

Clinical research: Protection of the “vulnerable”?

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In this age of evidence-based medicine, clinical research is critical for developing new therapeutics and determining the best way to use these therapies. To perform appropriate clinical research, researchers must adhere to ethical standards. These standards have developed in large part as a response to egregious violations of ethically appropriate behavior. In this respect certain populations have been identified as at risk of being treated inappropriately in medical research. Current ethical guidelines prohibit or severely limit what types of research can be performed involving these “vulnerable” populations. Although this might protect these populations, the lack of research on them might actually do harm in limiting their access to life-saving therapies. We explore the historical underpinnings of protecting the vulnerable populations and whether a newer ethical paradigm that would allow for protected research on these populations should be adopted by society. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Ethics, Informed consent, children, clinical research

In this era of evidence-based medicine, clinical research on human subjects has become critical for the advancement of new diagnostics and therapeutics in medicine. With the expansion of clinical research has come an understanding that certain ethical standards must be upheld when studying human populations. In many ways these standards have arisen from the Hippocratic Oath directive to “first do no harm.” However, history is littered with accounts of researchers straying from this doctrine and placing subjects directly in harm’s way without offering them any appreciable benefit. Throughout the last century, guidelines of medical ethics were developed to protect subjects involved in research. One of the concepts to emerge from these guidelines has been that certain populations are at a much greater risk of exploitation or misuse. Such “vulnerable” populations as children and prisoners have been given specific protections. Although concern for protecting these vulnerable populations is clearly necessary and important, it also has negative side effects. Most notably, by protecting vulnerable populations, we might have stifled adequate research involving these very subjects. In this

Abbreviation used

IRB: Institutional review board

article we will challenge the current definition of what composes a vulnerable population and discuss how to balance the need for protection of these individuals with the need for research involving them to generate evidence-based data for their own (and society’s) medical benefit.

RELEVANCE TO ALLERGY AND IMMUNOLOGY

As allergists and immunologists, the following question might arise: Why should we care about the ethics of clinical research? Allergy-immunology, like all medical fields, is moving away from anecdotal-based practice and into the age of evidence-based medicine. Practice guidelines, like the recent National Asthma Education and Prevention Project Expert Panel Report (National Asthma Education and Prevention Project Report 3), are being developed based on the results of randomized, double-blind, placebo-controlled trials, and an ethics committee or institutional review board (IRB) must now approve these trials.¹ Thus data presented from every trial we read has been influenced by review of an IRB. It is important to understand the ethical principles upheld by these organizations and to decide whether these principles are achieving their stated goals. Finally, as physicians, we continuously strive to increase medical knowledge, whether through performing medical research or providing advice to patients considering participation in clinical trials. Therefore it is important for us to understand the ethical implications of committing patients and ourselves to these studies.² Such consideration is of utmost importance to maintaining the integrity of our profession.

WHY PROTECT THE VULNERABLE?

In today’s medical ethics dialogue, vulnerable populations are those that are at risk of being misused in the course of medical research, either by coercion or a lack of knowledge or understanding (or ability to obtain and understand that knowledge). Those generally accepted as being vulnerable include children, prisoners, pregnant women, fetuses, mentally disabled persons, and economically or educationally disadvantaged individuals.^{3,4} The need to identify this population arose out of historical examples in which subjects were exploited for the purpose of medical experimentation. Before World War II and the evidence-based medicine era, clinical research was an informal part of medical practice. There were neither organized clinical trials nor research guidelines; physicians simply experimented with potential therapies on individual patients from their own practices. New medical information was thus anecdotal and based in large part on case

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reports. Participants of such “studies” were frequently unaware that the treatments suggested by their physician were in essence experimental.

This all changed after World War II, when the cruel and inhumane experiments performed by Nazis on unknowing Jewish prisoners were exposed during the Nuremberg trials. From these revelations arose a 10-point document, entitled the Nuremberg Code, which provided criteria that had to be fulfilled before human experimentation could proceed.⁵ Although the Nuremberg Code was developed as a means to deal with Nazi atrocities, it paved the way for the subsequent Declaration of Helsinki by the World Medical Organization. This document is an internationally accepted guide for the conduct of ethical medical research and, as such, continues to undergo revisions (now in its eighth such revision).

