Published in final edited form as:
Am J Bioeth. 2006 ; 6(3): W1–13. doi:10.1080/15265160600686281.

Strategies to Minimize Risks and Exploitation in Phase One Trials on Healthy Subjects*

Adil E. Shamoo and
University of Maryland School of Medicine

David B. Resnik
National Institute of Environmental Health Sciences, National Institutes of Health

Abstract

Most of the literature on phase one trials has focused on ethical and safety issues in research on patients with advanced cancer, but this article focuses on healthy, adult subjects. The article makes six specific recommendations for protecting the rights and welfare of healthy subjects in phase one trials: 1) because phase one trials are short in duaration (usually 1 to 3 months), researchers should gather more data on the short-term and long-term risks of participation in phase one studies by healthy subjects; 2) researchers should develop strict inclusion/exclusion criteria that exclude unhealthy or vulnerable subjects, such as decisionally impaired people, in phase one studies; 3) subjects should not participate in more than one phase one study at the same time and should wait at least 30 days between participating in different studies; 4) researchers should develop a database to keep track of phase one participants; 5) subjects should be guaranteed a minimum wage equivalent to the equivalent type of unskilled labor, but there should be no upper limits on wages; and 6) subjects should be allowed to engage in collective bargaining with research sponsors.

Keywords

phase one studies; clinical trials; ethics; safety; exploitation

Several tragic deaths have occurred in phase one trials in recent years.[1] In 1996, Hoiyan Wan, a 19-year-old healthy volunteer nursing student at the University of Rochester (Rochester, NY), died within 2 days after receiving a lethal dose of lidocaine during a bronchoscopy performed on her as part of a phase one study on the effects of smoking (Steinbrook 2002a). In 1999, Jesse Gelsinger, an 18-year-old with liver disease caused by a genetic defect, died in a phase one study in a gene therapy experiment at the University of Pennsylvania (Philadelphia, PA) (Nelson and Weiss 2000). In 2001, Ellen Roche, a 24-year-old healthy volunteer, died from inhaling hexamethonium, a chemical that induces asthma, in a phase one study at Johns Hopkins University (Baltimore, MD) Although the hexamethonium study was not officially classified as a phase one trial, it nevertheless had the same characteristics as other studies that involve the first introduction of a treatment in

*__Disclaimer:__ The ideas and opinions expressed in this article are the authors' personal views and do not represent the views of the National Institute of Environmental Health Sciences, the National Institutes of Health, or the United States government.

[1]The term "phase one trials" is part of the United States Food and Drug Administration's regulatory lexicon relating to INDs (investigational new drugs). The term is also commonly used to describe the first time a new drug, biologic or medical device is used in a human being. We will use this broader understanding of "phase one trials" in our article. Although our article will focus on phase one trials on new drugs, the points we will make should also apply to biologics and medical devices.

humans. As a matter of fact, the United States Food and Drug Administration (FDA) claimed jurisdiction for this case (Shamoo and Strause 2004). Some commentators have faulted the institutional reviews boards (IRBs) in charge of overseeing these three studies for poor supervision, monitoring, and research review. Others have proposed specific changes in human research regulations and procedures to protect subjects from harm (Steinbrook 2002b; Califf et al. 2003).

Most of the literature on phase one trials has focused on ethical and safety issues in research on patients with advanced cancer. Phase one clinical trials raise many different scientific and ethical issues, ranging from conducting research on vulnerably ill subjects, such as patients with advanced cancer, to testing vaccines on children. Our article will not focus on using cancer patients or children as research subjects in phase one trials since these issues have been discussed by others elsewhere (see Agrawal and Emanuel 2003; Ackerman 1995; Grady 2004; Kopelman 2000; Lipsett 1982; Tauer 2002). Instead, we will address an area that we believe has not received adequate attention in the literature, namely, ethical and safety issues related to phase one trials on healthy adult subjects. We also defend some proposals that researchers should consider adopting to protect the rights and welfare of healthy subjects in phase one studies, including: ensuring that phase one studies meet a worthwhile social goal; obtaining better data on the risks of participating in phase one trials; improving the reporting of adverse events; using independent, data safety monitoring boards (DSMBs); excluding unhealthy subjects; preventing subjects from participating in two different studies in less than 30 days; developing a database of phase one participants; attending more carefully to research design, especially reports from prior animal studies and the medical literature; protecting economically vulnerable subjects from financial incentives that may exert undue influence; paying subjects a fair wage; compensating subjects for injuries related to research participation; and allowing subjects to engage in collective bargaining.

PHASE ONE TRIALS

A phase one trial is one of the most important steps in the process of approving a new drug (or biologic or medical device). In order to develop and market a new drug or biologic in the United States, the manufacturer must submit an investigational new drug (IND) application to the FDA. To develop and market a new medical device, a manufacturer must submit an investigational device exemption (IDE) application to the FDA (FDA 2004). Companies usually conduct extensive animal studies to provide evidence to support IND or IDE applications. If the company has presented sufficient evidence that the drug, biologic or medical device is safe enough to use in humans, the FDA will issue the company an IND (or IDE) number and give the company permission to begin testing on human subjects. To obtain approval of the new treatment, the company must submit data to the FDA from controlled human experiments (clinical trials). Phase one studies are the first use of a new treatment in a human being. In a phase one trial, the goal of the study is to assess the drug's safety (Daugherty 1999). If the drug passes this test, the FDA will allow the company to initiate phase two studies in subjects with the disease to measure further safety and some efficacy. If the drug has adequate safety and efficacy, the company can conduct phase three studies to gather more data on safety and efficacy. At the completion of these studies, a company should have enough data to support its new drug application. The FDA examines this data to determine if: 1) the drug is safe and effective; 2) its risks outweigh its benefits; 3) the proposed labeling is appropriate; and 4) the methods use to manufacture the drug are effective at preserving its purity, quality, identity, and strength (FDA 2004). If the FDA approves the new drug, the company may also conduct phase four (or post-marketing) studies to discover new uses for the drug and gather long-term data on safety and efficacy.[2]

