Placebo Studies in Developing Countries: Ethical, but not Ideal

Korotkin, Scott

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Placebo trials in research are generally looked upon unfavorably. They are only tolerated when a standard of care treatment control is not available or feasible. In developing countries, where a significant portion of drug trials and medical research studies are conducted, placebo driven trials are more commonplace, but not without controversy. The atrocities of Nazi Germany and the Tuskegee Syphilis study in the United States have put humanitarians and bioethicists on high alert to prevent similar injustice. It is not surprising that the arguments against placebo driven studies are often made from the point-of-view of a parent or guardian looking after the well-being of a child participating in research. What about the patient's perspective? The intention of this paper is to evaluate if placebo trials in developing countries violate any of the four bioethical principles.

Autonomy

Simply stated, the principle of autonomy encompasses an individual's right to control what happens to their body. In Western culture, this is where informed consent plays its role. A patient should be able to make a decision whether or not they want to participate in a drug trial that includes a placebo arm. However, they need to understand all major aspects of the trial and treatment in order to consent. Can an individual make an informed decision without a complete understanding? Patient A lives in a developing country and is HIV positive. He is starting to show symptoms, and a major pharmaceutical company is starting a drug trial that includes his village. The researchers explain that there is a placebo arm to the study, telling him that he may or may not get the actual medicine. However, he will get medical care throughout the study, which will last a couple of years. Patient A knows that if he does not participate in the trial, he will not get medical treatment for anything. If Patient A makes a decision based on whether or not he gets medical treatment, is that an informed decision? Does he have to show some level of awareness and comprehension about the placebo or experimental drug and possible outcomes? It is possible to make an informed decision about participating in a trial solely on the basis of receiving medical care.

Beneficence

The researchers should act in the best interest of the patient. Well-intentioned individuals argue that placebo arm studies should not be conducted because it is not acting in the best interest of the patients assigned to the placebo group. In many instances, this is true, especially in the United States, where a patient in a placebo group would have access to another form of treatment if they dropped out of the study. Therefore, being randomized to the placebo group puts the participant in a condition that is worse than if they were not enrolled in the study. A research participant in a developing country is faced with different circumstances because of different levels of access to medical treatment. Those in the placebo group are not worse off than if they declined to participate in the study; they are better off because they are going to be provided medical care during the duration of the study. Assuming there is clinical equipoise in the research study to begin with, it is not known whether the placebo group is going to be better off or worse off that the treatment group. It is therefore in the best interest of the patients to allow the study with the placebo arm to take place because both arms of the study provide medical care.

Nonmaleficence

The researchers should not harm the patients involved in the research study. The main question with nonmaleficence is: is the placebo group being harmed? Some might argue that, when available, the omission of treatment, or standard of care, can be construed as harm being done to an individual in the placebo group. A good example to illustrate this is a hypothetical research study for a new malarial drug. Ideally, the new drug would be compared to the current standard of care for malaria. Comparing the new malaria drug to a placebo is clearly is not as good as comparing it to standard of care in terms of benefit to the subjects enrolled in the study. However, the difference of “good” is relative. It is difficult to keep in mind, that prior to the study, it is likely that the patients were getting no medical care. Therefore, the difference between providing a placebo, including medical care, and nothing is much greater than between a placebo and the standard of treatment. Is not providing the patient with standard of care harming them? It would be better for them to get the standard of care, but it is also acceptable that they are being provided with medical treatment and a placebo.[1]

It is similar to providing compensation for participating in a trial in the developing world. If a patient in a developing country was compensated the same amount as a patient in the United States, it would be deemed unethical and coercive because it would be an incredibly large sum of money. I am not implying that providing treatment and monetary compensation are equivalent, but it is worth considering. Another way to look at whether or not patients in the placebo arm are being harmed is by doing a risk/benefit analysis. What are the risks? The patient who gets randomized to the placebo arm of the study is not bearing any additional risk by being randomized to the placebo group. If they did not sign up for the study, they would not be receiving any treatment. The placebo group is also not getting any treatment. What about benefits? The patient does benefit from access to medical care for participating in the study. If they are suffering from secondary infection or another illness, they will still be treated. In fact, the placebo group is subjected to less risk than the experimental group. The experimental group gets the same medical care, but is given an experimental drug. Participants in this group have increased risk, with side-effects, but also have greater potential benefits. This is different from a placebo group in a country like the United States, where placing them in a placebo group would be doing them harm. A placebo group in the US would be subjected to additional risk because they have access to medical care and the trial would prevent them from being able to pursue the current standard of care.

Justice

Is there a fair distribution of the risks and benefits on the participants in the study? Are the patients risking too much by being randomized into a placebo group or the experimental group? Let us assume that a research study with an experimental arm and a control (standard of care) arm does satisfy the fair distribution of risks and benefits requirement. If that assumption is made, then the experimental and placebo study should also satisfy the requirement. Unless the drug being tested is going to only help developing countries, like a new malaria drug, the gains from studies involving patients in developing countries are going to be realized by the developed world.[2] Having a standard of care instead of a placebo is not going to change the “fair” distribution of risks borne by the participants during the trial or the benefits the world receives from the results of the study. Therefore, the risks and benefit analysis has to be done on the participants in the study. Once again, the placebo group is getting medical care that they would not be receiving otherwise. They are not bearing any additional risk by participating in the trial. The benefits gained from the study by the participants are going to be less for the placebo study versus the standard of care study, but not enough to disrupt a fair distribution of risks and benefits.

Making the case that placebo studies in developing countries are ethical is not a typical approach. It takes a deeper understanding of the frame of mind of the candidate and the environment they live in. Often ethicists use the structure and values of the United States to evaluate an issue, but they are sometimes insufficient. Pharmaceutical companies should use control groups that are given standard of care instead of placebos. Whether or not they should be required to do so is another question. From the perspective of the participants in research studies in the developing world, having a standard of care or placebo is not going to be a determining factor in their decision to participate.

NOTES

[1] After the study is concluded, without continuing to provide anti-malarial drugs to the community indefinitely, the individuals in the study will continue to get malaria.

[2] Would testing a new malaria drug that uses a standard of care as the control be ethical? In that situation, the control participants are getting a treatment that works and medical care. The experimental group is getting an experimental drug that may or may not work and medical care. Is that ethical?