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The Model for Compensation to Research "Volunteers " is Called Into Question

Medical research has a new tension and that is where does the volunteer fit in?

Medical research has a new tension and that is where does the volunteer fit in. Is he a subject if he is healthy or is he a patient desiring compensation?

You are listening to ReachMD, The Channel For Medical Professionals. Welcome to the Clinician's Roundtable. I am you host Dr. Maurice Pickard and joining me today is Dr. Jonathan Kimmelman. Dr. Kimmelman is an Assistant Professor in Biomedical Ethics Unit at McGill University.

DR. MAURICE PICKARD:

Thank you very much for joining us today.

DR. JONATHAN KIMMELMAN:

It is a pleasure to be here.

DR. MAURICE PICKARD:

To begin with the subject who is healthy and becomes involved in phase 1 testing. There is a tremendous amount of tension and concern about whether he is being coerced? What are some of the ethical issues that become involved in such a study?

DR. JONATHAN KIMMELMAN:

Well there are probably three major concerns when you are talking about healthy volunteer studies. Safety, payment, and value/validity. As for the safety, these trials are non-therapeutic. They escalate dose levels to a point where patients actually start to show toxicity, so they are in a fence designed for risk. What are the risks? It is hard to say because there really is not very good data out there on mortality rates. Most of these studies do not actually get published in the medical literature, but they certainly are anecdotal reports and experience with some pretty disturbing outcomes that occasionally and probably rarely happened with the studies, but occasionally occur. One example as in 1996 study at University of Rochester the death of Nicole Wan. Another example in 2001 was the death of Allen Roach at John Hopkins University. Neither these were of stage I studies, but they were healthy volunteer studies and I note that both of the studies occurred at universities again where there was some degree of public visibility for the studies. So what are the kind of serious adverse events that might occurred in these studies, the best data that we have out there indicates that serious adverse events are rare, but they do occur somewhere in the order as 0.4% to 3% or so, but again there are some lowered examples out there. Another example more recently was in 2006 study at Northwick Park Hospital in England of monoclonal antibody TGN 1412. In this study, 8

patients developed very, very severe immune reactions, some of them suffering irreversible harm.

DR. MAURICE PICKARD:

Actually, loss of fingers, I believe and toes in one particular subject.

DR. JONATHAN KIMMELMAN:

Correct, as I understand that. Now in that study, they were applying a drug at levels that were 500 times lower than the level what they start to see toxic affects in non-human primates. So you would have thought that it would be very, very safe study given that they were starting at such a low dose. So, occasionally these studies can pack surprises particularly when we are talking about really novel intervention like TGN 1412, which is targeting a novel biological pathway. What about mild adverse events? How often these occur? That also is hard to know. We do know that there are lot of mild adverse events that occurred in the placebo group. Many of these studies phase I studies are placebo controlled. The mind is very susceptible to suggestion and so when you are given a drug and told to report any kind of adverse events or discomfort, some people will immediately notice things in their bodies that they might not have noticed without the suggestion of how to receive the drug. But the rate at which volunteers experienced adverse events that are mild in these studies. Based on the current data, which is again very limited is somewhere in the order at 1.5 to 1.7 mild adverse events per subject. So, the question is they are consistent with the medicine with medical professionals and to inflect harm on one person for the benefit of others. In a sense it is after all, we do it all the time when we donate blood or when we donate organs in medicine, but the difference here is that we do not normally pay blood donors, we do not pay organ donors, where as we do pay medical subjects. So this leads really to the second big sort of ethical concern here, which is the issue of payment. So for about three decades now ethics code has expressed consistent concern about the ethics of paying subjects. The concern here is really about undo inducement. Respect for persons requires that we be very, very careful about giving payments in way that might compromise the best judgment of individuals. You might by paying too high an amount tempt individuals to make very, very short-term decision that fail to consider a possible long-term consequences and you also want to make sure that you do not by paying subject too much encourage them to compromise values and they considered to be very important to values like privacy for example. So the other concern is a concern about justice. If you pay subjects you are probably going to be selecting for people who need the kind of money and in particular the kind of money that these studies pay which was not you know it is not a princess wages or by any means and if the general consensus in ethics literature that subjects should not bear risks unless they are drawn from communities that are likely to be among the beneficiaries of the research. So we have poor subjects who are unlikely to have access to these interventions that are developed from these trials. Who are likely to be uninsured or under insured medically. Then, there is a concern that there is unfairness in the distribution of risks and benefits for studies like this and that leads really to a third concern, which is a concern about value and validity. So there is a general consensus that human study regardless of how beneficial it is for the volunteer or how remunerative it is categorically unethical if it does not produce reliable information and data. Now most studies indicated that phase 1 trial of participants are primarily motivated by money, roughly between 55%-95% of volunteers or subjects for these studies are motivated by the payment and not really introduce a series of validity concerns. #1, will subjects lie, if their motivation is money rather than promotion of science is an incentive to lie about certain things. They might withhold from investigators information about morbidities that could lead to them being excluded from the study. They might have participated in other studies where the drug might interact with another drug that they have received. They might hide pills under the tongue or they might be indifferent to adherence to the protocol. The second concern is about the personality type that might be drawn to these studies. The question is whether the individuals that are drawn to participate in these studies by the payment are truly representative of the population that might receive the drug and there is some indication in the literature, although again this data is not all that extensive that some of the subjects are there is sort of a thrill seeking tendencies among many subjects. Many of these subjects also have lower levels of anxiety than typical patients. Given the subjective nature of many of the kinds of adverse events that might be detected, psychiatric adverse events being one good example. This also might distort outcome assessment.

