Theorist’s Toy: Equipoise

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Debbie is a real patient in crisis. She is poised, with her pen faltering at the end of the consent form, and says, “You really are telling me that I’ll just take the tablets and I won’t know and you won’t know whether it’s the new wonder drug or placebo, and that there is a 1 in 3 chance it’s placebo?” The 8 capsules of olaparib or placebo will be hard enough to swallow, but in this moment, she’s choking on just how much dedication is required to be a participant in a randomized clinical trial (RCT). Debbie recently died and had quite literally laid down her life early in the pursuit of a greater good.

Poly(ADP)-ribose polymerase (PARP) inhibitors are an example of an increasing number of promising biologically targeted anticancer agents in which clinical trials have followed the science, with a compelling rationale. Predictive testing, acceptable toxicity, and early signals have confirmed efficacy in phase I trials. The FDA approved olaparib last year because of clinical benefit in patients with germline BRCA mutations who have received at least 3 prior lines of chemotherapy. Further, ovarian cancer is an example of a serious and life-threatening illness in which progression-free survival (PFS) is a tenuous end point for FDA registration studies. SOLO2, ARIEL3 (rucaparib), and NOVA (niraparib) are all placebo-controlled RCTs in platinum-sensitive recurrent ovarian cancer in which researchers are hoping to show improved overall survival as an important secondary objective.

Although we often cite equipoise as the trump card in the overlap between clinical care and scientific research, the ethics of equipoise are complicated and controversial. This played out on the front page of The New York Times during the development of vemurafenib. Equipoise is not the main justification for an RCT being ethical and, in a pure form, rarely exists. Very rarely with the newer treatments can we explain randomization in RCTs with a coin flip of equitable allocation, or the illustration of 2 envelopes; you get to pick, and both contain equally good options (Gore M, personal communication).

Medical research requires an evidence-based approach for informed decision-making in both clinical care and drug development. This evidence base can occur only if adequate numbers of individuals are willing to participate in clinical trials. However, participation in a clinical trial is very different from receiving standard medical care. It does not aim to provide personalized medical care to an individual. It may offer a participant some reasonable expectation of direct benefit, but that is not its primary objective. Its primary objective is the advancement of scientific knowledge and generalizable information. Conversely, routine clinical care may permit more flexibility in eligibility, dosing, monitoring, and follow-up than what is mandated in a research protocol.

Therefore, frank discussion between patient and physician is fundamental for both routine clinical care and clinical research. Indeed, entry on a clinical trial may be the most reasonable choice for an individual, but the word “participant” is used to identify a subject in a clinical trial, rather than “patient.” This evokes the concept of free will, voluntary enrollment, ability to discontinue participation, and knowledge of risk and benefit.

The traditional view is that RCTs are consistent with a clinician’s ethical duty to patients only if there is equipoise between the 2 arms. However, although the arms must have some balance for a physician to recommend entry onto a trial or for an Institutional Review Board (IRB) to approve it, the performance of a clinical trial is also associated with wider societal interests. There is considerable discussion of...
new proposals for more cost-effectiveness research in which the margin of difference between study arms is small and the improvements are small and incremental. This paradigm fits with the cooperative group strategy of comparing similar chemotherapy in patients with limited options and expert consensus that there will be little material difference in the outcome.

Clinical equipoise can be a difficult concept to define and is subject to the fallibility of expert opinion, variability in defining the amount of consensus required to call a treatment standard or reasonable, and problems in study design. A surrogate end point in a prior trial may not be appropriate for a decision regarding efficacy. There may be problems when interim data cause premature discontinuation of a trial. We have an ethical requirement to provide maximal benefits to study participants. This should complement the other aims of social value and scientific validity of a trial.

Some trials should not be undertaken, such has one that has an undue risk of harm relative to benefits. However, this can be difficult to make, particularly with vulnerable subjects, such as patients with cancer. A physician may have some personal bias that affects individual uncertainty regarding the value of each arm in a randomized trial, but some degree of collective uncertainty is required for the trial to proceed. The physician has the task of fully informing a prospective participant of the risks and benefits of the trial, what is “known” about the treatment arms, what is suspected, and what is not known. Medical knowledge is a continuous process, and the history of medicine is full of treatments that were believed to be of value that have since been abandoned. No evidence is available that people are harmed by being denied access to a promising but only partially evaluated treatment, and no regulations entitle patients to treatment with an unevaluated agent.

Patients join trials for many reasons, including a lack of available therapies, a desire to improve their personal medical care, insurance and financial issues, a desire to advance science, and a desire to improve the outcomes for future patients. They may be influenced by their medical caregivers, their friends and families, newspapers, current events, and social media. However, many studies have indicated the role of therapeutic misconception, referring to a participant’s perception of the goal of the trial being individual health improvement. Juxtaposed to this is the need for some reasonable expectation of direct benefit for most patients to want to enter a study. When there is truly no direct health benefit, participants may be motivated by altruism.

The extent of altruistic participation in research is unknown. A trial with no possibility of therapeutic benefit would require some altruistic motivation of a participant. This can be very difficult to measure and can be variable and unreliable. Distinguishing between a primary altruistic motivation and a subsidiary altruistic hope or desire may be impossible. It is also incumbent for the caregivers and the study designers to avoid any degree of exploitation, particularly with subjects who may be critically ill and have limited options.

The IRB plays a key role in the safe and ethical conduct of research. The IRB has the job of assessing the risk/benefit ratio and determining appropriateness. The IRB must determine whether the study is scientifically sound and whether the study design is likely to yield generalizable information and results. As an entity not conflicted in terms of a therapeutic relationship with the participant and not conflicted with the study, sponsor, or investigator, the IRB can provide a disinterested voice. It also has a primary responsibility in reviewing and approving the informed consent.

Informed consent is particularly important in randomized trials. The introduction must make it very clear to a participant why the trial is being undertaken, why one might be an appropriate candidate, and the risks and benefits of participation. The alternatives to participation must be carefully explained. The language must be reviewed, with an eye to the participant’s education level, clarity of explanation,
avoidance of promissory language, and compliance with the Common Rule regulations for human subject research.

Members of an IRB often have a sense of responsibility when considering the issues of patients versus science in clinical trials. Clear rules exist for navigating competing interests: the justification for the RCT has been carefully considered by all the stakeholders; risks have been minimized; the balance of benefit, costs, and risks has been found; and there is fair sharing of the burden by those who may benefit. Justice further requires that the societal responsibility has been considered impartially.

The main qualification for an RCT being ethical is that a well-informed patient volunteers to participate in the process of drug development, fully aware of the high bar for confirming that a new agent with promise is truly safe and effective. Trying to construct trials so that patients are passive pawns in the urgent needs of the drug development process fails the ethical necessity to involve them as coparticipants in this important and complex task. Wonderfully, basic scientific endeavors have produced exciting new agents, and the real world of clinical science has to realign with the high call to service. Medicine has moved beyond using RCTs for scarce resource allocation. Now, beyond theory and 50–50 toss-up access to an investigator’s clinical trial, clinical research must be a truly collaborative effort, and it is our privilege to do it in partnership with patients.

References