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Ethical Issues in Clinical Research: An Issue for All Internists

Jesse Gelsinger was 18 years old when he died after receiving an experimental drug in a gene therapy research trial. Jesse suffered from ornithine transcarbamylase (OTC) deficiency, a rare genetic disorder that affects the body's ability to eliminate ammonia. In the most severe forms, the accumulation of ammonia in the brain places newborns in a coma within 72 hours of birth and causes severe brain damage. Fifty percent of affected newborns die within 1 month, and an additional 25% die by the age of 5. Jesse was able to control his condition with a low-protein diet and medication—32 pills a day (1).

The study was a phase I study intended to test the safety of a treatment for babies with the fatal form of the disorder. Participants were divided into groups, with each successive group receiving a slightly higher dose. Jesse was in the group assigned to received the highest dose (1). Several hours after receiving his injection, Jesse developed a high fever. Over the next few days, Jesse slipped into a coma, developed liver and other organ failure, and deteriorated further until, 4 days after receiving the injection, he was declared brain dead (1,2). Life support was removed with his father's permission, and Jesse's death was reported to government officials (1).

Jesse's tragic death has prompted a reevaluation of gene therapy research and led to a moratorium on several gene therapy protocols (2–8). The concerns raised about this case are pertinent to all clinical research. In particular, physician-investigators need to pay particular attention to patient misunderstandings about the benefits and risks of research and to conflicts of interest.

Research with human participants raises ethical concerns because people accept risks and inconvenience primarily to advance scientific knowledge and to benefit others. Although some research offers the prospect of therapeutic benefit to research participants, phase 1 clinical trials are intended to test dosing and safety. Any therapeutic benefits to the participants would be uncommon and not the aim of the study. Nevertheless, research participants frequently possess a "therapeutic misconception," that they will receive direct clinical benefit from participating in research (9). Participants' trust in their physicians, health care institutions, and the research enterprise may enhance their expectation of benefit (10). Because of such hopes and misconceptions, patients may misinterpret the information given to them about the study (9). Both Jesse Gelsinger and his father Paul focused on the promise of the trial. Paul says that they were unaware that the trial entailed serious risks, such as hepatitis, liver damage, or death, or that gene therapy had not yet cured anyone (5,8). Although he had been told that the therapy would not benefit him, Jesse apparently hoped his participation in the trial would enable him to go off the highly restrictive diet that kept his condition under control (1). Paul says that he and Jesse were told that the therapy was working in some participants, and that, because Jesse was a mosaic (with affected and unaffected cells), his participation would "show exactly how well this works. (5,8)."

Another concern is that researchers may have conflicting interests that might impair their objectivity (11). The perception of a conflict of interest may be sufficient to create concerns and undermine public trust in research (12). For example, news reports after Jesse's death have suggested that the investigators in the study, in their desire to develop the first successful gene therapy technique, may have downplayed the risk of the intervention and failed to communicate the nontherapeutic nature of the research to participants (13). News reports have also drawn attention to the financial interest lead investigator James Wilson, MD, has in a biotechnology company that seeks to commercialize gene therapy techniques. The concern is that the commercial interests may have colored the investigators' decisions while conducting the study (13). These types of conflicting interests are increasingly common for both investigators and practicing clinicians as the financial stakes of medical research increase and more research is conducted outside academic medicine (4,14,15).

THERAPEUTIC MISCONCEPTION AND THE POWER OF THE PHYSICIAN-PATIENT RELATIONSHIP

Participants in research may have serious misconceptions about the purpose of the project. Some may not even be aware that they are participating in research (9,16). The

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language that investigators use (eg, "experiment" versus "research") may have significantly different meanings for participants and affect their understanding of their participation (9). Participants also may misapprehend the goal of research. Although the goal of research is to test a hypothesis and develop generalizable knowledge, many participants enter research studies to benefit personally (9,10). Many participants also do not understand randomization and expect decisions about which intervention they will receive to be based on their individual clinical needs (9). Some of these misconceptions may arise because patients apply their experience with physicians—who have an ethical obligation to place patients' interests first—to the research setting, which does not focus on the individual participant. These factors may explain why participants systematically misinterpret the risks and benefits of research participation, as noted in one study (9). In the Gelsinger case, the very term "gene therapy research" may have been misleading, implying that the project would primarily test effectiveness, rather than dosage and safety.

