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Randomized Controlled Trials in Environmental Health Research: Ethical Issues

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Abstract

Background—Randomized controlled trials (RCTs) are becoming increasingly common in environmental health research. Like all studies involving human subjects, environmental health RCTs raise many different ethical issues, ranging from obtaining informed consent, to minimizing risks, to protecting privacy and confidentiality. One of the most important issues raised by these studies is whether it is ethical to withhold effective environmental health interventions from research subjects in order to satisfy scientific objectives. Although environmental health investigators usually do not have professional obligations to provide medical care to research subjects, they have ethical obligations to avoid exploiting them. Withholding interventions from research subjects can be ethical, provided that it does not lead to exploitation of individuals or groups. To avoid exploiting individuals or groups, investigators should ensure that research subjects and study populations receive a fair share of the benefits of research.

Introduction

Randomized controlled trials (RCTs) are becoming increasingly common in environmental health research. The purpose of these experiments is to determine the effectiveness of an environmental health intervention. For example, Kercsmar et al (2006) conducted a study to determine the effectiveness of home remediation at reducing the morbidity of childhood asthma. This prospective, controlled trial involved 62 children with asthma living in homes with indoor mold. All of the families of the children received education and advice about asthma remediation. The subjects were randomly assigned to one of two groups: the remediation group, which also received household repairs designed to reduce the amount of mold in the home, and the control group which only received information on how clean mold from the home. The investigators took blood and urine samples from the children and dust samples from the homes. They analyzed the dust samples for fungi, dust mite, endotoxin, cockroach, and rodent urinary protein, and they analyzed the blood/urine samples for urinary cotine, peripheral blood eosinophil counts, immunoglobulin E, and total and allergen-specific serum. They found the remediation group had a significantly lower rate of asthma exacerbation than the control group.

RCTs are a very useful method in environmental health research but they also raise a variety of ethical issues, ranging from obtaining informed consent, to minimizing risks, to protecting privacy and confidentiality (Resnik et al 2005). One of the most important issues raised by RCTs is whether it is ever ethical to deny medical care to research subjects to satisfy scientific goals. To minimize bias, RCTs randomly assign subjects to an experimental group and one or more control groups. In some RCTs, known as placebo-controlled trials, at least one control

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group receives an inactive substance or placebo, instead of the treatment under investigation. The goal of a placebo-controlled study is to determine whether an intervention is more effective than a placebo. In active-control trials the control group(s) receives a currently accepted intervention and the experimental group receives a new intervention. The goal of an active-control trial is to determine whether the new intervention is more effective than the current one (s). Some trials compare the new treatment to a placebo and an accepted treatment. Because a current intervention is likely to have a significant effect on human health, whereas a placebo probably will not, comparative trials usually require a larger sample size than placebo-controlled studies, because the difference between the new intervention and the current one may not be very large (compared with the difference between the new intervention and a placebo), and the size of the sample needed to detect a statistically significant effect is inversely related to the size of the effect (Emanuel and Miller 2001).

Ethical Controversies

Although many clinical researchers and biostatisticians regard placebo-controlled RCTs as methodologically superior to comparative trials, placebo-controlled RCTs in clinical research are ethically controversial because the subjects in the placebo group may be denied an effective therapy. In some cases, subjects in the placebo group may be denied medical care. Many codes and guidelines state that it is unethical to withhold a proven effective therapy from research subjects with a serious medical condition (Levine 1988). The World Medical Association's Declaration of Helsinki identifies three situations when a placebo-controlled RCT would be ethical: 1) there is no therapy that has been proven effective, 2) when a placebo is needed to test the effectiveness of a currently accepted therapy, or 3) when the subjects in the clinical trial have a minor condition and do not run a risk of serious or irreversible harm if they are denied medical care (World Medical Association 2004). Freedman (1990) argues that the placebo-controlled RCTs are also ethical when the current therapy is a placebo, the current therapy is no more effective than a placebo, or the current therapy is so expensive that few patients can afford it (Freedman 1990).

Environmental health researchers do not conduct placebo-controlled trials, but they often design and implement studies in which subjects receive no intervention beyond education and counseling. In the study by Kercsmar et al (2006) the control group received education and advice about asthma remediation, whereas the experimental group received education, advice and remediation. In some studies, the tables are turned, and the experimental groups receive less than the control groups. Consider, for example, a study of lead abatement that led to a lawsuit against the sponsoring organization, the Kennedy Krieger Institute. The subjects in the experimental groups were families living in homes with lead paint. They received different levels of lead abatement ranging in cost from $1650 to $7000. The study also included two control groups, control group I, which received maximum lead abatement and control group II, which consisted of people living in houses with no lead paint. The goal of the study was to determine whether relatively inexpensive types of lead abatement are as effective as the most expensive types or lead-free housing. The investigators measured lead levels in dust, soil, and water samples collected at the homes and blood samples taken from children living in the homes. Measurements were made prior to the intervention, after the intervention, and at 12 and 24 month intervals (Institute of Medicine 2005).

Avoiding Exploitation

Regardless of whether the subjects are in the control group or the experimental group, the basic issue is the same: is it ethical to provide some research subjects with an effective environmental intervention that other subjects do not receive? This ethical quandary is particularly salient in clinical research, where the subjects are patients with diseases or medical conditions and the

researchers are physicians (or medical staff) with professional obligations to care for their patients (Levine 1988). Clinical investigators who provide their subjects with less than the best available care during a research study could be violating their obligations to promote the health of their patients. While the research subjects in environmental health research often have diseases or medical conditions, such as asthma, they are usually not the investigators' patients, so the investigators do not have professional obligations to promote their health. Even if environmental health researchers do not have a physician-patient relationship with their research subjects, one might argue that they still have an ethical obligation to avoid exploiting their subjects, and that this obligation implies duties to protect their rights and welfare (Morreim 2005, Miller and Brody 2002).