Of course, the Nazi atrocities were not the first time medical research subjects were inappropriately treated. One of the most notorious American examples is the Tuskegee syphilis experiment of the 1930s, in which over 600 black men were recruited under false pretenses and misinformed about procedures performed as part of the study. Probably most disturbing was the fact that information regarding potential treatment (the advent of penicillin therapy) was actively withheld from the “participants.” It was clear within a few years of the study’s initiation that the untreated group had more severe disease, yet the trial continued until the national press exposed such results in the 1970s, 40 years later.^{6,7} It should be of no surprise then, that the Belmont Report, written in response to the Tuskegee experiment, included such principles as respect, beneficence, and justice. It is also the Belmont Report that was the first ethical treatise to describe a vulnerable population and included “racial minorities, the economically disadvantaged, the very sick, and the institutionalized” as members of this group. Their vulnerability was based on the subjects’ “dependent status and their frequently compromised capacity for free consent.” The Belmont Report supported the protection of these populations from “the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.”³ It seems clear that the first documented description of the “protection of the vulnerable” as presented in the Belmont Report was in direct response to the exploitation of the African American subjects in the Tuskegee syphilis study.

In addition to the Tuskegee experiment, many other historical examples exist in which vulnerable subjects in medical research were improperly treated. For example, elderly patients were injected with live cancer cells without their consent or even knowledge during a study on the effect of transplant rejection performed at Brooklyn’s Jewish Chronic Disease Hospital in the 1960s.⁴ Mentally ill children, too, have fallen victim to unethical research. Children at the Willowbrook State Hospital in New York City, an institution for the mentally ill, were deliberately infected with hepatitis A virus to investigate its natural history and response to gamma globulin therapy. Parents had provided consent for the child’s participation in the study, but it was later revealed that the study investigators coerced this consent by limiting hospital admission to those who were willing to participate.⁸

History has proved that vulnerable populations, the imprisoned, economically or socially disadvantaged, or institutionalized, have been exploited for the sake of medical research. Clearly, investigators must recognize vulnerability and make every effort to protect those who are vulnerable or even

potentially vulnerable. The Nuremberg Code, the Declaration of Helsinki, and the Belmont Report are reminders of past ethical violations and help guide current ethical standards by establishing a constitution of medical ethics. Part of that constitution is the concept of protection of the vulnerable. Despite arising from the best of intentions and from an obvious historical need, the concept of protecting the vulnerable has created a situation that could be viewed as potentially harming those individuals it originally sought to protect. This is because the current notion of protecting the vulnerable has become almost synonymous with exclusion of these populations from clinical research, which in many ways enhances their vulnerability. We must therefore seriously consider the following: Do our current measures accomplish the goal of protecting vulnerable populations? Is our definition of “vulnerable” appropriate? Are we recognizing the truly vulnerable populations?

THE ROLE OF INFORMED CONSENT AND THE IRB

Vulnerability has been defined in current ethical dogma largely based on the lack of ability to provide informed consent. Thus some discussion of informed consent is integral to understanding the notion of protecting the vulnerable.

The most recent revision of the Declaration of Helsinki states the following:

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection.... Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.⁹

As the Declaration of Helsinki suggests, informed consent relies on the concept of autonomy. According to Rhodes,⁴ there are 2 definitions of autonomy. First-person autonomy is an individual’s “duty to be a good ruler over one’s self.” This definition refers to an individual’s ability to make an educated decision regarding his or her own fate or, in other words, to provide informed consent. Second-person autonomy refers to respect for the autonomy of others, or others’ respect of an individual’s ability to make an informed decision. Protection of the vulnerable, according to Rhodes, is paternalistic and disrespects both first- and second-person autonomy. Some vulnerable individuals (ie, the imprisoned or the socioeconomically disadvantaged) are capable of assessing risk and can decide for themselves whether they want to participate in a clinical trial. By protecting these individuals based on the assumption that they cannot make decisions for themselves, our current ethical guidelines condone disrespect for their autonomy. This is the complete opposite of what we should be doing: we should be enabling and respecting the autonomy of these individuals.

