JOURNAL OF CLINICAL RESEARCH BEST PRACTICES
Vol. 14, No. 2, February 2018 "Happy Trials to You"

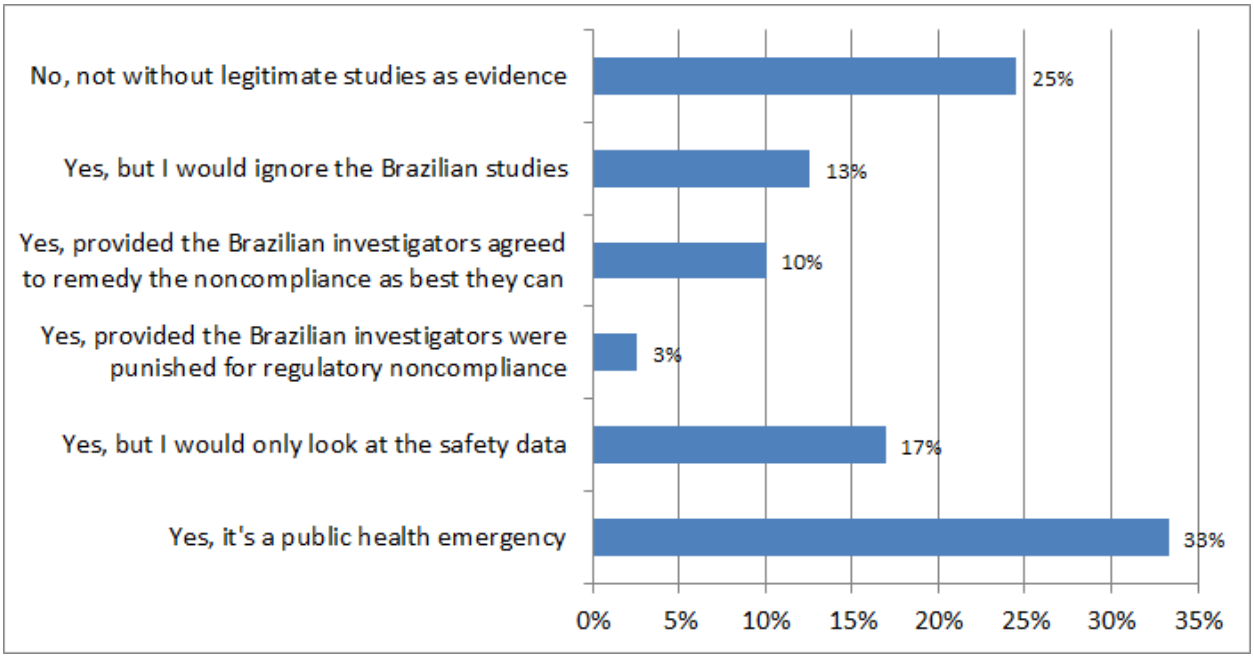
Clinical Research Ethics Question of the Month: Zika2 Epidemic

By Norman M. Goldfarb

You are a member of the board at Florida Central IRB. You are reviewing a Phase 2 vaccine study for Zika2, a deadly infectious disease that has recently emerged in Florida and is spreading fast. The only clinical studies discussed in the Investigator's Brochure were conducted in Brazil, where Zika2 originated. They provide scientifically sound evidence that supports the proposed study. However, you have just learned that, because of the emergency situation in Brazil, the investigators made the decision to conduct their studies without regulatory or ethics committee approval, in a vulnerable population, and without proper informed consent. The Brazilian manufacturer and investigators will not be involved in the proposed study. Time is of the essence. Will you vote to approve the study?

Results

Question 1. Will you vote to approve the study?



Of the 159 respondents, 33% would vote to approve the study because of the public health emergency, 25% would vote against approving the study without legitimate studies as evidence, 17% would vote to approve the study but would look only at the safety data, 13% would vote to approve the study but would ignore the Brazilian studies, and 10% would vote to approve the study provided the Brazilian investigators were punished for regulatory noncompliance.

A number of respondents stated that addressing the public health emergency was the decisive consideration.

A number of respondents said they would ignore the Brazilian studies and approve the proposed study as a Phase 1 study.

Several respondents questioned whether, given the haste of the Brazilian investigators and their ethical violations, their findings can be trusted.