Phase one studies last from a few days to a few weeks. They usually involve a small number of subjects (e.g., 20 to 80 participants). Phase one studies usually take place in a hospital or other clinical setting, so that researchers can closely monitor subjects. Some businesses even specialize in conducting phase one trials for pharmaceutical companies.[3] During a phase one study, researchers perform a wide battery of tests and examinations on subjects, such as complete blood count, urinalysis, liver enzyme function tests, electrocardiography, pulse oximetry, and measurement of blood pressure, pulse, respiration, and temperature. They also assess the patient's behavior and symptoms, such as dizziness, nausea, vomiting, shortness of breath, confusion, headaches, cramps, anxiety, and fatigue. In a phase one study, researchers escalate the dose of the drug to determine its maximum tolerable dose (MTD), which is the dose at which the drug produces toxicity, intolerable symptoms, or both. Subsequent studies (i.e., phase two and three) will attempt to determine whether the drug is effective at a dose below the MTD. Hopefully, the gap between the therapeutic dose and the MTD will be large, so that the drug will have a sizeable therapeutic window. Phase one studies also attempt to understand drug metabolism, absorption, and elimination, and the best mode of drug administration (i.e., intravenous versus oral).

SAFETY AND RISK

In thinking about the ethics of phase one studies, it is important to distinguish between studies on healthy volunteers and studies on very ill patients. One of the commonly accepted ethical requirements for research on human subjects is that the benefits of the study must outweigh the risks (Emanuel et al. 2000). The Common Rule, a federal regulation adopted by 17 agencies, requires that the risks of the proposed research must be reasonable in relation to the benefits (45 C.F.R. 46.111(a)(2)). When IRBs assess proposed studies, they may consider the benefits to the subject and society in addition to the risks to subjects, but not risks to society from the application of knowledge derived from the study (45 C.F.R. 46.111(a)(2)). All phase one studies involve considerable risks to the subjects because all such studies escalate the dose of the drug to the point of toxicity. Subjects can expect to experience significant discomfort or pain and medical problems such as abnormal respiration, heart rate, blood pressure, diarrhea, and compromised liver or kidney function (Miller 2000). Many new cancer drugs are first tested on patients with advanced cancer. In these studies, it is at least possible that the subject will derive some direct medical benefit from the research. However, because these experiments are designed to assess safety, not efficacy, the chance of a medical benefit for the subject, although real, is remote (Miller 2000). Nevertheless, because the subjects may gain some medical benefits from participation, most commentators agree that the potential benefits to the subject, when combined with the potential benefits to society, such as increases in knowledge and improvements in therapy, provide sufficient ethical justification for such research (Agrawal and Emanuel 2003).[4]

---

[2]Some claim that many phase four studies are unnecessary marketing ploys (Angell 2004).

[3]Phase I Clinical Trials Unit, Ltd. (2004), located in Plymouth, England, is a company that specializes in conducting phase one studies for drug companies. The company has a database of about 5,000 regular volunteers and a clinical staff of about 100 employees. It also has 61 beds, 21 monitored beds, a pharmacy, an ethics committee. It advertises that it can recruit many different types of volunteers for drug studies, including older men and women; sterilized men and post-menopausal women; obese subjects; and smokers and non-smokers. Volunteers stay at the company's facilities overnight or longer. The company claims that its facilities are comparable to a quality hotel, with televisions in every bedroom, lounges, landscaped gardens, and catered food.

[4]Phase one studies on sick patients have a range of other problems that we will not explore here, notably, the therapeutic misconception: subjects tend to believe that the study will provide them with a medical benefit even when they are informed that the purpose of the study is to develop medical knowledge and that they have a very small chance of deriving some medical benefit from participation (see Miller 2000). The data indicate that disclosure of the risks and benefits of participation in phase one trials is usually adequate, but very ill patients continue to hope that they will receive a direct medical benefit (Agrawal and Emanuel 2003; Daugherty et al. 1995; Horng et al. 2002).

Healthy, adult volunteers, however, cannot expect to receive any significant medical benefits from phase one studies, although they will receive a medical examination as part of their care. Although some subjects may participate in phase one studies in order to receive a medical examination, this medical benefit is very minor when compared with the medical harms that they will experience during the study. The lack of a significant medical benefit affects the risk/benefit ratio of the research. How can risks be reasonable in relation to benefits if only society benefits from such research? One way to answer this question would be to claim that subject receive non-medical benefits, such as money. Indeed, subjects in phase one trials can earn thousands of dollars, and many subjects participate in these studies on a regular basis (Lemmens and Elliott 1999, 2001; Dickert et al. 2002). An article published in 1996 estimated the median payment to healthy subjects for participation in phase one drug trials was $850 (Marrow 1996). Another study of payment for research participation found that the median cash payment for an interventional study was $445 and that payment was correlated with the amount of time spent in the study, the number of invasive procedures, and the number of tasks performed by the subjects (Latterman and Merz 2001). One person claimed to earn $7,000 as a research subject. Although this sounds like a lot of money, it amounted to a pay rate of only $9.71 per hour, since he had worked 720 hours (Anderson and Weijer 2001).

Although most people consider money to be a “benefit,” treating money as benefit for the purposes of reviewing research is usually considered to be inappropriate. According to the National Institutes of Health guidance for research subjects in its intramural program “remuneration should not be seen as a benefit to offset research risks in deciding whether a protocol should be approved. Risks that are otherwise unacceptable cannot be made acceptable by offering increasing amounts of money to subjects” (NIH 2004). The FDA has similar guidance for IRBs and researchers: “Payment to research subjects for participation in studies is not considered a benefit; it is a recruitment incentive” (FDA 1998). The reason why these agencies do not consider money to be a benefit is that treating money as a benefit could skew the risk/benefit ratio in research and justify unreasonable (very high) risks in research for the sake of money, which could increase harms to subjects and lead to exploitation. It is important note, however, that the federal regulations are silent on the question of treating money as a benefit (see 45 C.F.R. 46.111(a)(2); 45 C.F.R. 46.116(a)(3); 21 C.F.R. 50.25(a)(3); 21 C.F.R. 56.111(a)(2)). (We will return to the issue of payment later.)

