On the contrary, clinical equipoise ensures that the hope was justified—Charlie would be equally likely to benefit regardless of whether he enrolled in research. At the same time, it is the nature of research that the possibility of dramatic patient benefit (greatly surpassing the expectations with the standard of care) can only be a hope. If there had been certainty that he would see incredible benefit from the experimental drug, then the RCT would have been unethical to begin with. At the same time, participants must recognize that the experimental agent may also turn out to be harmful compared to the standard treatment. Indeed, robust safety data about an experimental intervention typically only becomes available in late-phase trials (and rare adverse events are typically detected in monitoring after the drug has been brought to market). Thus, the concept of clinical equipoise mitigates physicians' responsibility for patients' outcomes when those patients are assigned to the control group and when they are harmed by experimental agents.

The Problem of Knowledge Value

We have now shown how Charlie's not benefiting in the trial does not mean that he is receiving inferior care. Therefore, Dr. Malone does not have an ethical obligation, flowing from considerations of beneficence, to encourage him to withdraw from the study. Yet to say that beneficence is not a dominating principle in this case is not the same as saying

that it does not apply. So let us now consider the logical inverse of this obligation: whether it would be unethical for Dr. Malone to encourage him to withdraw from the study. As the scenario stipulates, she knows that there are other trials going on and suspects that Charlie could do better in one of those.

Yet, because Dr. Malone facilitated Charlie's involvement in the current study—let us call it "study A"—is she now obligated to encourage him to see it through? Or can she justify encouraging him to withdraw from study A and consider enrolling in study B? To be clear: if Charlie decides of his own accord that he no longer wants to participate—for whatever reason—this is his right, and there is no ethical tension. There is, however, an ethical tension between Dr. Malone's obligations to Charlie's best interest and to future patients and the research enterprise. Specifically, how would Charlie's withdrawal impact the knowledge value of study A?

Recruitment targets for late-phase clinical trials are typically determined on the basis of a statistical "power calculation." That is, one can calculate how many participants would be needed in order to reject the null hypothesis (i.e., that the two treatment arms are equally effective) with statistical significance if there is indeed a real difference between the experimental treatment and the control. The goal is then to recruit an adequate number of participants, so that whatever the trial's outcome, it is possible to make a valid causal inference: if the experimental treatment was superior to the control, then we can reject the null hypothesis and conclude that there is evidence of effectiveness, or if the difference was not statistically significant, then we can reject the alternative hypothesis and conclude that the experimental treatment is no better than the control. However, if a trial does not recruit—and retain—an adequate number of participants, then it is said to be "underpowered," meaning that it increases the chance of not rejecting the null hypothesis when one of the treatments is, in fact, better than the other.

Thus, in a world of limitless human and material resources, this statistical cost of Charlie's withdrawal might not matter so much. Study A might lose a bit of statistical power from his missing data points, but it might still have enough remaining participants to answer the investigators' primary research question. (And if too many patients drop out of the study, that fact itself can be sufficient to determine whether the experimental agents are effective.) If so, then Dr. Malone's dilemma would perhaps not be so difficult: if she has justified doubts about study A, then she should encourage Charlie to look into study B. After all, study B is also asking an important research question, and study B needs participants too!

Unfortunately, we do not live in a world of limitless resources for research. Once recruitment on a study has ended, dropouts might not be able to be replaced. Given that research risks for trial participants and research costs for society are supposed to be offset in part by the scientific knowledge generated (which will hopefully help future patients), every lost data point, in effect, worsens the ethical profile of the trial (by

increasing the likelihood of a faulty inference) and contributes to inefficiency across the research enterprise [8]. Consistent inefficiencies in research can also diminish public trust in the value of medical research. Thus, although any single patient's withdrawal from a study might not seem like a great waste when considered in isolation, it is important to consider the larger, social context and social cost of research when thinking about sound ethical guidelines for physician and patient decision making.

Further, as the vemurafenib case showed, experimental agents can generate promising results in early phases of research, only to lose some of their promise in later phases. Moreover, according to one recent study, there is only about a 1 in 10 chance that a new agent entering clinical testing will be proven to be effective [9]. Although the prospect that a struggling patient-subject may benefit in a different trial can be a tantalizing one, it must be considered realistically, in the broader context of the scientific process and in the long view of evidentiary standards for determining what constitutes an innovation.

Therefore, in discussing future options, Dr. Malone should explicitly explain this dilemma to Charlie, acknowledging his absolute right to withdraw and switch to the other study if he so chooses (since he may not share her commitment to improving the care of future patients). She should also discuss the realities of experimental medicine, explaining that research is uncertain by nature, and that the majority of new drugs fail in development [9]. Once that is said, if the shift from study A to study B can still be supported by a sound argument—explaining why switching to study B offers a better prospect of a good outcome than continuing on in study A and how switching still does not guarantee that Charlie will receive the experimental drug—then this expression of patient-centered care and beneficence might mitigate worries about scientific validity and efficiency. But the burden of proof should fall heavily on this explanation.

Can We Do Without Equipoise?

In closing, we should acknowledge the critical perspective that sees clinical equipoise as, at best, an inappropriate standard for ethical research [10] and, at worst, an incoherent concept [11]. In its place, critics have proposed that informed consent can do the proverbial heavy lifting in research ethics. That is, so long as a patient-subject is informed of, understands, and accepts the risks of participation, the research is likely ethically acceptable.

Although it would take us too far afield here to canvass the various arguments and counterarguments in this debate [12], it is worth noting that the ethical analysis of Dr. Malone's dilemma would look different without the concept of clinical equipoise. Her feelings of guilt, for example, are rooted in the fact that she is not in a state of *individual* equipoise. She truly believes that the experimental intervention in these studies is better than the control, and so (naturally enough) she feels responsible for Charlie's not responding well in the trial (and assumes that he has probably been assigned to the control arm).

Although Charlie's valid, informed consent might allow us to say that Dr. Malone should not feel guilty (because enrolling was his autonomous decision), the concept of clinical equipoise illuminates precisely *why* this guilt is misplaced: it is not her state of belief that makes Charlie's participation in the study ethically acceptable or unacceptable; it is the state of belief in the community of experts. When she presents a patient the option of enrolling in a study, she can honestly inform him or her about the state of her beliefs. She thinks MX320 is better than the standard treatment, and these trials provide access to that agent. However, there is no consensus in the community of medical experts that MX320 *is actually* better than standard treatment. Some of her colleagues might believe it is the same or even worse. Therefore, she thinks it would be reasonable for him to enroll.

The fundamental point is that clinical equipoise does more for the physician-investigator and the research enterprise than restrict the domain of acceptable scientific comparisons. It is also a concept for critical reflection, and, as Freedman notes in the block quotation above, it should be the beginning of a conversation between the physician and patient contemplating trial participation, which can include questions like these: *What is the state of medical knowledge? Why is this trial asking an important question? How does the likelihood of benefiting in study A compare with that of benefiting in study B or with the standard of care?* These questions are at the heart of genuinely informed consent, and their answers are illuminated through clinical equipoise.

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