Several respondents noted that not using the Brazilian results would discount the risks the Brazilian subjects took by participating in the study.

Several respondents said that the Brazilian studies were not "clinical research" but steps taken to address a public health emergency, so clinical research regulations would not apply.

Several respondents commented that what matters is the conduct of the *proposed* study.

One respondent expressed concern that accepting the Brazilian results would set a bad precedent.

Question 2. If you would not approve the study, what action or information would you want before you would approve it?

A number of respondents would want to know whether the Brazilian government approved or supported the studies, and what the Brazilian rules are for clinical research in a public health emergency.

Several respondents would want more information about the validity of the Brazilian results.

A number of respondents would look closely at any preclinical results.

One respondent would want to consult with the Brazilian ethics committee that should have reviewed the Brazilian studies.

Question 3. Would your decision change if you knew no Brazilian study participants had been harmed?

Only 20% of respondents would change their vote if they knew no Brazilian study participants had been harmed. This question was defective because it lacked the condition, "If you voted against approving the study…"

A number of respondents discussed the question of whether "scientifically sound evidence that supports the proposed study" means that the safety results were satisfactory.

Several respondents would want to know more about any subjects who were harmed.

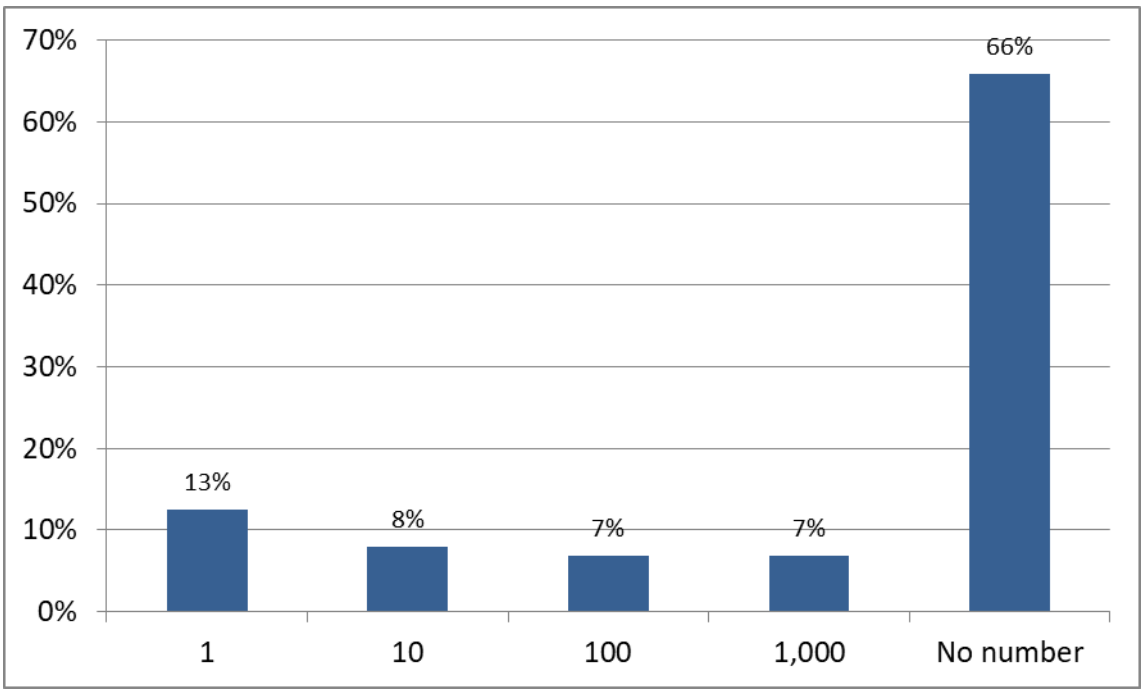
Question 4. Would your decision change if you knew the Brazilian manufacturer plans to distribute 10 million free doses of the new vaccine?

Only 7% of respondents would change their vote if they learned that the Brazilian manufacturer plans to distribute 10 million free doses of the new vaccine. This question was defective because it lacked the condition, "If you voted against approving the study…"

One respondent said that, "Manufacturers should not be able to buy their way out of ethics violations."

One respondent questioned the motives of the manufacturer — perhaps it would distribute the free doses because it is not sure the vaccine is safe enough to sell.