If money cannot be considered a benefit, then how can subjects in phase one trials benefit from participation? One might argue that subjects derive psychological benefits from participating in research because they find some personal fulfillment in contributing to the advancement of medical science and helping to develop treatments for diseases (Levine 1988). Although it is certainly true that many healthy research subjects in phase one trials have such altruistic motives, most of these subjects are probably more interested in earning money than in making a contribution to science or society (Lemmens and Elliott 1999). Thus, the psychological benefits to phase one subjects from participation are probably quite low. Very ill research subjects, however, who may die from their disease, are more likely to have altruistic motives (Miller 2000). Some may view their participation in a research study as a chance produce some good from unfortunate circumstances. The motivation of healthy subjects highlights another important difference between healthy subjects and sick subjects as research participants: sick subjects are more likely to derive psychological benefits from participation than healthy subjects, who are primarily interested in money.

If medical, psychological and economic benefits to subjects do not usually enter into the risk/benefit equation for phase one studies on healthy subjects, then how can the risks to these subjects be reasonable in relation to benefits? There would seem to be only two ways

of ensuring that risks are reasonable in phase one trials on healthy subjects: 1) the benefits to society must be great; and 2) the risks to the subjects must be minimized. Most people would agree that the benefits of phase one trials to society are usually very significant. Phase one studies play are key role in the process of testing new drugs. Without prior phase one trials, there would be no basis for developing safe dosage levels in phase two and three studies. Therefore, one can argue for conducting phase one trials in healthy subjects is justifiable on this strong utilitarian reasoning.

Some phase one studies have been conducted in which the benefits to society are questionable, however. During the 1960s and early 1970s, researchers tested cosmetic products and chemical warfare agents on prisoners (Hornblum 1998). These experiments, which violated the Nuremburg Code (1949) and the Declaration of Helsinki (World Medical Association 1964, and the many revisions) are now widely regarded as unethical. However, they did not violate United States laws at the time they were conducted because the National Research Act, which served as the legal basis for federal regulations on research on human subjects, was not passed until 1974 (Shamoo and Resnik 2003). More recently, pesticide companies have conducted phase one studies to determine how human beings respond to exposure to chemicals used to kill insects, such as aldicarb and dichlorvos. Some have argued that these experiments were unethical because they only benefited the companies and did not benefit society (Environmental Working Group 1998). The companies planned to use the data from the experiments to convince the Environmental Protection Agency to increase the allowable human exposure for these chemicals. The National Research Council has recently issued a report, which claims that pesticide studies can benefit society because they can provide information about the effects of pesticides on human beings, which can be used to promote human health and regulate pesticides (NRC 2004). We will not render an opinion on testing pesticides on human subjects in this article, but we will emphasize that key point that these experiments, to be considered ethical, must provide some worthwhile social benefit and minimize risks to subjects (see Resnik and Portier 2005).

What about the second way of ensuring that the risks of phase one studies are reasonable in relation to benefits? Do phase one studies minimize risks to subjects? Before we can answer these questions, we must answer a prior question: what are the risks of phase one studies? As we have already seen, there are *a priori* reasons to believe that phase one studies expose subjects to very high risks in research because they are designed to induce toxicity. Although there is some anecdotal evidence that phase one trials are dangerous, including three cases that have received a great deal of public scrutiny, there is very little empirical evidence concerning the risks of participating in phase one studies for healthy adult subjects. The available data pertain to phase one trials on cancer patients (Agrawal and Emanuel 2003) or vaccine trials on children (Grady 2004). Some studies have placed the mortality rate due to toxicity at 0.5% for phase one trials on cancer patients (Agrawal and Emanuel 2003). Even though there are no mortality data pertaining to healthy adults in phase one trials, one might argue that healthy adults probably have a lower mortality rate than cancer patients because they are healthier than cancer patients and can therefore better withstand the toxic effects of drugs. Although this conclusion seems reasonable, the research community still needs some solid data concerning the safety of healthy subjects.

One factor that makes it difficult to assess the safety of phase one studies on healthy subjects is that there is there is a great deal of variation in the definition and interpretation of adverse events (AEs) in clinical trials. Reporting of AEs plays a crucial role in protecting human subjects from harm because organizations that oversee research can use this information to decide whether to modify or stop clinical trials. Investigators are required to report such events to IRBs and research sponsors, who are required to report AEs to DSMBs and federal oversight agencies, such as the FDA and National Institutes of Health (Amdur and Bankert

2002). Although most investigators recognize that there is a duty to report AEs, they have some discretion in deciding whether to classify an event as an AE. The FDA defines on AE as “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment” (FDA 1995). The Common Rule requires the reporting of “unanticipated problems involving risks to subjects or others” (45 C.F.R. 46.103(b)(5)). Both of these definitions leave investigators considerable latitude in deciding whether and what to report. As a result, the same event might be treated as an AE by one investigator but not by another, depending on the investigator’s attitudes toward subject safety and research compliance. Clearly, the research community needs to do a better job of defining, recognizing, and reporting adverse events, but we will not comment any more about this topic here (see Califf et al. 2003; Liauw and O’ Day 2003; Shamoo 2001).

Even if AEs were carefully and uniformly reported, the data from AEs would address only the short-term risks of participating in a phase one study, not the long-term risks. We know of no long-term studies on the health of volunteers in phase one trials. Long-term studies, such as phase three or four studies, tend to focus on the health of subjects who are taking a drug for many years. What happens to healthy volunteers after a phase one study ends? Do these subjects have a higher risk of developing cancer, heart disease, liver disease, or a neurologic disorder? These are important questions to answer, especially because the subjects receive toxic dosages of drugs. Toxic exposure to a chemical, even for a relatively short time, such as a few days, could produce genetic, molecular, chromosomal or cellular changes that lead to disease, disability or death. To protect healthy subjects from harm and inform them about the risks of participation in phase one trials, the research community needs to answer these questions.

If we set aside for the moment these questions concerning the risks of participating in phase one studies, we can focus on different ways of minimizing risks. One of the most important ways of protecting patients from risks is to develop careful inclusion and exclusion criteria (Amdur and Bankert 2002). These criteria should help to make sure that the study will answer the relevant medical questions and protect subjects from harm. Researchers can use these criteria in deciding whether a subject is qualified to enroll in a study. To enroll in a phase one study on healthy subjects, subject must be, obviously, healthy. Unhealthy and pregnant subjects should be excluded from these studies. To apply this principle, researchers should conduct a thorough physiologic exam on the subject, learn about the subject’s medical history, and find out whether the subject has participated or is participating in any other phase one studies. Subjects should also give their bodies a chance to recover before enrolling in different phase one studies. We recommend that subjects have a minimum “washout” period of 30 days between participating in different studies. We recognize, however, that 30 days is a somewhat arbitrary number and that researchers need to gather more data relating to this recovery period. In some cases, a longer interval may be required, depending on how the human body responds to the drug. It is likely that some subjects will lie about their participation in phase one studies in order to earn money. To deal with this problem and ensure compliance with these requirements, the research community should keep a database for phase one trials. The database will allow researchers to know whether a subject has participated in a phase one study within the last 30 days. The database could also help researchers record data related to the safety of phase one studies.