Such reliance on informed consent for the protection of the vulnerable has exposed flaws in the IRB review process. As mentioned, IRBs were created as governing bodies to ensure that clinical trials were conducted in an ethical manner. One might then infer that approval by an IRB committee should deem a study as ethically appropriate. This inference is not correct. IRB review is often based on confirmation that informed consent will

be obtained from all participants and that all vulnerable populations will be protected, rather than considering the true ethical basis of a study.¹⁰ By focusing on an individual's ability to provide informed consent and whether the individual qualifies as vulnerable, these committees focus on the potential risk a trial might inflict solely on the individual.¹¹ Although this focus might seem appropriate, particularly within our highly litigious society, IRBs really should consider the ethical aspects of a study with respect to society as a whole. In other words, is the value of the question addressed by the study worth the risk that participation in such a study entails?

By focusing on a predetermined definition of vulnerable (ie, children, prisoners, and the socioeconomically disadvantaged), IRBs might overestimate the true vulnerability of certain populations.¹² For example, the imprisoned or institutionalized are not always vulnerable when it comes to autonomous decision making. Instead, their vulnerability lies in the lack of control they have over their daily lives and the subsequent dependence on the institution to which they are bound. Thus although they might be able to sign a consent form, should they really be allowed to if they lack the ability to make routine choices of daily living?

By linking the definition of vulnerability with the ability or lack thereof to provide informed consent, our current ethical paradigm is misguided in its efforts to protect the vulnerable. The IRB review process is one example of how this misguidance can perpetuate ethical misdirection. IRB review is considered red tape through which researchers must pass, and trials are designed with this in mind, thereby limiting the scope of research questions that are asked. Although created with the best of intentions, IRB committees often fall short of their original purpose and might actually perpetuate a misguided approach toward these vulnerable populations.

EVIDENCE-BASED MEDICINE AND PROTECTING THE VULNERABLE

In evidence-based medicine clinical research is what dictates guidelines or standards of care. As a result, research is critical for medical progress. The enforcement of protecting the vulnerable was initiated to ensure that such research was ethically appropriate. Ironically, by protecting the vulnerable, we have restricted their participation in clinical trials that have guided standards of care practice and thus have excluded them from the population to which such standards of care apply. By excluding children, prisoners, pregnant women, fetuses, mentally disabled persons, and economically or educationally disadvantaged persons, are we respecting their autonomy or disregarding it? Moreover, in our efforts to protect them, are we in fact depriving them of medical care that is available to the rest of the population? For example, evidence-based guidelines on the care of pregnant women and the mentally ill are rare. The same can be said for children, but they require special consideration, which we will address later. Nevertheless, with these populations, standard care essentially is based on anecdotal evidence and is not subject to the same scientific scrutiny as the care of nonvulnerable populations.

Of course, researchers must be sensitive to the potential for vulnerability when designing evidence-based trials and appreciate that particular vulnerabilities are inherent within the framework of such trials.^{2,13,14} One potential exploitation of the vulnerable is in the recruitment of patients for these studies. Most clinical trials offer free medication or free medical visits

for participants for the duration of the trial. It is highly possible that such an offer might be especially enticing to a vulnerable population (ie, the economically disadvantaged). These populations might be those that the Declaration of Helsinki describes as needing "special attention... [for] they may be subject to giving consent under duress."⁹ But is this really coercion? A similar example is Medicare's "coverage with evidence development," where a treatment that would not otherwise be covered could qualify if the patient agrees to participation in research. These examples represent situations in which medication or timely medical care, normally inaccessible to the patient, becomes available if they participate in research. Is it better to receive some care under the umbrella of trial-based therapy rather than none at all?⁴ Again, if we strongly adhere to protecting the vulnerable, these populations would fail to receive this care simply because they have financial hardship.^{15,16}

This is not to say that protecting the vulnerable in evidence-based medicine is a bankrupt concept. However, to accomplish appropriate protection, we need to understand inherent challenges in applying this concept within the paradigm of evidence-based medicine. Otherwise, as outlined, we might actually accomplish the opposite and harm the vulnerable. By excluding these populations from participation under the framework of protecting them from risks of evidence-based medicine, we have deprived them of the benefits, namely scientifically sound evidence-based standards of care.

