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Ethical Issues in Clinical Trials Involving Nanomedicine

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Abstract

Nanomedicine shows tremendous promise for improving medical diagnosis, treatment, and prevention, but it also raises a variety of ethical concerns. Because of the paucity of data on the physicochemical properties of nanoscale materials in biological systems, clinical trials of nanomedicine products present some unique challenges related to risk minimization, management and communication involving human subjects. Although these clinical trials do not raise any truly novel ethical issues, the rapid development of nanotechnology and its potentially profound social and environmental impacts, add a sense of urgency to the problems that arise.

Keywords

nanomedicine; nanotechnology; ethics; clinical trials

Introduction

Nanotechnology has moved quickly from the realm of science fiction into clinical research. Pharmaceutical and biotechnology companies and government agencies are beginning to explore and test a variety of applications of nanotechnology in medicine (or nanomedicine). Nearly a dozen nanoparticle-based therapies or imaging devices are currently in clinical trials, are awaiting clinical trials, or have already been approved by the Food and Drug Administration (FDA). Several nanotechnology treatments for cancer have been approved or are currently being tested on human subjects.[1],[2] The National Cancer Institute (NCI) has initiated a $144 million cancer nanotechnology initiative that will fund seven cancer nanotechnology centers of excellence.[3] Other countries are also spending large sums of government money on nanomedicine research and development.[1]

Industry analysts expect that within the next five years, nanotechnology will augment diagnostic testing and drug delivery. In ten years, it may be used in artificial biological structures for tissue repair and remodeling. Micro-machines are also on the horizon with many different medical applications, including destruction of cancer cells, drug delivery, diagnosis, and tissue repair.[4] According to many experts, the nanotechnology revolution will have as

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great an impact on biomedicine as the genetic revolution. The market for pharmaceutical applications of nanotechnology is expected to increase to about $18 billion per year by 2014.[5]

The public reaction to nanotechnology so far has been mixed. While there have not been many well-organized protests against nanotechnology, some environmental groups have raised concerns.[6] Surveys have shown that most people in the United States and Europe know very little about nanotechnology and have not formed definite opinions about it.[6] So far, media coverage of nanotechnology has been mostly balanced, with equal discussion of the benefits and risks of nanotechnology in mainstream newspaper stories.[6] Although some fictional accounts of nanotechnology, such as Michael Crichton's *Prey*, have sounded an alarmist tone, few popular writers have taken aim at nanotechnology.[7] One television series, *Jake 2.0*, portrayed nanotechnology in a positive light, as the hero used his nanotechnology-enhanced powers to protect society.

Scientists and government officials have cautioned that it is important to educate the public about nanotechnology and discuss ethical and social issues upfront to avoid creating a response similar to the uproar in Europe over genetically modified (GM) foods.[6] One explanation of why many consumers have had such a negative reaction to GM foods is that private companies, such as Monsanto, tried to impose their GM agenda on society without first engaging the public in an honest and open discussion of the social and ethical issues raised by this new technology.[6] Thus, it would be wise to explore the social and ethical issues raised by nanotechnology while this new advancement is still in its infancy.[8]

Nanotechnology raises many ethical and social issues that are associated with many emerging technologies, such as questions concerning risks to human beings and the environment and access to the technology, and several new questions, such as the use of nanotechnology to enhance human traits,.[9],[10],[11],[12] Because the physicochemical properties of nanoscale materials have not been fully studied, clinical trials involving nanomedicine present some unique challenges related to risk minimization, management and communication involving human subjects.[10],[13] Although these clinical trials do not raise any truly novel ethical issues, the rapid development of nanotechnology and its potentially profound social and environmental impacts, create a sense of urgency to the problems that arise and proposals for reforming the current system.

What is Nanotechnology?

Nanotechnology is the science and manipulation of matter in the range of 1–100 nanometers.[14] A nanometer (nm) is one billionth of a meter. A hydrogen atom is about 0.1 nm; DNA, 1–2 nm; a virus, 3–50 nm, and a red blood cell is 300 nm. Ultra fine particles (UFPs) are nanoparticles that occur naturally, such as volcanic ash, viruses or smoke, or result from human activities, such as fumes from automobiles, electric motors, and power plants.[13]

Manufactured nanomaterials have properties different from similar materials at a larger scale. Two characteristics of nanomaterials with a significant affect on biological activity are surface-area-to-mass ratio and physicochemical properties. Because nanoscale materials have a greater surface-area-to-mass ratio than larger particles and chemical reactivity occurs primarily on the surface of a material, there is more opportunity for biochemical interactions. Also, at the nanoscale, the quantum mechanical properties of the atom strongly influence the physicochemical properties of the material, conferring electrical, optical and magnetic properties not present in corresponding materials at a larger scale. Additionally, the fundamental properties of nanomaterials, such as melting point, color, and electrical conductivity may vary with size and shape of the material within the 1–100nm range.