Data monitoring also plays an important role in minimizing risk. Researchers, IRBs, DSMBs, research sponsors, and oversight agencies can each play a distinct role in data monitoring. Researchers play the most important role in monitoring data because they have the most direct knowledge of the subject’s medical condition. A researcher may decide to withdraw a subject from a study to protect the subject from harm. IRBs also play a very

important role in data monitoring because they can require researchers to modify or stop studies to protect subjects from harm or they can require researchers to inform patients about risks that arise during a study that were not disclosed during the original consent process (Califf et al. 2003).

DSMBs take a more expansive and long-term view of subject safety. DSMBs analyze the data from clinical trials to understand whether these trials have statistically significant risks. A DSMB can recommend modifying or stopping a trial to promote safety and minimize risks (Slutsky and Lavery 2004). Because DSMBs usually do not make any recommendations until a study had enough participants to draw statistically significant conclusions from the data, they offer little protection to the initial participants in a phase one study. To deal with this potential blind spot, we recommend that that phase one studies report data to a subcommittee of the DSMB consisting toxicologists and clinicians, who could follow the initial data in the study and could make recommendations relating to clinically significant risks before the DSMB takes action. This committee could offer valuable insight concerning subject safety because a risk might be regarded as clinically significant before it is determined to be statistically significant. For example, suppose that the first three subjects in a phase one studied all have breathing difficulties when taking a new drug. Three patients do provide not enough data to draw any statistically significant findings, but they might provide enough evidence for researchers to take actions, such as closer monitoring of respiration, blood oxygen levels, and dyspnea (shortness of breath), to protect the next 22 patients from harm.

Research design also plays an important role in promoting safety (Amdur and Bankert 2002; Levine 1988). There are many different types of design problems that can have an adverse impact on subject safety, such as unsafe procedures and tests, lack of adequate statistical power, insufficient animal studies, and poorly chosen measurements or endpoints. Negligent research design had a direct impact on Ellen Roche's death. Roche died from inhaling hexamethonium as part of a study on lung function in asthma patients and healthy patients. She, as well as several other volunteers, developed a persistent cough after inhaling hexamethonium. Studies conducted in the 1950s and 1960s showed that the hexamethonium can cause fatal lung inflammation. Neither the researchers nor the IRB knew about these studies when deciding to go forward with the fatal experiment because they did not review this older part of the literature. A thorough literature review would have indicated that asking subjects to inhale hexamethonium would be too dangerous (Steinbrook 2002b).

INFORMED CONSENT

If researchers have taken adequate measures to minimize risks to subjects, then this should help to ensure that the risks of a phase one study on healthy volunteers are reasonable in relation to the benefits. Would this be enough to justify type of a phase one study? Clearly not. In addition to addressing risks and benefits, ethical and legal standards for human research also require that informed consent will be sought and appropriately documented; privacy and confidentiality will be protected; and subject selection will be equitable (45 C.F.R. 46.111; Emanuel et al. 2000).

Informed consent is an important concern in any experiment on a human subject. Informed consent in research respects the subject's autonomous decision making and treats the subject as a person (National Commission 1979). Researchers who do not obtain adequate informed consent from subjects (or their representatives) also face civil liability (Morin 1998). Federal statutes specify the types of information that researchers must disclose to subjects. Subjects should be informed about the nature, purpose, and duration of the research; experimental procedures and tests; reasonably foreseeable risks and discomfort; potential benefits;

alternatives to participation; the extent to which confidentiality will be protected; one's ability to withdraw at any time without penalty or loss of benefits; whom to contact with questions; and, for more than minimal risk research, whether there will be any treatment or compensation for injury, if one occurs (45 C.F.R. 46.116).

Healthy subjects in phase one studies should receive the information that all research subjects are required to receive as well as information about the dose-escalation methodology. The subjects should understand that one of the aims of the study is to produce drug toxicity, which can cause pain or discomfort and pose significant medical risks (Brody 1998). Subjects should also understand that they will receive no direct medical benefits from their participation, although the study may benefit other people by helping researchers to evaluate the safety of the drug.[5] Another important concern that needs to be addressed is the fact that some potential researcher subjects may have psychiatric disorders, such as depression or schizophrenia. Researchers conducting phase one trials should assess the decision-making capacity of potential subjects and exclude subjects who are not able to provide effective informed consent due to decisional impairment.

UNDUE INFLUENCE

Some commentators have expressed the concern that financial compensation for research participation can undermine the subject's freedom of choice. According to some, money can be a coercive element, especially for people who are poor (FDA 1998; Macklin 1981). The lure of money, although very powerful, is not the same as coercion, which involves a threat to harm someone's interests (Grady 2001; Wilkinson and Moore 1997). An offer to participate in research would be coercive only if the alternative to participation would be a fine or some other punishment. Others are concerned that money could constitute an undue influence or inducement (Macklin 1981). According to this argument, an offer of money could constitute undue influence if it causes someone to act against his or her better judgment and takes risks that he or she otherwise would not take. Money can distort or bias judgment (Macklin 1981). If phase one studies on healthy volunteers did not pay subjects for their participation, then no one would participate. Therefore, the argument is that the offer of money distorts judgment and interferes with the subjects' ability to make a free choice.

There are some problems with this argument. The fact that people will not perform a task unless they are paid a considerable amount of money to do it is only proof that money influences judgment, not that it is an undue influence. Most people will not collect garbage, wait tables, change bedpans, pick fruit, work in coal mines, or teach kindergarten, unless they receive some financial or other reward for performing these tasks. Most people, even people with jobs that require considerable expertise, want to be compensated for their work. The argument that money causes people to participate in research who otherwise would not participate is only an argument that the offer of money succeeds in influencing their behavior.[6] What would make the influential power of money an undue influence?