If you are just joining you are listening to the clinician's roundtable on ReachMD, The Channel For Medical Professionals. I am here host Dr. Maurice Pickard and I am speaking with Dr. Jonathan Kimmelman and we were talking about the various tensions and stressors and ethical issues that become involved when we have healthy subjects involved in research.

DR. MAURICE PICKARD:

You know you touched one interesting thing that this research is not published. So you have people going through some risk, although relatively small and the data is not published and so across the country, there are researches that might benefit from the risk that other subjects are going through. Couldn't we have some kind of database to deal with this; I have actually talked to people on this show about phase I studies that deal with oncology patients and how the research is often not shared that there is a proprietary interest because it is funded by the pharmaceutical companies. How to respond to the need to spread this information?

DR. JONATHAN KIMMELMAN:

I think non-publication is a major concern, as I indicated earlier there is an absolute requirement that studies have value and validity before they are performed in human beings. Publication is the primary vehicle by which information obtained in human experiment is disseminated and made valuable in terms of it altering medial practice or even scientific practice and by not publishing you are _____ the primary mechanism of obtaining value of studies. The problem is that if you have an economy of drug development like that which exists in the most industrialized democracies, there is a major liability issue for companies in terms of making this information public and there is a tremendous amount of trade secrecy here. There are competitive disadvantages of revealing too much about a drug and so you have really an issue of ethics being intention with an issue of prevailing practice and commercial policy in terms of drug development. It is very difficult reconcile with those two things. I think, there are probably some ways that we might think about trying to resolve those two things. I think if we required publication of all phase I healthy volunteer studies, probably most people in pharmaceutical and biotech industry argue that it will be absolutely disastrous in terms of allowing them sufficient protection for developing products, but we might consider allowing say a one year or we know could be six months, could be two years, he could sort of debate about the lag, but allowing some kind of a lag between completion of the study and publication. Another option would be mandating that drugs companies publish these studies at the point of licenser of the product. At that point, there really should not be any important proprietary information that is buried here in these studies and might actually be interesting safety information in these studies, which certainly allow epidemiologist to get an idea of what levels of risks are associated with these kind of studies.

DR. MAURICE PICKARD:

You have talked mainly about phase I studies with healthy subjects. Is there other problems or tensions or ethical issues when we get into deal with phase I studies for oncology patients or patients who might be involved in phase I studies who have multiple sclerosis or rheumatoid arthritis for example.

DR. JONATHAN KIMMELMAN:

Sure. So, I would like to divide phase I studies into 3 broad categories in terms of kinds of individuals that they enroll. The first category is that healthy volunteer phase I study and these are the type of studies that are probably the largest volume any drug has to go through a normal or healthy volunteer study before getting life insurance, but there is also a category of drugs that are potentially very risky for which we consider it unethical to expose normal or healthy volunteers to those levels of risk. So, in field like cancer, HIV, many other areas where you talking about very, very powerful medications in the case of cancer medications that work primarily by their toxicity, these studies tend to enroll oncology patients and in particular for phase I studies, patients who are treatment refractory who really do not have standard of care options available to them. There is a third category of patients of phase I studies that comes up particularly in specialty area or in specialty research areas like gene transfer and these are the stable volunteer studies, but take a condition like hemophilia, there is a fairly adequate way of controlling bleeding in hemophiliac patients provided they have not developed neutralizing antibodies and that is to provide recombinant coagulant factor or blood replacement products. For some studies that are trying to test the product in phase I studies or gene transfer studies, they might ask hemophilia volunteers to go off their standard of care, so that they can measure the outcomes when volunteer receive the gene transfer agent. So, I think this is also a kind of category that lodges somewhere between the healthy subject and a treatment refractory subject. There are certain characteristics of these types of volunteers that are shared by healthy as well as by treatment refractory.

DR. MAURICE PICKARD:

Thank you Jonathan Kimmelman and thank you being our guest and I am Dr. Maurice Pickard your host and you have been listening to

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