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CASE STUDY

To Enroll or Not to Enroll? A Researcher Struggles with the Decision to Involve Study Participants in a Clinical Trial That Could Save Their Lives

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Abstract. Hundreds of thousands of clinical trials are conducted annually around the world, working to further scientific knowledge and expand medical treatment. At the same time, clinical trials also present novel challenges to researchers who have access to large pools of research participants and are routinely approached by pharmaceutical companies seeking to recruit subjects for clinical trials. This case study discusses the ethical dilemmas faced by a community health investigator who received an invitation to enroll people who inject drugs (PWID) into a clinical trial of a drug that promised a new treatment option for Hepatitis C. The author elaborates on the ethical tensions that he confronted between "doing good" and "avoiding harm. The paper suggests that issues of distributive justice should also be considered, particularly when the drugs being tested might eventually command prices that place them out of reach of the population enrolled in the trial. This case does not attempt to provide an ethical road map to assist researchers in similar circumstances, but rather to illustrate some of the considerations involved in making a decision about whether or not to participate in clinical trials research.

Keywords. Beneficence, Clinical Trials, Enrollment, Justice, Non-Maleficence

Introduction

Recently, I was approached by an investigator who wanted to enroll participants from a community health study that I was conducting of HIV and Hepatitis C risk among people who inject drugs (PWID). He wished to include them in an interventional clinical trial to find out whether they could adhere to and complete an experimental drug to treat Hepatitis C. There had been debates about whether this population would be able to follow an HCV drug regime, which involved taking 1 pill each day for 90 days. In addition, this interventional trial aimed to test whether participants would be able to avoid reinfection once they had completed the HCV treatment. Reinfection could occur if they were to

enter into contact with the HCV virus either through contaminated syringes or injection equipment. These were valid and important scientific questions that would produce valuable data regarding PWID and HCV treatment outcomes.

The drugs to be used were in Phase III of clinical testing; they had shown promising safety and efficacy results but had not yet been approved. A majority of participants in my study, around 80%, had tested positive for the Hepatitis C virus. This is not surprising given that Hepatitis C has reached epidemic levels in this population (Abadie, Welch-Lazoritz, Gelpi-Acosta, Reyes, & Dombrowski, 2016; Abadie, Welch-Lazoritz, Khan, & Dombrowski, 2017). Having access to more than 300 participants with a high prevalence of Hepatitis C made my study an interesting target for clinical research. In turn, participants with a Hepatitis C–positive, or reactive, result were also very interested in accessing treatment. While HIV transmission—or avoiding "the monster," as they informally call the virus—was participants' main concern, they were visibly distressed after learning of a positive Hepatitis C result. Some cried when they learned that they had the virus, and I heard others praying and thanking God effusively after learning that they were free of it.

The drugs involved in this interventional clinical trial mimic the action of drugs that had recently been approved, revolutionizing the treatment of Hepatitis C patients. That treatment is expensive, however, costing US$1,000 per pill; neither Medicaid nor Medicare covers the drug regimen in the area where I was doing the study, leaving patients infected with the virus and, in most cases, unable to access treatment without private insurance. Only if they were to reach an advanced stage of the disease would medical treatment become available. Enrolling them in this trial might well be the only opportunity many of them would have to access a potentially life-saving drug course. If everything went well, participants in the trial could be free of Hepatitis C in 3 months.

Yet I struggled to make my decision. First, I had a number of practical concerns about enrolling study participants in this trial because it would engender a significant disruption in our daily research activities. As a small team, we don't possess the capabilities to recruit participants for a large Phase III trial, which would involve activities such as collecting blood samples and dispensing medications to participants on a daily basis for almost a year. This would be a significant commitment, and new funding assumed by the trial's sponsor would be required to cover costs since our federal funding had very strict conditions preventing us from engaging in any activity unrelated to the original study aims.

An additional concern was that since our participants had only consented to be enrolled in our community health study, their participation in the clinical trial would require a new submission to the Institutional Review Board (IRB) with a corresponding consent form, carefully explaining the goals, risks, and benefits of this new trial. Because the consent form that participants had signed when they joined our present study had not mentioned involvement in any other research, we could not simply invite them to participate in the clinical trial.

Even before prospective participants could give their consent to participate, however, the new study itself had to be submitted to the IRB and then approved. In this case, the IRB would be not an independent body located in an academic setting but an "in-house" IRB funded by the trial's sponsor. While this arrangement is not unusual in industry-sponsored clinical trials, the ties with the pharmaceutical industry gave me pause. Because they act much more quickly than do academic IRBs, and with much less oversight, critics argue that these industry-sponsored IRBs often do not go beyond rubber-stamping protocols.