The "undue influence" argument claims that money can bias or distort judgment. What could this possibly mean? We should not confuse distorted judgment with mere influence. The fact that people respond to money is not proof that money distorts their judgment. For judgment to be distorted, money must somehow have an affect on how people carry out various processes that require judgment, such as understanding facts, assessing arguments, responding to norms, or interpreting and weighing evidence. Can money have this effect?

[5]Because the subjects in these studies are healthy, not sick, they are less likely to succumb to the therapeutic misconception. See op cit, note 4.

[6]A recent study by Bentley and Thacker (2004) shows that money can influence the decision to participate in research but that it does not blind subjects to high risks.

Can people be so overcome by the influence of money that they cannot perform these cognitive tasks? If money really can distort judgment, then almost all of our economic transactions are irrational because money is involved in all of these transactions and therefore, according to this view, distorts them. Thus, if someone asks you to take a job that offers you much more money than your current job but has some drawbacks, such as living in a town with high crime and pollution, you cannot think clearly about this decision because money distorts your judgment. You cannot make a free choice. We think this is an untenable position. If money had this type of effect on people, then almost all of our economic decisions result from undue influence, not free choice.

However, we do think that money can distort judgment—and therefore constitute an undue influence—in some situations. Consider the case of the hurricane victims who need some clearing some fallen trees from their yard. A tree removal company offers to remove their trees for an extremely high price that would constitute price gouging. The victims might decide to accept this offer, despite the high cost, because they have no reasonable alternatives given their dire circumstances. We would consider this to be a paradigm case of undue influence. The hurricane victims' judgment is distorted because they do not have another reasonable alternatives. The company is taking unfair advantage of the hurricane victims' bad fortune (Wertheimer 1996). Could a similar situation occur in clinical research? We believe that it could. Vulnerable subjects, who have a diminished capacity to give consent, are particularly susceptible to undue influence. Monetary (as well as non-monetary) offers to participate in research could have an undue influence on someone who is vulnerable as a result of his or her disease or social or economic circumstances. Researchers should take extra measures to protect vulnerable subjects (Macklin 2003).

For example, if a subject has no reasonable alternatives for earning money besides participating in a phase one trial, then the offer of money could be considered an undue financial influence. If the subject enrolled under these circumstances, then the researchers would be taking advantage of the subjects' economic vulnerability (Macklin 2003). Additionally, if a subject has no reasonable alternative for receiving an effective treatment, then the offer to participate in a phase one trial, which has some potential medical benefit for the subject, may be considered an undue non-financial influence. A patient who is dying from cancer may have no reasonable alternative but to participate in a clinical trial. Whether an offer of money (or treatment) should be considered to be an undue influence depends on the circumstances of the person receiving the offer.

For most phase one trials in the developed world, undue financial influence will not be a significant concern because most participants have other ways of earning money besides participating in phase one studies. Undue financial influence may be a significant problem, however, when the study is expected to include subjects who lack economic power, such as prisoners and very poor people living in developed or developing countries. The federal regulations concerning research on prisoners already prohibit them from participating as healthy volunteers in phase one studies because these studies do not fit into the four types of research permitted on prisoners (see 45 CFR 46.306). To protect subjects who live in the developing countries from undue influence, we recommend that researchers from developed nations should be allowed to conduct phase one studies on healthy subjects in a developing nation only if: 1) researchers do not offer money to the subjects (but they may offer non-monetary benefits such as health care or education); 2) the drug being tested will help treat or prevent an important disease in that nation; 3) there are plans to share the benefits of drug development with people from the developing nations; and 4) researchers have consulted with and obtained approval from local leaders concerning plans to test and develop the drug (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries 2004; Shamoo 2005). We think it is especially important to prevent

pharmaceutical companies from using people in developing countries as cheap labor to test drugs that will only be used in the developed world, because this would constitute an egregious form of exploitation, a topic to which we now turn.

What about protecting economically vulnerable subjects in the developed world from undue influence? This poses a difficult dilemma for researchers. One way to protect economically vulnerable subjects from undue influence would be to exclude subjects from participating in phase one trials who have no other reasonable way of earning money. One could exclude subjects based on characteristic related to economic vulnerability, such as education, employment, or income. There are some serious problems with this approach, however. Excluding economically vulnerable subjects from participating in phase one studies could skew the population in the study, which could bias the study results and lead to an inequitable selection of subjects. Furthermore, this strategy would encourage subjects to lie about their economic circumstances in order to participate in the study and earn money. Moreover, excluding economically vulnerable subjects is denying the subjects the right to participate if they wish to do so. We should not equate economic vulnerability with lack of sound judgment.

Another strategy for protecting economically vulnerable subjects would be to establish a very low wage for research participation (i.e., a wage that is so low that it would not distort the judgment of participants who may be economically vulnerable). There are problems with this approach as well. First, researchers will have difficulty recruiting subjects if they offer a very low wage. Second, offering subjects a low wage could lead to exploitation, a problem that we now consider.

EXPLOITATION

What usually matters most when it comes to offering subjects money is not coercion or undue influence, but exploitation. Exploitation has been a major concern in several recent controversies in research ethics, especially for research conducted in the developing world (Macklin 2003; Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries 2004; Resnik 2003; Shamoo 2005). Several commentators have expressed the concern that pharmaceutical companies may exploit poor, uneducated subjects in phase one studies (Emanuel 2004; Lemmens and Elliott 1999; Lemmens and Elliott 2001; McNeill 1997). Phase one studies on healthy subjects, according to this criticism, take advantage of cheap labor.

To evaluate this critique, it is important to say a few words about exploitation. Exploitation involves taking advantage of someone unfairly. The exploiter gains something from the transaction or relationship with the exploitee. Exploitative relationships or transactions always involve at least one of the following elements: 1) harm to the exploitee; 2) defective consent from the exploitee; or 3) an unfair or inequitable distribution of benefits. For example, slavery is a form of exploitation that involves all three elements: slavery is harmful to slaves; slaves do not consent to slavery; and slave-owners benefit far more from slavery than slaves. Some forms of exploitation may involve only one element: for example, a business that seeks to protect itself from legal liability by putting exculpatory language into the fine print in its contracts may exploit its customers by the use of deception. Exploitation, like other moral concepts, comes in degrees: some relationships or transactions, such as slavery, are highly exploitative whereas others, such as writing contracts with fine print, are minimally exploitative (Resnik 2003; Wertheimer 1996).