Nanomaterials often have unique—and unexpected—chemical or physical properties that can be useful in different applications.[14] Some popular shapes of nanomaterials include, tubes (nanotubes), rods, wires, belts, brushes, particles (nanoparticles) and shells (nanoshells).[15] Because they can transmit one electron at a time, carbon nanotubes may function as electrical conductors, insulators, chemical sensors and biological sensors.[16] Nanoparticles with potential industrial and medical applications include fullerenes, C60 carbon shells, and quantum dots.[15].

Nanomedicine Clinical Trials

As noted earlier, two main types of nanomedicine products are currently in clinical trials: diagnostic tests and drug delivery devices. Researchers have developed an assay that uses gold nanoparticles to detect proteins, DNA, and other compounds found in biological samples. The main difference between this diagnostic test and a standard biochemical assay is that the indicators are nanoparticles.[1] A study of the efficacy of this diagnostic test would pose minimal risk to human participants because the subjects would not need to be exposed to nanomaterials, only their tissue samples would be exposed. However, researchers are also developing diagnostic tests that expose human subjects to nanomaterials. In one application, investigators are exploring the use of quantum dots, with their size-dependent fluorescence, to illuminate organs, such as lymph nodes, and tumors. This type of application would be similar to the use of radioactive dyes to elucidate body structures. The employment of quantum dots may pose risks to human subjects because the dots contain heavy metals that have the potential to diffuse into surrounding tissue over time and disrupt cellular functions.

One of the drug delivery devices undergoing clinical trials is a nanoparticle shell containing a chemotherapy agent. The shell will not release its payload until it encounters a cancer cell in the body. When this happens, the shell binds to the surface of the cancer cell, the chemotherapy agent enters the cancer cell, and the cell begins to die. This drug delivery system is literally a “magic bullet” because it specifically targets malignant cells. Researchers hope that it can improve the effectiveness of chemotherapy by minimizing the impact of chemotherapy on healthy cells.[1] However, it is also possible that nanoshells used to deliver drugs will accumulate in the body and cause damage. The FDA classifies this device as a “combination product” because it combines a drug (chemotherapy) and medical device (the nanoparticle shell).[17]

Before initiating a clinical trial involving a nanomedicine product, manufacturers in the United States must present data to the FDA from pre-clinical studies involving animals, human cells or tissues, or chemicals *in vitro*.[18] These studies are designed to determine whether the product is safe to use in humans. Pre-clinical drug studies, for example, describe the biochemical, toxicological, and pharmacological properties of the drug to determine a safe human dose. When the FDA determines that the drug is safe enough to introduce in humans, it gives the manufacture permission to conduct a small study (25–100 subjects), known as Phase I trial, to determine the maximum tolerable dose in human beings. If a drug is safe enough to use in humans, the FDA will allow the manufacturer to conduct larger studies (100–500 subjects), known as Phase II trials, to investigate the drug’s efficacy and to gather additional data pertaining to safety. If the drug makes it past this stage, the FDA will allow manufacturers to conduct much larger studies (500–3000 subjects) to gather more data on safety and efficacy. When Phase III testing is complete, the FDA will examine the data to determine whether to approve the manufacturer’s new drug application (NDA) to market the drug in the United States. If the FDA approves the NDA, the manufacture may start selling the drug and may also conduct additional studies, known as Phase IV trials (or post-marketing studies), to gather additional information about safety, efficacy, dosing, side-effects, and adverse reactions. The

FDA encourages but does not require Phase IV studies. The FDA also encourages physicians who prescribe the drug to report any adverse reactions or other safety concerns.[19]

A duly constituted institutional review board (IRB) must approve any study involving an investigational drug, biologic, or medical device. The IRB is charged with evaluating the ethical aspects of the study and protecting the rights and welfare of the research subjects.[20] In deciding whether to approve a study, the IRB must determine whether 1) risks will be minimized; 2) risks will be reasonable in relation to expected benefits to the subjects (e.g. medical therapy) or society (e.g. the knowledge gained); 3) provisions for data and safety monitoring (if appropriate) will be adequate; 4) informed consent will be properly sought and documented; 5) selection of subjects will be equitable; 6) protections for vulnerable populations (if appropriate) will be adequate; and 7) privacy and confidentiality will be protected.[21] We will not discuss all of these criteria for IRB approval of research, since we think that nanomedicine does not raise any especially challenging issues for some of them. Instead, we will focus on the first four criteria in the list, which deal with the minimization, management, and communication of risks.

