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Clinical Research Ethics Question of the Month: An Auction for Participation

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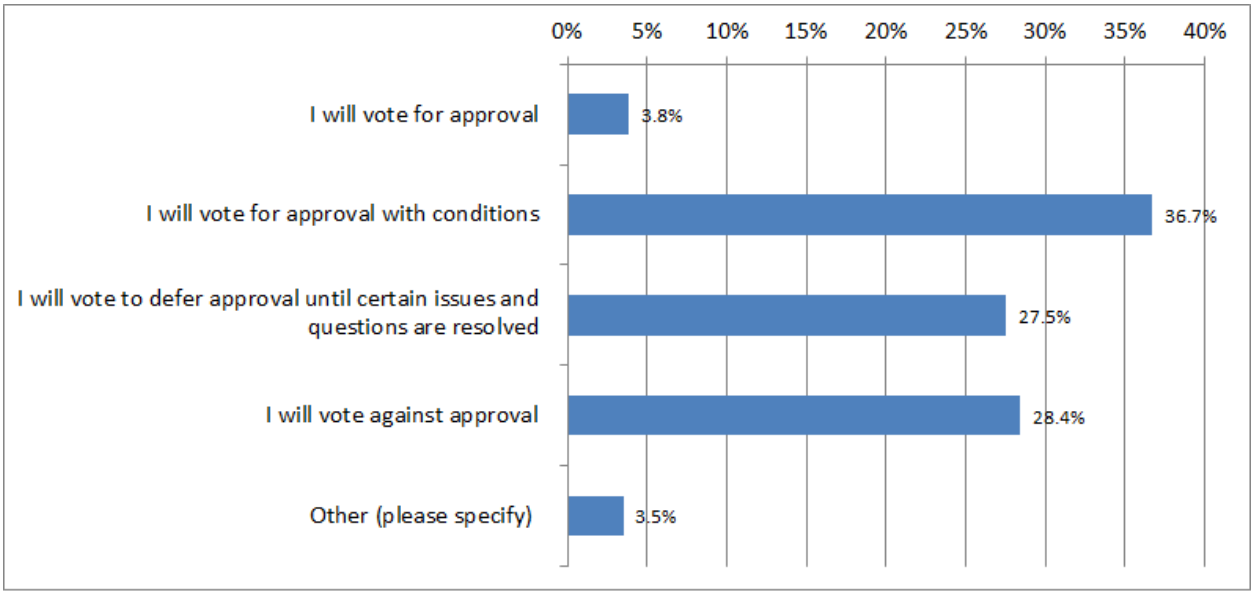
You are a member of an IRB reviewing a study protocol for a new artificial heart that, if approved by the FDA, will likely save many lives. The study sponsor, a very small company, plans to test the device in patients who will probably die without the device. It cannot afford to test the device with an adequate sample size, so it proposes to increase the sample size with funds raised by auctioning off the right to participate. Any delay in approval will likely cost lives. Will you vote to approve the study? You have no other information to make your decision and no clever way to dodge it.

Results

Question 1. How will you vote?