Most people will agree that relationships or transactions that involve harm or problems with consent are exploitative. But what about relationships or transactions in which neither party is harmed and there are no problems with consent? These situations are what Wertheimer

calls “mutually advantageous” exploitation (1996, 14–15). In these situations, exploitation occurs because the relationship or transaction is unfair or inequitable to one of the parties. Consider sweatshops in developing nations. A company decides to move its textile factory to developing nation to take advantage of cheap labor and lax regulations. Although the workers and employer both benefit from this relationship, one might argue that the employer exploits the workers because he does not share the benefits of this relationship with the workers fairly. He reaps enormous profits from his low labor costs.

A similar situation could occur in phase one trials. Like the sweatshop owner, a research sponsor could take advantage of cheap labor by recruiting subjects who are willing to work for a low wage. The sponsor would be exploiting the subjects by paying them less money than they deserve. How does one determine whether subjects are being underpaid and, therefore, exploited? There are several different approaches to the question: the market model, the wage model, and the reimbursement model (Dickert and Grady 1999). According to the market-based approach, the value of the labor is whatever the companies will pay. It does not matter whether companies offer subjects $5.00 per hour or $500 per hour. Most laborers in the United States are paid according to the market model. Doctors, lawyers, school teachers, mechanics, engineers, musicians, artists, and athletes earn what their employers will pay. Many different writers have criticized the market approach. As we noted previously, the major concern expressed by most researchers is that companies might offer subjects too much money, which could lead to undue influence. However, we have argued that this is usually not a problem in research. On the contrary, the main problem with the market approach is that the drug companies might offer subjects too little money. Although some small degree of exploitation is almost impossible to avoid in research, researchers have an ethical duty to minimize exploitation of subjects, and this duty implies an obligation to pay subjects fairly (Resnik 2003).

The wage model provides a method for ensuring that subjects do not earn too much or too little money. According to this approach, subjects should be paid a wage equivalent to the wage paid to unskilled laborers. The rate of payment for this work would be about $10.00 per hour, with a higher payment for tasks or procedures that are particularly demanding or uncomfortable (Dickert and Grady 1999). The wage payment model can avoid the problem of undue influence by ensuring that subjects are paid only as much as other people working in unskilled jobs. If a person can choose between working on a construction site or participating in a phase one study and the two jobs pay almost the same amount, then money should not have a significant influence on that person’s decision.

The wage model minimizes the potential for exploitation by ensuring that subjects are paid no less than the wage earned by unskilled laborers. However, the wage payment model may not avoid the problem of exploitation in research if it sets wages for research subjects at a level well below the market rate. Suppose, for example, that the wage is set at $10.00 per hour but that companies would be willing to pay $20.00 an hour. In that case, companies would be keeping money that they would otherwise share with research subjects. The companies could take advantage of labor that is available at a price far below the market price. Indeed, if the research community took steps to restrict wages for research subjects, they could incur legal liability under anti-trust laws, which forbid restraints on trade (Hovenkamp 1999). Limiting the amount of money that a worker can receive for labor inhibits that worker’s ability to earn a living and participate in the free market. To address these issues, the wage model should not place any upper limits on wages: it should establish a minimum wage but no maximum wage.

A third approach to payments to research subjects, the reimbursement model, treats research participation as a type of altruistic behavior that should be shielded from economic motives

and forces. According to this model, subjects should not earn extra money for participating in research, but should only be compensated for their lost wages, travel, and other expenses. This model appeals to people who are concerned about treating research subjects as commodities and do not want subjects to be motivated by money (Dickert and Grady 1999). Although the reimbursement model may apply to some contexts, such as pediatric research or research on very ill patients, it clearly does not apply to participation in phase one trials on healthy subjects. Most healthy subjects participate in phase one studies to earn money (Lemmens and Elliott 1999; Kass, personal communication). Thus, they should be paid a fair wage for their participation. If subjects are only reimbursed for their time, effort, and expenses, it is possible that subjects with low-paying jobs would receive a very low payment, whereas subjects with high-paying jobs would receive a high payment. This model could create situations that would be patently unfair because two different subjects could receive different payments for the same type of work. The model could also lead to lead to exploitation if poor subjects are paid very little money for their participation.

FREE WAGE MODEL

We believe that the approach to paying healthy subjects in phase one that best avoids exploitation is a modified wage approach. We call this the *free wage model*. Subjects should be guaranteed a minimum wage equivalent to the wage paid to unskilled laborers, but there should be no upper limits on payments to subjects. If companies are willing to pay subjects more than the minimum wage, then they should be able to do so. This will help to ensure that subjects receive a fair share of the benefits of research. The corporation should not be the only one reaping the benefit from subjects' willingness to take risks for public good. Fortunately, this is in part the practice of private phase one units as evidenced from the advertisements for subjects in urban tabloids (Baltimore City Paper 2005). However, this does not always occur in research. It is time to codify the free wage model so that researchers will practice what they often preach. We live in a society in which people are compensated for taking risks. There is no fundamental ethical justification for the current prohibition on open-ended compensation for healthy volunteers in phase one trials. One can argue that restricting payment to healthy volunteers in phase one trials is exploitative. In our society wages are mostly governed by the law of supply and demand, with some limits in particular situations. Justice demands that all workers, including healthy participants in phase one studies, receive fair compensation for their labor.

Besides paying subjects a fair wage, what other measures need to be taken to minimize exploitation? In the last century, societies have implemented many different measures to protect the rights and welfare of workers. We believe that some of these measures also apply to the human research setting and can help minimize exploitation. These include: worker's compensation, disability, occupational safety, collective bargaining, a minimum wage (Anderson and Weijer 2002; Lemmens and Elliott 1999), and health care coverage for the study related procedures. Two of these measures—a minimum wage and occupational safety —we have discussed earlier when we discussed payment and safety/risk minimization issues. We shall now consider the other three.

Most people who work for government or private industry can receive compensation for injuries incurred on the job. Workers compensation programs pay for medical and living expenses needed to rehabilitate the injured employee. If the employee develops a chronic, medical problem, workers compensation programs will also help defray the employee's expenses. If the employee becomes disabled, disability programs provide the employee with a source of income. In the United States, employers are required by law to provide workers compensation and disability programs for their employees. Most fulfill these obligations by paying money into an insurance pool.