Risk Minimization

There are many different methods and procedures that investigators can use to minimize risks to research subjects, such as conducting a thorough literature review to understand the potential risks of research documented in previous animal or human studies; developing criteria for excluding subjects who are likely to be significantly harmed while participating in the study; carefully monitoring of clinical data during the study; reporting adverse events to the IRB and study sponsor; following-up with subjects after the study is finished; and using standard operating procedures to ensure consistency in the implementation of the study design.[20], [22]

Since the risks of human exposure to nanomaterials have not been well studied at this time, understanding and predicting risks is the most significant challenge for risk minimization. A new discipline known as nanotoxicology examines the effects of nanomaterials on organisms and the environment.[23] Nanotoxicologists are conducting *in vitro* studies using animal and human cell systems to characterize the basic chemical and physical properties of nanomaterials. They are also conducting *in vivo* experiments using rodent model systems to provide information about absorption, distribution, metabolism, and excretion of nanomaterials. The NCI has established a laboratory to conduct *in vitro* and *in vivo* experiments on nanomaterials that may be used in cancer treatment or diagnosis, and the National Toxicology Program (NTP) at the National Institute for Environmental Health Sciences (NIEHS) is conducting *in vitro* and *in vivo* research on dermal application of metal oxides.[24] The NIEHS, the Environmental Protection Agency (EPA), the National Science Foundation (NSF), and the National Institute for Occupational Safety and Health (NIOSH), have also devoted considerable resources to studying the risks of exposure to nanomaterials.[14]

To understand the risks of nanomaterials to animals and humans, it is important to grasp some basic facts about nanomaterials. First, the risks of nanomaterials may vary according to the route of exposure, such as dermal, oral, respiratory, and intravenous.[13] Second, because there is tremendous diversity among nanomaterials, it is not possible to make any generalizations about the safety of all nanomaterials: one must consider each type of material separately.[13] Third, the risks of exposure to manufactured nanomaterials may be different from the risks of exposure to the naturally occurring nanoscale materials, the ultrafines, since humans have had millions of years of evolution to adapt to natural exposures.[13] Fourth, the size, shape and physicochemical properties of nanomaterials are very dependent on their microenvironment and may change once they enter an organism. For example, a 100 nm particle could break apart

into 100 particles that are 1 nanometer in size or agglomerate into microscale size particles. Serum or lung surfactant proteins may coat the nanoparticles. Changes in size, shape, and composition may, or may not, be accompanied by changes in the quantum properties of the material. Fifth, like some heavy metals, such as mercury or lead, nanomaterials may accumulate in the body and exert toxic effects.[25]

Researchers – federal, academic, and industrial – are just beginning to understand how acute exposure to nanomaterials activates the body's defense mechanisms: the inflammatory and oxidative stress responses, and innate and adaptive immunity. Because nanomaterials, by definition, have novel properties, they may affect animals and humans in unpredictable ways. Studies have shown that nanomaterials may not be retained in the exposure organ. For example, inhaled nanoparticles can traverse the alveolar endothelium and enter the capillaries, and particles can penetrate the skin and translocate to the lymph nodes.[13] When nanoparticles enter the circulatory system, they are transported to the liver, spleen, lymph nodes, and bone marrow.[13] Additionally, nanomaterials can traverse cell membranes and accumulate in the mitochondria and cross the blood-brain barrier.[26] [27] Chronic exposure studies that investigate accumulation of nanomaterials in the human body have not been performed to date, nor have large-scale studies investigating potential novel biological responses. While some of the risks of nanomaterials are known, many are simply not known at this point, and much more research is needed.[13]

