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ETHICS CASE

Enrolling Research Participants in Private Practice: Conflicts of Interest, Consistency, Therapeutic Misconception, and Informed Consent

Commentary by Armand H. Matheny Antommara, MD, PhD, and Kristin Stanley Bramlage, MD

Dr. D'Amato is a partner in a nonacademic gastroenterology clinical practice. One of his patients is Matthew, a 17-year-old with type 2 diabetes, nonalcoholic hepatosteatosis (NASH, or fatty liver), dyslipidemia, and obesity. Dr. D'Amato has been following him for the past three years, and, despite nutritional and exercise counseling, Matthew has been unable to change his dietary habits and lose weight. Dr. D'Amato's biggest concern is treating Matthew's fatty liver, which is leading to elevated liver enzymes, inflammation, and possibly cirrhosis. Currently, the most effective treatment for NASH is weight loss. There are a few phase 2 and 3 clinical trials testing the safety and efficacy of vitamin E and other novel therapies.

At a recent clinical visit, a liver needle biopsy revealed inflammation but no signs of cirrhosis for Matthew. Dr. D'Amato stresses to Matthew the importance of losing weight and adopting a healthy lifestyle before he shows signs of developing cirrhosis. Matthew tells Dr. D'Amato that he has heard about a phase 3 clinical trial for a new monoclonal antibody. He asks Dr. D'Amato about the possibility of enrolling in the trial.

As it happens, Dr. D'Amato and his colleagues are recruiting eligible participants for this trial run by a pharmaceutical company. The pharmaceutical company compensates Dr. D'Amato for the care of enrolled patients during their participation and also gives him \$5,000 for each patient he suggests who ends up being eligible and enrolling in the trial. Dr. D'Amato thinks that Matthew may be eligible for the trial, but he does not know to which arm—standard treatment or experimental treatment—Matthew would be assigned.

Matthew's mother, who has been extremely supportive of her son throughout his illness, does not want him to enroll in the study. If there is a way to reverse the NASH through weight loss, then she does not want to expose her son to the risks associated with the clinical trial. Dr. D'Amato agrees with Matthew's mother, but, given the seriousness of his condition and his past history of noncompliance with his weight loss regimen, there might be a chance that if Matthew were randomized to the drug arm of the study, he would benefit.

Commentary

This case highlights the importance of managing conflicts of interest; enrolling patients consistently; minimizing therapeutic misconception; and evaluating potential benefits, risks, and alternatives of enrolling in a clinical trial.

NASH is the most severe form of nonalcoholic fatty liver disease (NAFLD) and can progress to advanced fibrosis, cirrhosis, and liver failure, requiring transplantation. NAFLD is associated with obesity but is also believed to be influenced by genetic factors and environmental exposures. As noted above, the current standard of care for the treatment of NASH is weight loss [1]. Nobili and colleagues, for example, conducted a study of children with NAFLD in which all children were prescribed lifestyle intervention and were randomized to either alpha-tocopherol (vitamin E) and ascorbic acid (vitamin C) or placebo. Both groups demonstrated a significant improvement in liver histology at 24 months, but there was no significant difference between groups [2].

For the sake of argument, let us assume that Dr. D'Amato has offered Matthew and his family a comprehensive multidisciplinary weight loss intervention that includes long-term dietary modification, decreased sedentary activity, moderate daily exercise, and behavior change skills [3]. In spite of these efforts, Matthew has been either unwilling or unable to lose weight or to maintain his weight loss.

Managing Conflicts of Interest

Dr. D'Amato should seek to prevent his interest in advancing the knowledge in his field and his commitment to individual patients from [conflicting](#) and, if they do, the latter should generally take precedence. Dr. D'Amato is being compensated for enrolling participants in a clinical trial. This compensation should cover Dr. D'Amato's additional expenses of enrolling participants rather than induce Dr. D'Amato to refer potential participants. Compensation should be consistent with Dr. D'Amato's usual professional fees. The pharmaceutical company [should not](#) offer, and Dr. D'Amato should not accept, an inappropriate level of compensation, and clearly excessive payments may be considered "kickbacks," and would be illegal [4].