Given these concerns, I had to take extra care in analyzing the research protocol, paying attention to anything that might compromise study participants. Suddenly, I realized that I had become a de facto gatekeeper. My refusal to enter into an agreement with the study sponsor would effectively end the possibility of conducting this trial on this population. The pharmaceutical company that sponsored the trial would then be forced to find

another researcher with access to the population it was targeting or suspend the trial altogether.

But my most serious concerns were not instrumental, but ethical. While I am not a physician, as a researcher I still have a fiduciary duty to do good and to protect participants enrolled in my study from harm. While any treatment involves risks, a clinical trial, even in its last stage, brings new risks; finding out the nature of these risks and their seriousness is precisely the reason why clinical trials are conducted in the first place. To complicate matters further, my knowledge of the latest treatments for Hepatitis C and related clinical trial outcomes is limited. I wanted to contribute to a promising and well-designed scientific protocol that could produce relevant data about HCV treatment of PWID, as well as to ensure placement in a promising drug course for study participants. But I needed to be reassured that participants would not be harmed by their trial participation.

If I were to decide that the risk/benefit equation was acceptable and that there were clear gains to be had by entering this trial, should I actively recommend doing so to my study participants? On the one hand, I was inclined to enroll them in a trial that would provide access to an otherwise unavailable HCV drug treatment. But, on the other hand, I struggled to recommend this course of action. My obligation toward study participants was to inform them about the possibility afforded by this new Phase III trial, allowing them to then make an autonomous decision about whether or not to enroll. Should I go beyond this, deciding to participate in the clinical trial first and then actively recommending enrollment to prospective research subjects? But would it be paternalistic to recommend that vulnerable participants enroll in such a trial, even if the benefits clearly seemed to outweigh the risks? And then a related worry arose. Would it be a conflict of interest to recommend their enrollment in the clinical trial, since not only would I be associated with it, but I would also benefit?

This dilemma kept me awake many nights: Would it be better to take a cautionary approach, waiting until the drug was finally approved, hoping that prices could be lowered over the years, or should I jump at what might well be the participants' only chance to access a drug regimen that might cure them?

Clinical Trials for Hepatitis C Drugs

Hepatitis C is a viral infection of the liver than can cause cirrhosis and liver cancer. The virus is transmitted through blood and, at least in the US, affects mainly people who inject drugs through shared needles and other injection equipment. Until recently, treatment involved injecting an extremely toxic drug for more than a year. Many patients interrupted their drug course midway due to side effects; of those who completed it, fewer than half were free of the virus. In 2013, the FDA approved a new polymerase-inhibiting drug that interrupts the mechanisms the virus uses to replicate in the body, thus revolutionizing the treatment of Hepatitis C. But it comes with sticker shock: US$80,000 dollars for the entire 3-month treatment course.

Inspired by this scientific achievement and enticed by the prospect of an extremely lucrative market for the new polymerase- and protease-inhibiting hepatitis drugs, pharmaceutical companies competed to produce similar formulations. Today, a number of drugs can be used in combination to effectively treat Hepatitis C, and others are being developed. Before reaching the market, however, all new drugs must undergo extensive clinical trials to prove that they are safe and effective. Most clinical trials in the US or abroad currently are not conducted by the pharmaceutical companies directly, but are outsourced to contract research organizations (CROs) that compete with each other, all promising to navigate around ethical and regulatory obstacles (Petryna, 2009).

None of these novel life-saving Hepatitis C drugs could have been developed without the participation of clinical trial research subjects. It should come as no surprise, then, that the ability to recruit a large pool of subjects has become a competitive advantage pursued by CROs in their search for business opportunities (Fisher, 2008). The faster that willing and able research subjects can be recruited, the sooner a clinical trial can begin. Since bringing a

drug to market already takes many years, delays in subject recruitment can further extend the development and testing process. Time is literally money (Abadie, 2010).

Now the opportunity to enroll study participants was knocking at my door. I could see the potential to advance clinical research, but I could not avoid thinking about the possible risks. As a non-physician, much less an expert on Hepatitis C, how could I make the correct decision?

Ethical Dilemmas: Beneficence versus Non-Maleficence

I struggled with this issue for many days. The tension between potentially helping participants enrolled in my research, and my concerns that the clinical trial might harm them because the drug was still undergoing testing and had yet to be approved, reflects two well-known bioethical principles: beneficence and non-maleficence. *Beneficence* is the obligation to do good, or to help, and involves a calculation of the relationship between risk and benefit. *Non-maleficence* stresses the avoidance of doing harm (Beauchamp & Childress, 2001).