Although pre-clinical studies will play an important role in minimizing the risks of nanomedicine, animal experiments have significant limitations. The first of these limitations is that there may be differences in the way that humans and the animal models used in pre-clinical testing (usually rodents) react to the same material or substance. Because there may be differences in how animals and humans absorb, distribute, metabolize, or eliminate a substance or material, something that is not toxic to animals at a low exposure might be toxic to humans at a low exposure and vice versa.[28],[29] As illustrated by a disastrous Phase I trial conducted in the United Kingdom in 2005, biological materials that do not cause a significant immune system reaction in animals can cause a significant immune response in humans.[30] Six research subjects in this study became critically ill after receiving a monoclonal antibody known as TGN1412. Animals receiving TGN1412 showed no signs of toxicity when administered 500 times the human dose. TGN1412 triggered a severe immune reaction in the six research subjects, which had not been observed in animals.[31] This incident should serve as a warning to researchers who are planning to expose human subjects to substances or materials that may trigger an immune response, such as some types of nanomaterials. To improve their understanding of the risks to human subjects posed by a substance or compound, investigators should conduct human cell and tissue studies to identify any potential differences between animals and humans, in addition to animal studies.[30]

A second limitation of pre-clinical research is that animal studies generally last from 28–90 days and rarely investigate the long-term effects of new drugs, biologics, or medical devices. [32] However, some of the harmful effects of materials may only materialize after many years of exposure. For example, most cancers in human beings develop after many years or even decades of exposure. To determine whether a chemical is a carcinogen, animal studies usually expose animals to mega-doses of the chemical over a much shorter period of time and measures rates of malignant and non-malignant tumors and other changes related to carcinogenesis. The theory behind this methodology is that carcinogenesis is a dose-dependent phenomenon, so that a high exposure for a short time-frame should provide useful information about a low exposure over a long time-frame.[33] But some forms of carcinogenesis—and other disease etiologies—may not conform to this model. To model the effects of long-term human exposure to nanomaterials, researchers may need to consider conducting dosing studies that last several years or more.[34]

Although our main concern in this article is that false negative data (or a Type II Error) from pre-clinical animal testing may erroneously suggest that a type of nanomaterial poses a low risk to humans, we also realize that false positive data (Type I Error) from pre-clinical studies might prevent the development of beneficial therapies and devices. Some substances that are harmful to animals may pose little risk to humans. For example, mega-doses of saccharin cause cancer in laboratory rats but lower doses of saccharin probably do not pose a cancer risk to humans, because saccharin forms toxic salts in rat bladders during urination but not in human bladders.[35] Studies on genetic, metabolic, immunologic, and physiologic differences between animals and humans can help investigators deal with both of these problems with extrapolating from animals to humans.

Once Phase I trials of a nanomedicine product are complete and investigators have permission to conduct Phase II studies, the next challenge for minimizing risks will be to understand the long-term risks to humans. As noted earlier, investigators gather data on the risks of drugs, biologics, and medical devices during the four phases of clinical testing, and the FDA may continue to receive adverse event reports for many years after a product has been on the market. Data and safety monitoring boards (DSMBs) can play a crucial role in risk minimization during clinical trials by carefully analyzing risks, adverse events, and other problems.[36] Information from DSMBs can be useful to IRBs, sponsors, and research subjects. Since clinical trials that expose human subjects to nanomaterials may involve more clinical uncertainties than conventional clinical trials, DSMBs should consider taking additional precautions to protect research subjects in these studies, such as monitoring data more frequently and thoroughly, and developing stopping rules that place the obligation to protect the safety of subjects ahead of the obligation to develop definitive results.

While DSMBs can help monitor and minimize risks, they only address risks that materialize during the course of a study; hence, they do not help to minimize long-term risks that occur after the study is completed. Indeed, most clinical trials do not last long enough to detect long-term risks to subjects or patients, such as diseases that result from genetic damage or tissue damage. The first three phases of clinical trials usually last no more than seven years, and post-marketing studies, if conducted at all, last only a few additional years. Diseases resulting from genetic or tissue damage, such as cancer, may take decades to develop. Most smokers do not develop lung cancer until age 50, after 30 or more years of exposure to tobacco smoke.[37] Adverse event reporting, which may continue for decades, only covers obvious harms, such as toxic drug reactions. To understand whether the administration of a nanomedicine over a long period of time increases the risk of an adverse health outcome one would need to conduct a longitudinal study of research subjects and/or patients who are exposed to the medicine. Manufacturers probably will not sponsor such studies, since the FDA does not require them for product approval, and the outcomes could negatively impact the marketability of products. To protect the public from these potential harms, government agencies should sponsor longitudinal studies of research subjects and/or patients who are exposed to nanomaterials for many years.