A participant's misunderstanding may be exacerbated by the role of physicians in research, both as investigators and referrers to trials. Physicians exert considerable power within the physician-patient relationship, and patients are inclined to follow their physicians' advice (10). Patients understand offers to participate in research to be recommendations for their care (10). They also may agree to participate in research if their physicians ask because they want to please them or fear that the quality of their care will be negatively affected if they refuse (4). According to the *New York Times*, even the noted Princeton University health care economist Uwe Reinhardt agreed to join a clinical trial to please his physician (4). The concerns for patients are greater when the treating physician is also the investigator, because the patient may not understand that the physician's interests may be divided between loyalty to the patient and interest in the research. In some cases, it may be better for the patient not to enroll in the study or to drop out of the study and receive individualized care that differs from the research protocol. An investigator, however, may attempt to persuade a patient to enroll or continue in the study to serve the research objectives. Special care must be taken to ensure that the patient/participant understands the physician/investigator's divided interests and, where possible, to separate the roles (10,17).

In addition, patients' trust in their physicians, medical institutions, and the research enterprise may lead them to agree to participate in research without critically reviewing information about the trial (10). For example, participants' trust in their physicians or medical institution may cause them to make up their mind to participate before they see a consent form. Accordingly, physicians must take care how they present research studies to patients. This factor is particularly important because physicians themselves frequently overestimate the benefits of experimental interventions and participation in clinical trials (10). Participants' trust in the research may also prevent them from looking critically at the research proposal.

The Gelsinger case provides evidence of how hope and trust may influence participant understanding. It is impossible to know whether and to what extent the Gelsingers' understanding was influenced by their own desire to believe in the trial or by the investigators' statements or enthusiasm for their trial. However, because participants tend to misunderstand the risks and benefits of being research participants, scientists need to be particularly careful to balance presenting information regarding potential benefit with cautionary information about risks.

CONFLICTING INTERESTS

In the aftermath of Jesse Gelsinger's death, critics have alleged that other interests clouded the investigators' judgment. For example, some have suggested that the scientists may have pressed forward with the OTC trial despite some negative data, in hopes of becoming the first to fulfill gene therapy's promise (13). Concerns have also been raised over Dr. Wilson's financial interests in a biotechnology firm that he founded. The company—which provides 20% of the funding for Dr. Wilson's laboratory—reportedly has contracts relating to genetic therapy techniques directed toward the liver, such as the one used in this study. This financial relationship may have created pressure to develop a marketable product (13). Dr. Wilson took steps to prevent his business interests from influencing the study, including ceding control over patient care decisions to a colleague (13), but these financial interests have evoked concerns that they may have influenced his decision making.

Recent news reports suggest that physicians increasingly have financial interests in clinical research (4,14,18). The financial incentives for physicians are substantial. Because pharmaceutical companies want to speed the progress of a drug to market, they frequently offer incentives to physicians for each patient enrolled in company studies. Physicians may receive thousands of dollars for each enrolled patient, with additional thousands of dollars in incentives for meeting enrollment targets within a specified time period (4). Top recruiters can earn as much as $500,000 to $1 million a year (4,14). Drug companies are increasingly using private physicians for both recruitment and research and may ask them to conduct studies outside of their expertise (4).

These significant financial incentives may create conflicts of interests that jeopardize patients' health and well-being. In the extreme cases described by journalists, phy-

sicians allegedly ignored study criteria to enroll patients and reap the financial rewards associated with the enrollment. In some cases, physicians reportedly falsified medical records or data to enroll patients. Physicians have also allegedly kept patients in a study despite complications, which, in some cases, resulted in death (4,14,18). For example, one physician under contract with a drug company to test an experimental antipsychotic drug reportedly enrolled a hospitalized suicidal schizophrenic woman in the study even though suicidal patients were excluded in the protocol. The patient's symptoms had been controlled by medication before enrollment in the study. However, to participate in the study, the patient had to be taken off that medication for 2 weeks. During that time, her condition worsened, but the patient continued in the study. After 3 days on the experimental medication, she was given a pass to leave the hospital unaccompanied and committed suicide while on leave (14).