CHILDREN AND VULNERABILITY

The difficulty in developing evidence-based guidelines for the treatment of children because of ethical concerns related to pediatric clinical research has been well documented. Historically, there have been monumental discoveries made by experimenting on children in ways that by today's standards would be unquestionably ethically inappropriate. The development of the smallpox vaccine originated because of Jenner's inoculation of his own children.⁸ Likewise, the pertussis vaccine emerged largely as the result of experiments that Alfred F. Hess, the Medical Director of the Hebrew Infant Asylum in New York City, conducted on his patients. He also used the children to study pediatric anatomy and physiology of digestion and went so far as to deprive the children of orange juice, fruits, and other dietary staples so that he could study diseases like rickets and scurvy.⁸ Thus experimentation on children is not a foreign concept in the field of medicine and has led to much new medical advancement, but frequently these improvements in medical care were based on experiments that would be inappropriate by today's standards. Because of the stringent restrictions on pediatric research, major advances in pediatric evidence-based medicine are rare at best.

One area that is particularly weak because of such tight regulation is that of pediatric pharmacotherapeutics. It has been estimated that as many as 80% of drugs prescribed by pediatricians have never been systematically studied in children.¹⁶ Although they are used on children, no specific data regarding dosing, efficacy, or risk is known about these drugs because of the lack of clinical trials in children. Because our society is unwilling to subject children to human experimentation, most pediatric medical therapies are based on pharmaceutical industry-sponsored studies that are inherently subject to bias, inferences from studies of adults, or, worse, anecdotal evidence. Without a change in our current paradigm of ethical research, this situation is unlikely to improve.

History provides multiple examples in which such reluctance has not only hindered medical progress but actually harmed the very children who were supposedly being protected. One example is the use of phenylketonuria screening in children. Today, this newborn screening is common practice and mandated in most states. Dr Robert Guthrie developed a phenylketonuria screening test in 1959 by using the simple principle that phenylalanine can facilitate bacterial growth in a culture medium with an inhibitor. Rather than subject children to trials to test the efficacy of the test, the test was released. Unfortunately, it had a significant false-positive rate. Numerous children who had a benign form of hyperphenylalaninemia were falsely identified as having phenylketonuria. These children were thus subjected to not only the psychosocial consequences of having such a rare and chronic condition but also the severe dietary restrictions and deprivation of phenylalanine that actually led to brain damage and kwashiorkor in some instances.^{17,18}

Clearly, the issue of pediatric research is a delicate and complicated one. Although there is no question that the potential vulnerability of children should always be recognized and respected, it is less clear whether such vulnerability should always exclude them from clinical trials. Perhaps their vulnerability actually justifies their inclusion in the experiments conducted to establish guidelines for medical care.

PEDIATRIC ASTHMA TRIALS

One area of particular concern to allergists and immunologists is pediatric asthma. Several important questions remain that have not yet been answered by our medical research: Among children who wheeze early in life, who will have asthma and who will not? What is the effect of early intervention on the development of asthma and progressive lung disease? For the reasons outlined above, addressing these issues head-on is almost impossible within the current framework of "ethical research." Obtaining informed consent, ensuring beneficence or a favorable risk/benefit ratio, and choosing adequate outcome measures are important challenges in designing clinical trials for the pediatric population.¹⁹

To illustrate these challenges, we can specifically look at the question of whether early intervention prevents the progression of lung disease. First, as with all pediatric trials, how can true informed consent be obtained? The most recent revision of the Declaration of Helsinki addresses this issue: for a research subject who is legally incompetent, physically or mentally incapable of giving consent, or a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.⁹

As Burns asserts,⁸ parents can represent their child and act on the child's behalf in proceeding with medical treatment. Parents can do the same with regard to participation in medical research. However, this permission should not be misinterpreted as consent on the child's behalf. Rather, the parent can only give permission on behalf of that child or assent for the child. As a result, true informed

consent is impossible to obtain in pediatric clinical research. In general, the consent of the parents has been accepted as the consent of the child, but informed consent can be obtained only from the actual participant.^{8,20} Do we then not perform these trials?

Second, outcome measures are not particularly well defined in asthma. For example, say data from bronchoscopy has the most potential in generating objective data from asthma trials. The risks inherent in such an invasive procedure and associated anesthesia certainly are not insignificant.²⁰ Thus how could such immediate risk be justified when the effect of the trial's intervention is a long-term question? This issue raises a third point, a problem that occurs in all trials with a similar design: the issue of beneficence. It is impossible to ensure beneficence or even nonmaleficence in these experiments.²¹ Without this assurance, can we justify the inclusion of children in trials that might require invasive testing, treatment, or withholding of treatment that will not reveal benefit or harm until many years later?