A third challenge for risk minimization is to understand rare adverse reactions (1 case out of 1000) of nanomedicine products. Clinical trials usually do not include enough subjects to detect rare side effects. One needs to follow 3,000 research subjects to have a 95% chance of detecting a rare drug reaction, but drugs often enter the market after being tested on fewer than 1,000 subjects.[38] As a result, more than half of all new drugs require revisions in their safety information after they have been on the market, such as labeling changes or black box warnings.[38] To avoid this problem, enrollment in pre-marketing clinical trials should include at least 3,000 total subjects and manufacturers should be required to conduct post-marketing studies.[39]

Risk Management

Risk management in clinical trials involves the identification and assessment of risks and benefits and the balancing of risks and benefits. As noted earlier, the federal research regulations require that risks to research subjects be reasonable in relation to benefits to the subjects or society. All prominent international ethics guidelines, such as the Helsinki Declaration and the Council for the International Organization of Medical Science (CIOMS) Guidelines have similar requirements.[40] To determine the reasonableness (or justification) of risks, one must have sufficient information about both sides of the equation. One of the most important distinctions in the ethics and regulation of research is the distinction between research that poses no more than a minimal risk to subjects and research that poses more than a minimal risk.[41] If the risks of a study are minimal, the benefits need only be more than minimal for the risks to be justified. For example, providing 50 ml of blood is considered to be a minimal risk.[41] The risks of a study that only requires subjects to provide 50 ml of blood for assay development would be reasonable, provided that benefits from the knowledge gained are more than minimal. The clinical trial mentioned earlier, in which researchers are developing a diagnostic test that uses gold nanoparticles to detect biochemical compounds, would probably be classified as a minimal risk study, if the main risk of the study is providing a blood or urine sample.

If the risks of a study are more than minimal, the benefits must also be more than minimal. Additionally, special protections for vulnerable populations, such as children, fetuses, and prisoners, apply to more than minimal risk research.[41] In thinking about research that poses more than a minimal risk to subjects, it is important to distinguish between research that offers subjects a medical benefit, such as diagnosis, treatment, or knowledge about their condition, and research that does not.[42] Risks to subjects that are much greater than minimal can be justified only if subjects are expected to receive direct, medical benefits. For example, chemotherapy can involve many different risks, such as nausea, weight loss, nerve damage, anemia, neutropenia, thrombocytopenia, fatigue, hair loss, infections, dizziness, headaches, emotional problems, and even death. Nevertheless, the risks of a Phase II clinical trial investigating a new chemotherapy agent can be justified if the benefits to the subjects (e.g. treatment) and society (e.g. new knowledge) are expected to be very significant.[42] If the risks are more than minimal and the subjects are not expected to receive direct, medical benefits, the risks will be reasonable only if the risks are not much greater than minimal and the benefits to society are large. For example, the risks to subjects in Phase I drug trials are usually more than minimal, since Phase I studies are designed to study the toxic effects of medications in human beings. Nevertheless, the risks of a Phase I clinical trial involving a new drug can be justified if the risks are not much more than minimal and the benefits to society (e.g. knowledge gained and drug development) are great.[43]

If a study that exposes research subjects to nanomaterials, the risks will probably be more than minimal. Thus, the expected benefits to subjects or society must outweigh these risks for the study to meet ethical and legal requirements. Let us consider, for a moment, the risks and benefits of a study involving the nanoparticle drug delivery device mentioned earlier. A Phase I study of the device could enroll healthy or unhealthy subjects. Although most Phase I studies of new drugs include only health adults, many Phase I studies of new cancer treatments enroll cancer patients.[44] Since the nanomedicine device is designed to deliver chemotherapy, let us assume that the subjects will be cancer patients. Although Phase I cancer trials are not designed provide medical benefits to the subjects, there is often the slight chance that subjects will receive some medical benefit from their participation. Assuming that the risks of this study would be more than minimal, the benefits would also need to be more than minimal for the study to be justified. Since the subjects may not receive any benefits, the question we would need to ask is whether society would receive any benefits.

As noted earlier, the potential benefits to society of a device that targets chemotherapy to cancer cells are potentially very high, since the device could enhance the effectiveness of chemotherapy and help to reduce its side effects. For chemotherapy, the potential benefits of a drug delivery device are straightforward and uncontroversial. However, suppose that the device is designed to help deliver a therapy that has been proven to be safe and effective with few side effects, such as the administration of insulin for diabetes. The risks of this type of device might be more difficult to justify, since the benefits of the device might not be very significant. It may be may be difficult to justify other types of research that involves exposing human subjects to nanomaterials when patients already have access to safe and effective therapies, since exposure to nanomaterials may create unnecessary risks.