We believe that healthy subjects in phase one studies, like all workers, should receive compensation for injury or disability. Some research sponsors and institutions have adopted policies offering subjects compensation for research-related injuries (Scott 2003). Although many commentators have argued that justice and fairness require that research subjects should be compensated for injury (Capron 2004; National Bioethics Advisory Commission 2001; Scott 2003), the federal regulations do not require research sponsors to adopt such policies. The Common Rule only states that subjects in research that involves more than minimal risk should be informed about any plans to compensate them for injuries, but it does not say that research studies must include such plans (45 CFR 46.116(a)(6); 21 CFR 50.25(a)(6)).

To minimize exploitation in phase one studies on healthy subjects, compensation for research-related injuries should not be optional in these studies: it should be mandatory. The United States research regulations should require that phase one studies of new drugs, biologics, or medical devices, which are conducted on healthy subjects, should have plans for compensating subjects for research-related injuries. The IRB should have the authority to approve or disapprove of these plans. Compensation for research-related injury programs should be funded in the same way that workers compensation programs are funded: employers (research sponsors) should pay money into an insurance pool, which would provide coverage for their employees (research subjects). Like other workers compensation programs, the program should be no-fault and would be administered by a separate agency. Compensation would be granted if the evidence shows that the injury was caused by research participation. If subjects are not satisfied with the outcome of the research compensation system, they would still have the optional of addressing their concerns through the legal system (Scott 2003). However, subjects would be required to submit their claims to the compensation system before pursuing a lawsuit.

Finally, research subjects should be able to use collective bargaining to promote their rights and welfare. Workers in many different industries have formed unions to negotiate with companies for higher benefits and better working conditions. Unions help to empower workers and control companies. Although many different government agencies are charged with protecting the rights and welfare of research subjects, we know of no union that serves this function. In the United States, there are some laws that restrict union activities, but we are not aware of any laws that specifically prohibit research subjects from forming a union.

CONCLUSION

In this article, we have examined some of the ethical and safety issues related to using healthy adults in phase one trials. Phase one studies play a crucial part in the development or new drugs, biologics, and medical devices, and we believe that such studies should continue to take place. However, these studies also raise serious ethical and safety concerns, which the research community needs to address. In this article we have discussed some proposals and recommendations for protecting the rights and welfare of healthy adult subjects in phase one studies. In addition to the safeguards accorded to clinical trials in general, we recommend additional safeguard specific to phase one trials. These are: 1) Because phase one trials are short in duration (usually 1 to 3 months), researchers should gather more data on the short-term and long-term risks of participation in phase one studies by healthy subjects; 2) researchers should develop strict inclusion/exclusion criteria that exclude unhealthy or vulnerable subjects, such as decisionally impaired people, in phase one studies; 3) subjects should not participate in more than one phase one study at the same time and should wait at least 30 days between participating in different studies; 4) researchers should develop a database of phase one participants; 5) subjects should be guaranteed a minimum wage equivalent to the equivalent type of unskilled labor, but there should be no upper limits

on wages; and 6) subjects should be allowed to engage in collective bargaining with research sponsors.

Acknowledgments

This research is supported in part (to David B. Resnik) by the intramural research program of the National Institute of Environmental Health Sciences, National Institutes of Health. This paper was also supported in part (to Adil E. Shamoo) by a grant from Fogarty International Center/NIH 1R25TW007090-01.

References

Ackerman TF. The ethics of phase I pediatric oncology trials. IRB. 1995; 17(1):1–5. [PubMed: 11653060]

Agrawal M, Emanuel E. Ethics of phase 1 oncology studies: reexamining the arguments and data. Journal of the American Medical Association. 2003; 290:1075–1082. [PubMed: 12941681]

Amdur, R.; Bankert, E. Institutional review board: Management and function. Boston, MA: Jones and Bartlett; 2002.

Anderson J, Weijer C. The research subject as wage earner. Theoretical Medicine and Bioethics. 2002; 23:359–376. [PubMed: 12516838]

Angell, M. The truth about drug companies. New York, NY: Random House; 2004.

Baltimore City Paper. 2005 Mar 16. p. 102-107.

Bentley J, Thacker P. The influence of risk and monetary payment on the research participation decision making process. Journal of Medical Ethics. 2004; 30:293–298. [PubMed: 15173366]

Brody, B. The ethics of biomedical research. New York, NY: Oxford University Press; 1998.

Califf R, Morse M, Wittes J, Goodman S, Nelson D, DeMets D, Iafrate R, Sugarman J. Toward protecting the safety of participants in clinical trials. Controlled Clinical Trials. 2003; 24:256–271. [PubMed: 12757992]

Capron A. When experiments go wrong: The U.S. perspective. Journal of Clinical Ethics. 2004; 15:22–29. [PubMed: 15202353]

Daugherty C, Ratain M, Grochowski E, Stocking C, Kodish E, Mick R, Siegler M. Perceptions of cancer patients and their physicians involved in Phase I trials. Journal of Clinical Oncology. 1995; 13:1062–1072. [PubMed: 7738612]

Daugherty C. Impact of therapeutic research on informed consent and the ethics of clinical trials: A medical oncology perspective. Journal of Clinical Oncology. 1999; 17:1601–1617. [PubMed: 10334550]

Dickert N, Emanuel E, Grady C. Paying research subjects: an analysis of current policies. Annals of Internal Medicine. 2002; 136:368–373. [PubMed: 11874309]

Dickert N, Grady C. What's the price of a research subject? Approaches to payment for research participation? New England Journal of Medicine. 1999; 341:198–203. [PubMed: 10403861]

Emanuel E. Ending concerns about undue inducement. Journal of Law, Medicine and Ethics. 2004; 32:100–105.