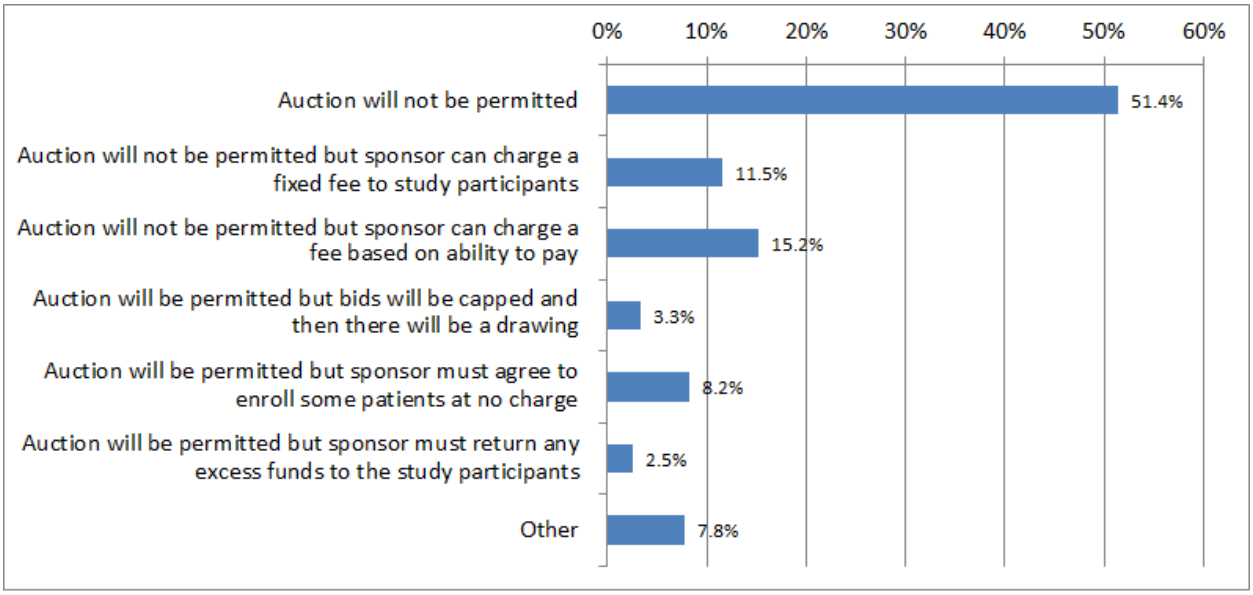


Only 3.8% of 313 respondents would vote to approve the study as proposed. Of the others, 36.7% would vote for approval with conditions, 27.5% percent would vote to defer approval until certain issues and questions are resolved, and 28.4% would vote against approval.

Two respondents would advise the sponsor run a pilot or feasibility study with the number of subjects it can afford and then use those results to secure additional funding.

The pertinent CMS and FDA rules are complicated, but one respondent stated that the FDA allows the recoupment of the actual cost of the device in device studies [in direct cost terms, a small fraction of the cost of a study]. One respondent suggested obtaining CMS approval for the device so Medicare and insurers could cover the cost of the device. One respondent stated that any fees must be the minimal necessary for the actual cost of the device, per FDA regulations.

Question 2. If you will vote for approval with condition(s), what would the most important condition be?



Of the respondents who would vote for approval with conditions, 51.4% would not permit the auction. Other respondents would require less restrictive conditions.

One respondent suggested the auction be based on percentage of income rather than absolute dollars.

Question 3. If you will vote to defer approval until certain issues and questions are resolved, what would they be, and what answers would you be looking for?

One respondent stated that the IRB cannot approve the study because the selection of subjects would not be equitable.

One respondent asked how the sponsor would pay for treating complications if its funding is not adequate. One respondent questioned whether the sponsor would be able to cover the cost of follow-up and any required treatment for patients after the study.

Several respondents questioned the merits of a company that cannot raise funds to test such a promising device, and its ability to conduct the study properly without taking shortcuts.

Question 4. How did you vote and what was your reasoning?

One respondent stated that, once the device is on the market, it could be made available to patients who cannot afford to pay.

One respondent noted that the patient population for this study is highly vulnerable because it is a life-or-death situation for them.

One respondent stated, "I have been involved in two start-ups in which the devices would have a profound positive impact on mortality and morbidity. Development of each and the necessary capital came down to funding and market value, not medical necessity."

One respondent questioned whether the study would be biased because wealthy people have different diets and lifestyles than poor people.

One respondent noted that, in the U.S. healthcare system, the wealthy subsidize medical care for the poor, so how is this study any different? [For example, people with high incomes pay more than low-income people to fund Medicare. U.S. patients pay more for pharmaceuticals than people in developing countries.]

Several respondents expressed concerns about coercion.

One respondent suggested that the sponsor use crowdsourcing to finance the study, [a plausible approach, given the assumption that wealthy patients would be willing to pay a high price to participate, but assuming the payments would come from patients that would live long enough to receive the device post-approval].

Discussion

Ethical Considerations

The auction proposed for this study violates the Belmont Report's principal of justice because wealthy people would have an advantage over poor people in obtaining the *benefit* from participating in the study. On the other hand, since the device is experimental and only "likely" to "save many lives" (and not necessarily those of the study participants), any risks and other *burdens* of the experiment will fall on the wealthy, so the injustice would be to them, while the benefits would accrue to the general population. However, according to the Belmont Report, social justice allows the burden of an experiment to be borne by those best able to bear it.

The auction does not appear to violate the principle of respect for persons (and the related questions of autonomy and voluntariness) because mentally competent people have the right to decide for themselves how much they are willing to pay to participate in the study. However, how many people have the ability to coolly reason their way through such a high-stakes decision?

According to the Belmont Report, "Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance." Thus, the auction is not coercive, but does it involve undue influence? According to the Belmont Report, "Undue influence…occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable." Given the stakes, perhaps all potential participants are "especially vulnerable."

The Belmont Report defines "beneficence" in the principle of beneficence as "(1) do not harm and (2) maximize possible benefits and minimize possible harms." The auction would cause harm to the extent that it causes people to act against their own best interests by paying "more that they should," but who is to say what that amount should be? Application of the rule, "maximize possible benefits and minimize possible harms," would not be violated if the auction allows the study to proceed, with the financial burden borne by those most able to bear it. If poor people are unable to participate, they would not be *harmed* by the study, just not *benefited*, but they might be harmed if the study is not conducted.