Although such extreme cases are rare, the subtle effects of conflicting interests are more common. Some conflicting interests are inherent in research. For example, physicians gain prestige, grants, and promotions through their research and publication of their work. Accordingly, they have an interest in recruiting and maintaining participants in their studies that may be in conflict with the best interests of participants. This personal interest is an accepted part of research. However, ethical problems may arise if scientists' personal interest and commitment lead them to overestimate the benefits or underestimate the risks of a study. Their belief in the promise of an intervention may make it difficult for them to review evidence objectively and, if necessary, halt an ongoing study. In extreme cases, the pressure to publish may lead scientists to claim authorship on papers to which they contributed minimally, to enroll ineligible participants, or even to falsify or fabricate data (4,14,18–22).

Financial interests or incentives in research create considerable concern because they may lead to bias in the design and conduct of the study, the overinterpretation of positive results, or failure to publish negative results (11). For example, critics charge that the OTC study investigators may have discounted evidence of others that the adenovirus vector they were using might trigger life-threatening inflammatory reactions (13), which could be particularly dangerous for people with OTC (23). Some have also suggested that investigators disregarded evidence that Jesse Gelsinger's liver function was impaired at the time he was given the injection, perhaps because they did not want to delay the study (2,23). Dr. Wilson's financial interest in the gene therapy technique has also been suggested as a motive. Investigators who hold stock options in sponsoring companies may reap huge rewards if the drug or device under study proves effective and may suffer financial losses if clinical trials are delayed or yield negative results.

Responding to Ethical Concerns in Research

In many respects, the face of clinical research is changing (15). The lines between research and clinical practice and between academic medicine and industry are blurring. Full-time clinicians who did not anticipate participating in research may find themselves involved in research in some way. To address this changing landscape, all physicians need to be made aware in their training of the ethical issues that may arise in clinical research and understand how those interests may be addressed. Physicians can take the following steps to address the ethical problems we have discussed (17,24).

Try to Ensure that Participants in Clinical Research Are Well Informed

Researchers should understand that disclosing information on a consent form does not guarantee that subjects comprehend the essential features of the research project. Physicians need to appreciate that they wield considerable power with patients/participants and that their choice of words can influence decision making. Physicians need to make sure that patients understand that participation in a clinical trial is voluntary and will not influence their care. They also need to make clear whether they are recommending the patient participate in a trial or merely offering the opportunity. Because participants frequently misinterpret the risks and benefits, physicians also should check that patients have comprehended the key aspects of the trial and correct any misunderstandings. If the subject agrees, it is often useful to have a relative or friend present when the investigator explains the research project. If the physician is also the investigator, then, whenever possible, another member of the research team should handle consent discussions and follow-up visits that are part of the study.

Minimize Conflicting Interests

Investigators can minimize conflicting interests in their clinical trials. For example, blinding investigators and participants to which intervention the participant is receiving and using an independent data safety monitoring board can prevent bias in assessing outcomes and interpreting interim data. For industry-sponsored research, investigators should have control over the primary data and statistical analysis and the freedom to publish findings whether or not the drug or device is found to be effective (25,26). Physician-investigators should also discuss their research plans with colleagues. Formal and informal peer review provides an excellent mechanism for evaluating the risks and benefits of research and identifying areas of concern.

Disclose Conflicting Interests

For people to make informed decisions about participating in a clinical trial, physicians need to disclose pertinent conflicts of interests. In a landmark court case, the California Supreme Court declared that physicians need to "disclose personal interests unrelated to the patient's health, whether research or economic, that may affect the physician's professional judgment" (27). Some individuals more closely scrutinize a study in which the investigators have a direct financial stake. Furthermore, disclosure of conflicts of interests are salutary because they deter researchers from entering into questionable financial arrangements that would be difficult to justify to the public or to their peers.

Ban Certain Situations that Lead to Conflicts of Interest

Some conflicts of interest are so problematic that they should be prohibited, not merely disclosed (24). Researchers in clinical trials and members of data safety monitoring boards, as well as their families, should not hold stock or stock options in the manufacturers of the therapies they are studying in a clinical trial (28,29).

The recent tragic case of the death of a young man enrolled in a phase I clinical trial dramatizes how difficult it can be to inform patients about a clinical trial and how even the perception of conflicts of interest may undermine public confidence in clinical research. The need to provide a strong evidence base for clinical medicine will require physicians to be involved in clinical research. Even physicians who are mainly practitioners may be asked to participate in clinical trials. Thus, training programs in internal medicine should ensure that all residents and fellows, even those planning a primarily clinical career, understand the ethics issues pertinent to clinical research.

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