Question 5. If you would vote "no," and your vote would be decisive in rejecting the study, how many lives would the study need to save to change your vote from "no" to "yes"?



Of the 88 respondents, 66% would not change their vote regardless of the number of lives that would be saved. Thirteen percent of respondents would change their vote to save a single life and 21% would change their vote to save 10-1,000 lives.

Several respondents said human subjects protection should be the paramount concern of an IRB.

One respondent pointed out that the question is nonsensical since the whole point of the proposed study is to save lives.

Discussion

IRB Review and Ethical Considerations

U.S. IRBs have the authority to review studies that have been submitted for review and approval, but not previous studies that have already been conducted elsewhere. However, 21 CFR 50.24(e) states: "If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section [requirement for informed consent] or *because of other relevant ethical concerns* [italics added], the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation."

This provision appears to give the Florida Central IRB *carte blanche* to consider anything relevant to the ethical conduct of the study under review. It could therefore reject the Zika2 study on the grounds that (a) information from the Brazilian studies is necessary to grant approval, (b) those studies were unethical, and, therefore, (c) conducting a study based on information obtained unethically would also be unethical.

What makes conducting a study based on information obtained unethically unethical? Disapproving the Zika2 study would not protect the participants in the Brazilian studies. To the contrary, it would discount their contributions. Given that the Brazilian studies "provide scientifically sound evidence that supports the proposed study," there is no safety issue to justify disapproval on ethical grounds. The only ethical basis for disapproving the study is that it would set a precedent that might encourage future unethical studies.

Before reaching this conclusion, the IRB might want to learn more about any approval or other involvement of the Brazilian government, as well as the pertinent Brazilian laws and regulations. However, the Nazi government was fully involved in its own grotesque medical experiments, and that did not make those experiments ethical.

If setting a problematic precedent is the IRB's ethical concern, it must weigh that long-term concern against the near-term public health situation. After World War II, the U.S. government gathered all the documents and debriefed all the Nazi doctors it could find to obtain information of military and medical value. By 1984, more than 45 publications had made reference to the Dachau hypothermia experiments alone. (http://www.nejm.org/doi/full/10.1056/NEJM199005173222006) The use, if any, of such data has been widely debated. One option is to use the data but include a statement condemning the scientists who collected it for their unethical practices.

U.S. Government Involvement

In a U.S. public health emergency, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) authorizes the Department of Health and Human Services (HHS) to take appropriate actions, including "conducting and supporting investigations into the cause, treatment or prevention of the disease or disorder." (https://www.phe.gov/Preparedness/legal/Pages/phedeclaration.aspx and https://www.phe.gov/preparedness/legal/pahpa/Pages/pahpra.aspx)

Under PAHPRA, HHS also has authority to skip the proposed clinical trial and just start distributing the vaccine without further research. A second option would be for HHS to start distributing the vaccine to the highest risk populations and, in parallel, conduct the Zika2 study. In this scenario, the Florida Central IRB could defer review to HHS authority. The Centers for Disease Control and Prevention (CDC), an agency of the HHS, has seven IRBs, including IRB "S," which "meets as needed for response and preparedness activities." A third option would to delay distribution of the vaccine until a study approved by CDC IRB S proves it is safe and effective. IRB S would face the same ethical questions as Florida Central IRB, but it might be better prepared to answer them.

Ethical Balancing

The question was defective, but it appears that very few respondents were impressed by the Brazilian manufacturer's plan to distribute 10 million free doses of the vaccine. This suggests that respondents either did not consider that offer to be attractive or, more likely, that IRBs should conduct their reviews without considering the ethics of compensatory actions outside clinical research.

The question was defective, but it appears that at least some respondents would consider how many lives the study would save when weighing the ethical shortcomings of the Brazilian studies.

Next Month's Question

You are a member of an IRB reviewing a Phase 2 study for cardozamine, a new drug for treating stress. One of the exclusion criteria in the protocol is: "Educated or employed as an

attorney." The cover letter on the application explains that the study sponsor has been sued on three occasions by attorneys who were study subjects, and does not want it to happen again. Will you vote to approve the study? Read the full question and give us *your* answer at: https://www.surveymonkey.com/r/TRQYPXN

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

Author

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.