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EDITORIAL COMMENT

When Business and Science Clash, How Can We Avoid Harming Patients?

The Case of AVOID-HF*

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The ethics of using randomization to figure out what works in medicine have been aggressively debated since the first randomized trials were performed, more than 60 years ago (1,2). Traditionally, the practicing physician has a duty to put the best interests of the patient above all else. Tradition has had little to say, however, about physicians often lacking adequate information to assess what those best interests actually are. The central ethical conflict raised by randomized trials is that, in most trials, patients voluntarily forgo the pursuit of maximum personal benefit to support the larger social goal of enhancing generalizable knowledge. Under those circumstances, for a randomized trial to be ethical by modern sensibilities, certain conditions must be met (3). These include not only true informed consent, but also the potential to enhance knowledge, use of scientifically sound methodology, and a favorable risk-benefit relationship.

Many different sorts of problems can arise during the course of a trial that can prevent it from running to completion and fulfilling its scientific and social objectives. Among these are evidence of unexpected harms sufficient to require stopping the trial prematurely, evidence from interim efficacy estimates by the Data and Safety Monitoring Board that there is no chance with the planned sample size of showing the hypothesized benefits, and failure by the investigators to enroll sufficient numbers of patients to permit the study to run to completion given the funds available to support it. Each of these cases represents a circumstance under which the risk-benefit relationship for the trial becomes unfavorable and the ethical grounds for continued enrollment are no longer met. In other words, patients are usually exposed to some level of risk when they consent to participate in a randomized clinical trial. At the same time, participating in a trial provides benefit through the generalizable knowledge that is expected (scientific understanding, improved care for future patients). The patients who participate may also benefit individually, if they are randomized to a therapy that is not otherwise available and that therapy turns out to be superior to conventional care. But, of course, the patients are told as part of informed consent that no guarantee of such benefit can be offered to participants. While the reasons patients offer for participating in clinical trials vary, helping other similarly situated patients in the future is typically at the top of the list. When a trial is no longer able to offer the potential for such benefits, most ethicists would argue that the trial risks, even if quantitatively small, outweigh the benefits, and continuation is no longer ethical.

When trials are funded by private rather than public sources, additional ethical complexities can arise in the conduct of the study. For example, when publication of results deemed unfavorable is suppressed for business reasons by a commercial sponsor, many would argue that the social contract that underlies the clinical trial enterprise is undermined. Clinicatrials.gov registration, requirements together with new U.S. Food and Drug Administration and European Medicines Agency rules about public

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results reporting for certain types of trials, constitute an important step in making such unilateral actions more difficult for private companies. The overarching implication of all this is that when commercial sponsors undertake human subjects research, they accept certain social obligations that may trump what they consider to be in the best interest of their business.

SEE PAGE 95

From time to time, commercial sponsors of research have decided, for purely business reasons unrelated to safety or efficacy concerns or trial conduct problems, to terminate an ongoing trial. In current issues of the *American Heart Journal* and *JACC: Heart Failure*, the design and primary results manuscripts, respectively, are published from an important heart failure trial that was terminated prematurely by its sponsor (4,5). AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure), a randomized controlled clinical trial of adjustable ultrafiltration versus adjustable IV loop diuretics in acute decompensated heart failure, conducted with the intent to test whether time to first heart failure event would be lower with adjustable ultrafiltration. This was planned to be an 810-patient study with sufficient statistical power to answer the primary endpoint questions. As seems common in trial terminations for business reasons, the sponsor funding the research was purchased mid-trial by another company, and the trial was stopped. Thus, only 221 patients were randomized into the study before sponsors support ended. The first heart failure event in 90 days occurred in 25% of the adjustable ultrafiltration patients and 35% of the adjustable loop diuretics patients, and the time to the first event, the study primary endpoint, was longer in the former arm: 62 days versus 34 days ($p = 0.106$). Secondary endpoints, such as rehospitalization rates and days hospitalized for heart failure and cardiovascular re-hospitalization days and rates, were all more favorable for the ultrafiltration arm, but ultrafiltration was associated with more serious adverse events deemed related to the study product (14.6% vs. 5.4%).