Initially, I felt overwhelmed by the responsibility presented by these two competing obligations. On the one hand, I have a responsibility to do good, or to help participants enrolled in my study. While it was not my obligation as a researcher, facilitating access to a life-saving drug that otherwise would not be available to them would be an unmitigated good. And if the trial proved successful, it would provide scientific evidence that treating PWID with this drug regimen was both feasible and effective, a finding that could potentially open new therapeutic opportunities for this population.

On the other hand, I was also obliged to protect study participants from harm by avoiding doing anything that would place their lives or well-being at risk. Unfortunately, this obligation is more clearly defined in the case of physicians than it is for biomedical researchers. How are we to understand harm in a context not of treatment but of research participation, and, more importantly, how do we balance the competing obligations of beneficence and non-maleficence?

An important condition to consider is that benefits should outweigh risks (Levine, 1986; Emmanuel, Wendler, & Grady, 2000; Freedman, Fuks, & Weijer, 1992). Clearly, a situation in which subjects bear risks without receiving corresponding benefits should not be considered. But while the burden of risk falls always onto individual trial participants, the benefits can extend beyond the individual who undergoes the clinical trial (World Health Organization, 2001; Weijer & Miller, 2004; Sieber & Tolich, 2013). In the case of such "social benefits," it might be ethical to subject a consenting individual to a high level of risk if this correlates with a potentially high benefit for society as a whole. Given what was known about this drug, it seemed that the benefits could outweigh the risks since it could add another powerful therapeutic weapon to the arsenal of Hepatitis C treatment while showing apparently no more risks than the drugs that had already been approved.

I felt reassured by the fact that the drug to be tested mimicked the action of those that were already on the market and that constituted the standard of care for this condition. According to the data already reported in Phases I and II, the drug seemed to be safe with few side effects, and highly effective. The trial would yield evidence about HCV treatment outcomes among PWID while providing a good opportunity to make available an otherwise unaffordable course of drugs to poor drug injectors living with Hepatitis C. After much thought, I was leaning toward agreeing to involve study participants in this clinical trial.

But I struggled with an additional concern. Would it violate participants' autonomy if I strongly recommended this course of action for them? I did not want to force or coerce them into participating in this trial in any way. In addition, I was also aware of the possible conflict of interest involved, since I would receive financial compensation from the pharmaceutical sponsor to cover operating costs. One possible approach would be to present the information about the trial to study participants and let them make an informed and autonomous decision about whether or not they wanted to participate. But I believed that in this case, my goals and the interests of study participants were aligned and

that no coercion was involved. One might discount this view, finding it paternalistic (or worse, authoritarian) based on the argument that the principle of beneficence should not override research subjects' autonomy. But how free or voluntary is consent once a participant is informed that this might be his or her only opportunity to access treatment? In particular, I wanted to avoid transmitting to study participants the idea that they would be involved in the trial simply to receive treatment. Clearly, this should not be the goal behind their participation; doing so would involve falling prey to the therapeutic misconception.

The fight to bring life-saving HIV therapies to market provides a good model for thinking about this ethical problem. Instead of opposing the principle of beneficence to the research subjects' right to autonomy, the history of AIDS activism shows that researchers, disease activists, and patients can form alliances not only to further pharmaceutical research, but also to make sure that the benefits of this research would not price out millions of potential patients. I see myself as a disease activist following in the footsteps of AIDS researchers who, decades ago, made the decision to strategically engage with the pharmaceutical industry in order to test promising protease inhibitors. I would argue that prospective trial participants are not coerced into enrolling; rather, they are in a position to make the conscious decision to try to gain access to treatment that they otherwise could not afford.

Still, there was something about the extremely high price of these new types of HCV drugs that gave me pause. Could I ask study participants to join a clinical trial that, if successful, would produce a drug that most PWID might not be able to afford?

Pricing Politics

While patients and clinicians are excited about these new inhibitor drugs, their high prices—sometimes US$100,000 or more—are a concern to everybody from insurers to health policy experts to disease advocates. Of 10 drugs that start preclinical tests, only 1 completes the whole process and is approved as not only safe but also effective. Therefore, those that reach the market not only have to pay back the research costs incurred over the many years of their own development but also must support the cost of the drugs that fail. Some critics argue, however, that research costs are highly overestimated by the industry and that most expenses go to marketing and not to drug research (Angell, 2005). Others suggest that drug prices do not only reflect the economics of drug production, or the laws of supply and demand, but are a political calculation, reflecting not what the drug actually costs but how much the industry thinks it can get away with charging. The Nobel Prize in Economics winner Jeffery Sachs recently estimated in his *Huffington Post* blog that Gilead, the maker of Sovaldi, one of the drugs that has become the standard of care for HCV treatment, spent only $US500 to produce a drug that it is selling for close to US$1,000 dollars per pill (Sachs, 2016). Reacting to the controversy, Gilead argued that the high price reflected research costs, but it also made an agreement with many developing countries to provide the drug at a very steep discount.