It is important to note, however, that there have been several large, randomized, multicenter trials (eg, the Tucson Children's Respiratory study and the Steroid Treatment as Regular Therapy in Early Asthma trial) that have contributed to the treatment of pediatric asthma.^{22,23} These studies, however, have been primarily observational, phase IV or at best phase III trials looking specifically at the efficacy of a particular treatment or the natural history of the disease. Nonetheless, the sheer number of adult trials far outweighs the number performed in children, and this is in a disease that predominately affects children. Results from such trials have certainly contributed to the field of pediatric asthma, but the limitation in their scope translates to a limitation in their contributions.

DISCUSSION

Acknowledging the vulnerability of certain populations is critical to ensuring that clinical research is conducted in an ethically appropriate way. However, whether our current definition of vulnerable is appropriate is controversial. A frequent consequence of the current definition is that the so-called vulnerable populations are automatically excluded from trials. This blanket exclusion limits their autonomy and in many ways only serves to increase their vulnerability because their medical care cannot be based on evidence-based research, as is that of the general nonvulnerable population.

How then can we then truly protect these individuals? We could start by changing the atmosphere of clinical research. The concept of a vulnerable population suggests a relationship of exploitation, with researchers as exploiters and subjects as the exploited. Instead, research should be viewed as a partnership in which both investigators and participants are working together for the betterment of medical practice.

Thus how can such a partnership be achieved? The first step could be taken by ethical review committees. IRBs could modify their concentration such that the individual is not the major focus of consideration; the effect on society as a whole would also be considered. Of course, the individual should not be overlooked, but instead of reviewing a study based solely on its effect on a single person, IRBs could consider the trial in light of its potential to improve medical care for the general population.

Others have made similar proposals. For example, Emanuel²⁴ presented 7 principles of ethical research that would "aim to minimize the possibility of exploitation by ensuring that research

subjects are not merely used but are treated with respect while they contribute to the social good.” They include social or scientific value, scientific validity, fair subject selection, favorable risk/benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects. These 7 principles summarize the requirements included in the major ethical references, including the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki. Instead of being created in response to a tragically unethical historical event, Emanuel’s guidelines are more “universal” and can be applied with some degree of “adaptation to particular cultures, health condition and economic settings.” In other words, he presents his principles as general concepts rather than a checklist that should be fulfilled before proceeding with research. In fact, because these principles are flexible, he urges practitioners to interpret them within their unique context and circumstance, while keeping the general idea in mind. Respect for potential and enrolled subjects, for example, includes consideration of vulnerability, but the vulnerable population is not a predefined group and might vary according to the experiment.

Rhodes⁴ has taken a different approach. In our current paradigm compensation complicates the focus of clinical trials. A physician can receive financial reimbursement for enrolling patients and a patient can receive free medical care or prescriptions for participation. One way to eliminate this factor, as expressed by Rhodes, would be if participation in some aspect of clinical trials was a mandatory civil responsibility. By allowing all citizens the opportunity to explore and choose clinical trials on their own, we respect autonomy in the proper sense and allow true informed consent (as opposed to an explanation of a clinical trial from someone who is involved with or related to the trial). This approach truly exemplifies what can be accomplished when, within the paradigm of clinical research, the partnership is not one among individuals (ie, physician and patient) but between medicine and society as a whole.

CONCLUSION

Clearly, as with all ethical discussions, the division between right and wrong is not clear-cut. There are certainly no easy remedies to the challenges inherent in conducting ethically appropriate human clinical research, including the notion of the protection of the vulnerable. This concept was created out of the best of intentions but now has led to an almost immediate exclusion of such vulnerable populations from clinical research. Therefore these populations—children, prisoners, pregnant women, fetuses, mentally disabled persons, and economically or educationally disadvantaged persons—are being excluded from reaping the benefits of evidence-based medicine: the medical therapy and practice that has been tested and validated. As a result, this exclusion ultimately enhances the vulnerability of these individuals. Researchers, as well as practitioners, must be aware of this problem, and an ongoing dialogue among and within these groups must continue if we hope for any sort of remedy. We believe that our best solution involves changing the current paradigm of medical research and developing more fluid

guidelines of what is considered ethically appropriate. With a more relativistic view of the vulnerable, it will be much more possible to provide the benefits of evidence-based medicine to these populations without exposing them to further undue risk.

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