Enrolling Patients Consistently

Matthew has become aware of a clinical trial in which Dr. D'Amato is enrolling patients. If Matthew fulfills the inclusion criteria, Dr. D'Amato's withholding information about the trial from him would be inappropriate. It would be paternalistic for Dr. D'Amato not to offer Matthew the opportunity to enroll in the trial because he is concerned that enrollment might be a disincentive to Matthew to continue to try to lose weight. Not offering the option to all of his patients who fulfill the enrollment criteria might inappropriately bias the sample.

Minimizing Therapeutic Misconception

If Matthew is eligible for the trial, he needs to be aware of the differences between research and clinical care. Dr. D'Amato should address any therapeutic misconception—the false belief that the primary purpose of the trial is to provide medical benefit to the participants or that the research procedures are individualized to them [5]. It is particularly important for Matthew and his mother to understand the concept of randomization and the possibility that he will not receive the investigational agent.

Evaluating the Potential Benefits, Risks, and Alternatives

Dr. D'Amato, Matthew, and his mother should also [discuss](#) the potential benefits, risks, and alternatives of participation. In terms of potential benefits, monoclonal antibody treatments have proven effective in treating other gastrointestinal diseases, such as Crohn disease and ulcerative colitis [6]. If Matthew were assigned to the experimental treatment arm, he might see some improvement in his NASH.

The potential risks of participating in the trial should also be discussed. Characterization of the risks should be based on the results of animal studies, phase 1 trials, and experience, if any, with the investigational drug for other indications. For example, carries such risks as serious infections, including tuberculosis and invasive fungal infections; malignancies, including lymphoma; severe hepatic reactions; and hypersensitivity reactions [6]. The agent may also have unknown or unanticipated risks that may only become apparent during the trial or in postmarketing surveillance. Finally, there may be risks associated with the study procedures.

The alternatives available to Matthew would include not participating in this specific trial or participating in another trial. As of May 2015, for example, adolescents with NASH were being recruited for a controlled trial comparing weight loss surgery/vertical sleeve gastrectomy and a comprehensive lifestyle intervention [7].

Because Matthew is a minor, his mother would have to provide her permission, and he would have to provide his assent to enroll in the trial. When he turns 18, Matthew would have to give his consent to continue to participate. If Matthew's mother's concerns cannot be adequately addressed and she withholds her permission, Matthew cannot enroll until he turns 18 (if the trial includes participants of that age).

Conclusions

NASH has become more frequent with the increasing prevalence of obesity [1]. Treating obesity is difficult, and pharmaceutical alternatives or adjuncts may be attractive to patients. Dr. D'Amato should seek to balance his interest in advancing the care of patients with NASH and his commitment to Matthew, and he should not accept undue inducements to enroll patients in clinical trials. It is reasonable for Matthew to be interested in enrolling in this trial and for Dr. D'Amato to be concerned that enrollment

might undermine Matthew's weight loss efforts. Dr. D'Amato's concern is not, however, a sufficient reason to withhold information about the trial from Matthew. In seeking Matthew's assent and his mother's permission, it is important for them to be aware of the goals of the trial and its potential benefits, risks, and alternatives.

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Armand H. Matheny Antommaria, MD, PhD, is an associate professor in the Division of Hospital Medicine at the University of Cincinnati College of Medicine and a general pediatrician at Cincinnati Children's Hospital Medical Center, where he also directs the Ethics Center and holds the Lee Ault Carter Chair in Pediatric Ethics.

Kristin Stanley Bramlage, MD, is a pediatric gastroenterologist and a staff physician in the Division of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's Hospital Medical Center. She has a special interest in patients with nonalcoholic fatty liver disease.

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