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? Journal of the American Medical Association. 2000; 283:2701–2711. [PubMed: 10819955]

Environmental Working Group. [Accessed September 9, 2004] The English patients. 1998. Available online at: http://www.ewg.org/reports/english/englishpr.html

FDA. [Accessed September 9, 2004] Clinical date safety management: Definitions and standards for expedited reporting. 1995. Available online at: http://www.fda.gov/cder/guidance/iche2a.pdf

FDA. [Accessed September 8, 2004] Guidance for institutional review boards and clinical investigators. 1998 update. 1998. Available online at: http://www.fda.gov/oc/ohrt/irbs/toc4.html#payment

FDA. [Accessed September 7, 2004] Drug applications. 2004. Available online at: http://www.fda.gov/cder/regulatory/applications/nda.htm#Introduction

Grady C. Money for research participation: Does it jeopardize informed consent? American Journal of Bioethics. 2001; 1(2):40–44. [PubMed: 11951886]

Grady C. Ethics of vaccine research. Nature Immunology. 2004; 5:465–468. [PubMed: 15116109]

Hornblum, R. Acres of skin. 2. New York, NY: Routledge; 1998.

Horng S, Emanuel E, Wilfond B, Rackoff J, Martz K, Grady C. Descriptions of benefits and risks in consent forms in Phase I oncology trials. New England Journal of Medicine. 2002; 347:2134–2140. [PubMed: 12501226]

Hovenkamp, H. Antitrust. 3. St. Paul, MN: West Publishing; 1999.

Kass, N. Personal communication/unpublished data in an e-mail 9/22/04. 2004.

Kopelman L. Children as research subjects: a dilemma. Journal of Medicine and Philosophy. 2000; 25:745–764. [PubMed: 11262635]

Liauw W, O'Day R. Adverse event reporting in clinical trials: room for improvement. Medical Journal of Australia. 2003; 179:426–428. [PubMed: 14558867]

Latterman J, Merz J. How much are subjects paid to participate in research? American Journal of Bioethics. 2001; 1(2):45–46. [PubMed: 11951887]

Lemmens T, Elliott C. Guinea pigs on the payroll: The ethics of paying research subjects. Journal of Accounting Research. 1999; 7:3–20.

Lemmens T, Elliott C. Justice for the professional guinea pig. American Journal of Bioethics. 2001; 1(2):51–53. [PubMed: 11951892]

Levine, R. Ethics and the regulation of clinical research. 2. New Haven, CT: Yale University Press; 1988.

Lipsett M. On the nature and ethics of Phase I clinical trials of cancer chemotherapies. Journal of the American Medical Association. 1982; 248:941–942. [PubMed: 7097961]

Macklin R. Due and undue inducements: On paying money to research subjects. IRB. 1981; 3(5):1–6. [PubMed: 11649367]

Macklin R. Bioethics, vulnerability, and protection. Bioethics. 2003; 17:472–486. [PubMed: 14959716]

Marrow, D. New York Times. 1996 Sep 29. Swallowing bitter pills for pay: trials of human guinea pigs; p. A101996

McNeill P. Paying people to participate in research: Why not? Bioethics. 1997; 11:390–396. [PubMed: 11655118]

Miller M. Phase I cancer trials. A collusion of misunderstanding. Hastings Center Report. 2000; 30(4): 34–43. [PubMed: 10971892]

Morin K. The standard of disclosure in human subject experimentation. Journal of Legal Medicine. 1998; 19:157–221. [PubMed: 9658739]

National Bioethics Advisory Commission. [Accessed September 14, 2004] Ethical and policy issues in research involving human participants. 2001. Available online at: http://www.georgetown.edu/research/nrcbl/nbac/human/oversumm.html

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. [Accessed September 21, 2004] The Belmont report. 1979. Available online at: http://www.fda.gov/oc/ohrt/irbs/belmont.html

Nelson, D.; Weiss, R. The Washington Post. 2000 Jan 31. Gene test death not reported promptly; p. A12000

NIH, Office of Human Subjects Research. [Accessed September 8, 2004] Information on remuneration of research subjects on the intramural research program. 2004. Available online at: http://ohsr.od.nih.gov/info/sheet20.html

NRC. Intentional human dosing studies for EPA regulatory purposes: Scientific and ethical issues. Washington, DC: National Academy Press; 2004. Available at: www.nap.edu [Accessed September 15, 2004]

[Accessed September 9, 2004] Nuremburg Code. 1949. Available online at: http://ohsr.od.nih.gov/guidelines/nuremberg.html

Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Moral standards for research in developing countries: From reasonable availability to fair benefits. Hastings Center Report. 2004; 34(3):17–27.

Phase I Clinical Trials Unit. [Accessed September 9, 2004] About us. 2004. Available at: http://www.phase1ctu.com/textaboutus.html

Resnik D. Exploitation in biomedical research. Theoretical Medicine. 2003; 24:233–259.

Resnik D, Portier C. Pesticide testing on human subjects: Weighing benefits and risks. Environmental Health Perspectives. 2005; 113:813–817. [PubMed: 16002367]

Scott L. Research-related injury: Problems and solutions. Journal of Law, Medicine and Ethics. 2003; 31:419–428.

Shamoo A. Adverse event reporting: The tip of an unknown iceberg. Journal of Accounting Research. 2001; 8:197–218.

Shamoo AE. Debating moral issues in developing countries. Applied Clinical Trials. 2005; 14(6):86–96.

Shamoo, A.; Resnik, D. Responsible conduct of research. New York, NY: Oxford University Press; 2003.

Shamoo, AE.; Strause, L. Monitor. 2004 Spring. Closing the gap in regulations for the protection of human subjects in research. 2004

Slutsky A, Lavery J. Data safety and monitoring boards. New England Journal of Medicine. 2004; 350:1143–1147. [PubMed: 15014189]

Steinbrook R. Protecting research subjects—the crisis at Johns Hopkins. New England Journal of Medicine. 2002a; 346:716–720. [PubMed: 11870258]

Steinbrook R. Improving protection for research subjects. New England Journal of Medicine. 2002b; 346:1425–1430. [PubMed: 11986426]

Tauer C. Central ethical dilemmas in research involving children. Journal of Accounting Research. 2002; 9:127–142.

Wertheimer, A. Exploitation. Princeton, NJ: Princeton University Press; 1996.

Wilkinson M, Moore A. Inducement in research. Bioethics. 1997; 11:373–389. [PubMed: 11655117]

World Medical Association. [Accessed: September 9, 2004] Declaration of Helsinki: Ethical principles for medical research involving human subjects. 1964, 1975, 1983, 1989, 1996, 2000, 2004. Available online at: http://ohsr.od.nih.gov/guidelines/helsinki.html