What value does the information from this intentionally incomplete trial have in advancing our understanding of how best to treat patients hospitalized for decompensated heart failure? With continued adverse safety signals (as seen in the CARRESS-HF [Cardiorenal Rescue Study in Acute Decompensated Heart Failure] trial) (6), no significant difference in weight loss or B-type natriuretic peptide, and a longer length of stay with some statistical trends (but not statistical significance) in the reduction of heart failure and cardiovascular events, the data are not clear enough on the balance of benefits versus risks to move ultrafiltration into standard of care or to give it a favorable guideline recommendation.

Was the action of the sponsor in this case unethical? Did it have any obligation to the patients who had already entered the trial to see things through to the pre-specified conclusion? Did it violate the social contract (patients agree to participate in research and researchers/sponsor agree to use the resulting information to enhance scientific understanding and clinical care) that underlies and maintains the health of the clinical research enterprise? Although it is tempting to offer easy condemnation of the decision to terminate in this case, things are never as simple as they might at first appear.

Clearly, the patients should be thanked for participating in this clinical trial. Although the trial does not settle any big questions, the data are being published and will be available to future research teams working in the area. That is good news for the patients who gave of themselves in this trial, and it is good that the investigators pursued this result with such tenacity, despite the lack of continued financial support for study activities. For this, we commend the principal investigator and the investigative team. However, the trial was not without problems even before the decision to terminate. The trial was probably too complex and inadequately funded (admittedly, it is always a difficult matter to adjudicate what level of funding is "fair"), and both factors likely contributed to the poor recruitment rates. Was termination of the trial without concordance of the Executive Committee or the Data and Safety Monitoring Board, when no stopping rule had been triggered, misconduct on the part of the sponsor? Legally, sponsors often retain this right for themselves, typically explicitly specified in the contract between the sponsor and investigative site.

But even if termination was "legal" in a contractual sense, was it ethical? The patients provided informed consent to participate in the trial, and they were led to believe that their participation would support the development of new generalizable knowledge. Their participation was deemed acceptable by Ethics Committees in large part because these anticipated benefits were felt to outweigh the risks the participants might face from enrolling in the trial. As soon as the sponsor makes the decision to prematurely terminate a study for business reasons, with no scientific or safety concerns, the ethical grounds used to justify enrollment of patients into the trial up to that point is erased: the patients already enrolled accepted the

JACC: HEART FAILURE VOL. 4, NO. 2, 2016
FEBRUARY 2016:106–8

risks of the trial; the benefits may no longer be obtainable (7).

Although previous editorialists have come out strongly critical of companies that terminate clinical trials for business reasons, trial termination decisions are probably infrequently due to a single factor (8–10). If the trial is proceeding poorly, with slow enrollment and a projected budget to finish that substantially exceeds the original budget, how far can we go in obligating the sponsor to finish what was started? The National Institutes of Health are now aggressively monitoring their large clinical trials with the intention of early termination of underperforming trials. In a sense, that too is a "business decision," where the funds that are saved from the terminated trial are reinvested in other research that may yield more for the public good.

Business goals may also help shape the design of clinical trials so as to emphasize certain treatment benefits and minimize treatment risks, for example by using intermediate or surrogate endpoints or smaller sample sizes that yield insufficient power to examine hard clinical outcomes or to clarify the risks of uncommon adverse effects (11). Do such trials raise ethical concerns? They usually do not, but perhaps they should. Biomedical companies are often driven by profit, regardless of altruistic intent. That motivation has yielded many powerful new therapies that have helped millions of patients and will help millions more in the future. If we try to compel companies to satisfy abstract societal goals over their own motivations, what might be the unintended consequences? Would we, for example, reduce the motivation to undertake trials where the probability of success is not already known to be high? Sponsors already perform triage on their pipelines every day, choosing this therapy for continued study and that therapy for the scientific trash heap. A different way to think about the problem is in terms of incentives. Commercial sponsors are simply doing what we have incented them to do, given the structure of the markets for innovative medical products and services (12). If the costs of getting new therapies approved for clinical use were lower, might the termination of trials for business reasons become less necessary for sponsors? Although the outcome in the AVOID-HF trial is very disappointing for those of us who thought the potential of intensive decongestion in acute heart failure deserved testing in an adequately powered trial, the trial does not offer a clear "teachable moment" regarding sponsor ethical misconduct. In our current regulatory environment, with the very high cost of bringing new therapies to market, our best defense against more AVOID-HF trial cases is to only start trials that are designed efficiently, budgeted adequately, and clearly feasible in terms of enrollment targets. If we can achieve that, we will have done much to ensure that the contribution of patients enrolling in our trials is not wasted.

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