Regulatory Considerations

The U.S. Code of Federal Regulations includes three pertinent rules:

> Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. (21 CFR 56.111(a)(2))

The auction would comply with this rule to the extent that participants do not "overpay" to participate. The IRB could require the sponsor to cap auction bids, but that would require the IRB to determine for each participant the value of his or her life.

> Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons. (21 CFR 56.111(a)(3))

Selection of subjects by auction would not equitable because it would disadvantage some people based on their lack of wealth. However, the IRB could address this issue in two ways: It could (a) require the study sponsor to include in the study an acceptable proportion of non-wealthy people, as subsidized by the wealthy and/or (b) require the auction to be based on percentage of wealth (provided enough high-paying wealthy people are allowed to participate). Participants, in aggregate, should not pay more than the sponsor needs to conduct the study, treat adverse events, and follow up after the study.

> When some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. (21 CFR 56.111(b))

The auction might unduly influence people to bid "more than they should," but that would be a problematic assessment for an IRB. However, the IRB could, for example, prohibit bids that would impoverish people.

"FDA Information Sheet – Sponsor-Investigator-IRB Interrelationship (1998 Update)" states:

> Investigational Device Exemption (IDE) regulations allow sponsors to charge for an investigational device, however, the charge should not exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.7(b)]. A sponsor justifies the proposed charges for the device in the IDE application, states the amount to be charged, and explains why the charge does not constitute commercialization [21 CFR 812.20(b)(8)]. FDA generally allows sponsors to charge investigators for investigational devices, and this cost usually is passed on to the subjects.

The pertinent regulations state:

> A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not…commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling. (21 CFR 812.7(b))
>
> If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device. (21 CFR 812.20(b)(8))

Several important points can be made:

- The regulations do not prohibit charging for participating in a study, but leave it to the IRB to determine whether "any such charges are appropriate and equitable." (FDA GCP Q&A "Policy on Charging Patients" 4/25/16) The question of whether the payments generated by the auction are appropriate and equitable is addressed above.
- "FDA generally allows sponsors to charge investigators for investigational devices, and this cost usually is passed on to the subjects."
- The price charged is relevant only if the purpose is to commercialize the product.
- The purpose of this study is not to commercialize the device.
- FDA might reject the sponsor's IDE application because, *in its view*, the auction might generate payments that "exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device."
- FDA might reject the sponsor's IDE application because, *in its view*, the cost to develop and manufacture the artificial heart should be amortized over a commercially feasible number of devices, not just over the few units needed to conduct this study. Or, it might find that the auction amounts to "constructive" commercialization, regardless of the sponsor's stated intent.
- Questions related to commercialization and pricing of the *device* are under the purview of the FDA, not the IRB.

Conclusion

At a fundamental level, the real question is whether a study that promises to save lives should be cancelled or delayed because it violates sound ethical principles but does not actually harm anyone, except to the extent that wealthy participants might pay a higher financial price than "they should," a problematic judgment, at best. Thus, the auction mechanism would not *harm* poor people; it just would not *help* them on an equitable basis. On the other hand, delaying or cancelling the study might very well cause them harm after the device would have reached the market.

This situation is very different than one in which vulnerable (e.g., poor) people are enticed or coerced to participate in a study that might harm them in order to generate knowledge that would benefit others. (Any study that pays a fixed patient stipend violates this principle, if only to a miniscule degree (i.e., there might be "influence" but not "undue influence").

For most respondents, the auction mechanism just seems wrong on a visceral basis, so they would vote to block or delay the study. Some of these respondents explained their decision based on regulatory or ethical considerations, but none of them commented on how their decision might cost the lives of both study participants and future patients. To what extent do IRBs and other ethics committees weigh this tradeoff in real life? Do we appreciate the ethical burden this tradeoff places on each IRB member?

Next Month's Question

Researchers have identified a previously unknown but fairly common viral disease in certain developing countries: infant maternalitis, in which an infant is born with a serious allergy to the mere presence of his or her mother. For reasons that are not understood, even awareness of the mother's presence can provoke the condition. You are a member of an IRB reviewing a study protocol for a painless, inexpensive test that would, with 100% accuracy, identify infants with this disease so they can be separated from their mothers before the

disease appears. After that, the condition becomes permanent and untreatable. The protocol requires consent by both parents. Will you vote to approve the study?

Read the full question and give us *your* answer at:
https://www.surveymonkey.com/r/V6NC2D2

Please send your ethical conundrums to ngoldfarb@firstclinical.com.

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