Millions of patients all over the world are infected with the Hepatitis C virus, and it is particularly rampant among PWID; some observers consider Hepatitis C to be an epidemic among this population (Aceijas & Rhodes, 2007; Bao & Li, 2009). Such high prices make it extremely hard to treat all of those who need the drug most. Developing countries can go bankrupt trying to cover such costs, but even in rich countries such high prices place a big strain on healthcare budgets, private insurance, and HMOs (Hill, Khoo, & Fortunak, 2014). It is tragic that exorbitant Hepatitis C prices place life-saving drugs out of reach for millions of patients. Untreated, many will suffer and possibly experience a preventable death.

A Way Forward

With an increasing number of clinical trials designed to bring new drugs into their research pipelines, pharmaceutical companies will continue to contact researchers regarding access to large pools of potential subjects. While all researchers face the same considerations, non-physician researchers confront a particular set of dilemmas and obligations with even less ethical guidance. I have noted

one main tension, that between the obligation to help research participants, or beneficence, and the obligation to do no harm, or non-maleficence. While there is no simple solution to this dilemma, I hope that this narrative provides some guidance to those who find themselves in a similar position.

What motivated me to consider the possibility of enrolling study participants in this trial in the first place was the opportunity to answer a valid scientific question regarding the ability of PWID to successfully complete a full HCV course while avoiding reinfection. Additionally, I was intrigued by the possibility that a well-designed Hepatitis C clinical trial might be the best way to provide these patients with access to a potentially life-saving drug. Finally, I also recognized that if the trial was successful, it would strengthen the drug arsenal available to treat Hepatitis C, and competition for market share would contribute to lowering its price.

With a therapy carrying such a high price tag, the issue of access cannot be avoided. While the ethical principles of beneficence, non-maleficence, and autonomy are part of any toolkit of bioethics analysis, the principle of justice often does not receive the same degree of attention. In particular, questions of distributive justice—who has access or who receives which kind of treatment (Rawls, 1971)—are especially salient in this case, in which poor PWID are being asked to assume the risks of enrolling in a clinical trial for HCV. For those lucky enough to complete the drug regimen and avoid reinfection, becoming free of HCV is indeed a great outcome. But what about the millions of PWID in the US and abroad who struggle to obtain HCV treatment? Would they be able to afford the new drugs at these prices?

While it is true that a full HCV drug course is still cheaper than a liver transplant, we can and should do more to ensure treatment access, perhaps borrowing a road map from AIDS activism (Farmer, 2014). While antiretroviral therapy was initially extremely expensive, the involvement of community activists and governmental intervention through subsidies and patent-breaking laws together led to a dramatic reduction in prices and an increase in drug availability (Biehl, 2009). But an important role was also played by researchers, who allied with HIV patients and their advocates and used clinical trials as an opportunity not only to produce scientific knowledge about treatment, but also to expand therapeutic opportunities for patients.

Postscript

The reader might wonder what happened with the trial that I was invited to join. The answer is: nothing. Although I had concluded that this was something that I wanted to explore further, after a few initial conversations about the conditions of our collaboration, the contact from the CRO disappeared without a trace. I don't know if the trial will be conducted among another population in the same area, or if it will be conducted elsewhere, or be discarded altogether. Clinical trials can provide valuable opportunities to contribute to scientific knowledge, and may allow patients to test new treatments or novel drugs, but in all cases their benefits should be weighed against their risks.

Reflection Questions

1. Since they were originally formulated a few decades ago, the principle of respect for autonomy seems to have gained priority in detriment of the principle of justice. With drug prices reaching exorbitant levels—more than eighty thousand dollars for a full HCV treatment—placing access beyond the reach of many, shouldn't bioethicists reconsider the way we think about justice?

2. The principle of beneficence establishes the requirement of a social good, as one of if its main criteria. But drug prices seem to benefit the pharmaceutical industry while depriving many of much needed drugs. With this in mind, how do you think we should interpret this principle?

3. Imagine you or somebody you know has the opportunity to participate in a clinical trial. What elements would you need in order to make an informed decision? And an ethical one?

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