Exploitation in biomedical research involves taking unfair advantage of human subjects (Resnik 2003). Some of the most egregious cases of unethical research, such as the Nazi experiments on concentration camp prisoners and the Tuskegee syphilis study, have involved exploitation. Exploitation involves at least one of three elements: harm, disrespect, or injustice (Wertheimer 1996). For example, in the Tuskegee study, the investigators showed a lack of respect for the subjects by failing to inform them that they were participating in medical research. The subjects never consent to be in an experiment. The investigators harmed the subjects by failing to provide them with an effective treatment for syphilis (penicillin) when it became available in the 1940s (Jones 1993). In the Nazi experiments, the subjects never consented to the procedures they underwent. They also experienced significant pain and suffering, often resulting in mutilation, disability, or death (Proctor 2006).

Exploitation can occur even when subjects are not significantly harmed and they consent to participate in research. Exploitation may happen when subjects do not receive a fair share of the benefits of research (Resnik 2003). To determine what constitutes a fair share, it is necessary to examine each case and consider all of the different benefits that accrue to the different parties involved in research. People who may benefit include: the subjects, the researchers, research sponsors or institutions, and other people with the subjects' disease or condition. A study would exploit the research subjects if all of the parties derive considerable benefits from the research, except the subjects. For example, a Phase I drug trial that pays impoverished, healthy subjects a small wage for taking significant risks and experiencing significant pain and discomfort would be exploitative (Shamoo and Resnik 2006). A Phase II clinical trial of a new diabetes medication that requires the subjects in the control group to receive a placebo would be exploitative, because there are inexpensive, effective treatments available for diabetes and there are serious health consequences of not taking medication for diabetes (Miller and Brody 2002).

Exploitation can also occur when a population (or country) does not receive a fair share of the benefits of research (Resnik 2003). To avoid exploiting a population in research, a research study should provide results that are useful and meaningful to the population being studied. For example, suppose that investigators test a new drug on subjects in developing country and the drug will be so expensive that few people living in the country will have access to the drug when testing is complete. One might argue that this type of research is exploitative because the population does not receive a fair share of the benefits of research (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries 2001). In the last decade, pharmaceutical companies have been conducting clinical trials in developing nations in order to save and research and development costs. Some commentators view this as an ominous trend, due to the potential for exploitation of populations and research subjects (Shah 2006).

Applications

Let us apply this analysis of exploitation to some environmental health studies. Consider the study by Kercsmar et al (2006) once again. Parties who benefited included the research subjects in the experimental group (education, advice, asthma intervention), the control group (education and advice) the investigators (publication, career advancement), the investigators' institutions (publication, prestige), and the research sponsors (publication, prestige, goodwill). Although subjects in the control group did not receive the intervention, they did receive some education and advice. The main reason why the study was conducted was to determine whether a type of asthma remediation technique is effective. The subjects in the experimental group benefited from receiving asthma remediation, education, and advice. The subjects in the control group did not receive the intervention, but they did receive education and advice. Since the there was no proven effective remediation technique prior to the initiation of the study, the subjects in the control group were not denied an intervention that had been proven effective. Thus, even though some of the subjects received less than others, they still received a fair share of the benefits. The population being investigated benefited from knowledge concerning the effectiveness of asthma remediation at preventing asthma exacerbations. So, one might argue that this study neither exploited the research subjects nor the population.

For another (more controversial) example, consider the Kennedy Krieger lead abatement study. Parties who benefited included the subjects in the experimental groups (some form of lead abatement) and the subjects in the control group I (full lead abatement). The researchers benefited from publication and career advancement, the institutions benefited from publication and prestige, and the sponsors benefited from publication as well. One question this study raises is whether not providing the subjects in the experimental groups with full lead abatement constituted exploitation, since effective lead abatement techniques were available when the study began. Although effective lead abatement methods were available, they were very expensive and the subjects would not have been able to afford them. Even the subjects in the group given the least amount of lead abatement received more than they would have received, if they had not participated in the study. Receiving some form of lead abatement was a fair benefit, since they would have no lead abatement without participating in the study (Buchanan and Miller 2006).

The population also benefited from knowledge concerning the efficacy of lead abatement methods that are less expensive that the full amount of lead abatement. Although some have argued that the fairest thing to do would have been to spend money to give the full amount of lead abatement to all of the people who needed it, instead of developing cheaper methods for abating lead (Spriggs 2004), that money was not available at the time that the Kennedy Krieger study was designed and implemented. There was not sufficient political support in the local, state or federal government to pay for all the houses that needed lead abatement to receive it. Money was available to conduct experiments on cheaper forms of lead abatement. Given the economic, social, and political context of the study, developing affordable methods of lead abatement was a fair benefit to the population (Buchanan and Miller 2006).

Conclusion

Like all research involving human subjects, environmental health studies raise many different ethical issues. One of the most important issues is whether it is ethical to withhold effective environmental health interventions from research subjects in order to satisfy scientific goals. Although environmental health investigators usually do not have professional obligations to provide medical care to research subjects, they have ethical obligations to avoid exploiting them. Withholding interventions from research subjects is ethical, provided that it does not lead to exploitation of individuals or groups. To avoid exploiting individuals or groups,

investigators should ensure that research subjects and study populations receive a fair share of the benefits of research.

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