In thinking about balancing the benefits and risks of research, investigators and IRB members should consider not only risks to subjects, but also potential risks to members of the research team (second parties) and others (third parties). While human research regulations and guidelines tend to focus on risks to human subjects, researchers also have an ethical obligation to address potential harms to second and third parties when designing and implementing research.[45] Because nanomedicine experiments might expose people to nanomaterials other than the subjects, these experiments could cause harm to research staff, fetuses, breast-fed infants, or even family members. It is also possible that the manufacturing process used to make nanomaterials for medicine could cause harm to factory workers as well as the environment.[11] Because most experiments that pose risks to second and third parties also provide significant benefits to the research subjects and society, deciding how to balance benefits to subjects and risks to second and third parties is not an easy task, especially when risks may be speculative or unknown.[45]

Risk Communication

The final issue we will consider in this article concerns that communication of research risks to human subjects during the informed consent process. Almost all research regulations and guidelines require that subjects (or their representatives) provide their informed consent to participate in a study.[40] Investigators should inform subjects about the study's goals, procedures, benefits, risks, costs, confidentiality protections and alternatives to participating in the study.[42] Investigators should also inform subjects about new findings that may affect their willingness to continue participating in the study and provisions to compensate subjects for research-related injuries, if any.[42] Although investigators and subjects often regard informed consent as simply another form to sign, informed consent should be much more than a document: it should be a process in which investigators and subjects communicate about the research.[42] Investigators should explain their study in lay-language, and subjects should feel free to ask questions.

The therapeutic misconception is a well-documented problem that can undermine risk communication in research. The therapeutic misconception occurs when a research subject fails to understand the difference between medical research and medical therapy. As a result, they may believe, mistakenly, that the studies they are participating in are actually a type of therapy, or they may overestimate the medical benefits that they may receive from their participation and underestimates the risks.[46],[47] Although many clinical studies combine medical research and medical therapy, there are important differences between the two. In research, the primary goal is to develop knowledge that can help other patients or society. In therapy, the primary goal is to benefit the patient. A research study may include tests or procedures whose sole purpose is to collect data for the study, whereas therapy only includes tests or procedures designed to diagnose or treat the patient.[20] Since the distinction between research and therapy is sometimes not even clear to researchers, it is not surprising that laypeople often fall prey to the therapeutic misconception. Hope is another reason why people

succumb to illusion. People who are sick will believe that they are receiving something that will help them get well, even though they have been told they are participating in research. [46]

The therapeutic misconception may also affect the informed consent process in nanomedicine research, especially if biomedical researchers, government officials, business leaders, and journalists exaggerate nanotechnology's medical potential. People exposed to this hyperbole may enter a clinical trial already expecting to receive medical benefits from their participation. For a historical precedent, consider gene therapy. In the 1990s, many people touted gene therapy as the next medical breakthrough. There is evidence that the therapeutic misconception has affected the consent process in gene transfer clinical trials by instilling false hope in research subjects.[48]

Although investigators should be concerned about avoiding the therapeutic misconception when communicating risks to subjects, they may also encounter the opposite problem. Research subjects may overestimate the risks and underestimate the benefits of nanomedicine, especially if nanomedicine and nanotechnology receive negative publicity from the media and political interest groups. Potential research subjects who encounter this bad press may have a negative impression of nanomedicine and avoid enrolling research studies that could benefit them or society. For a historical precedent, consider public opposition to GM foods in Europe, which has been fueled by environmental and consumer groups, farmers, politicians, and the media. [8] GM foods are currently illegal in Europe, but they are legal in the United States. One might argue that Europeans have developed an irrational fear of GM foods that is hampering the development of useful and safe foods and crops.[49] For want of a better term, we will refer to this problem as the malevolent misconception.

Investigators should take steps to dispel the therapeutic misconception and the malevolent misconception during the informed consent process. They should describe the benefits and risks of nanomedicine clearly and candidly in the consent document and in their oral communications. Investigators should neither overestimate nor underestimate the risks that research subjects may encounter. Investigators should continue to discuss risks and benefits after subjects have enrolled in a study, informing subjects of new developments that may affect their assessment of risks and benefits.

Conclusion

Nanomedicine has the potential to offer immense benefits to human health, but it also raises a variety of ethical, social, and legal issues. In this article, we have examined problems that arise in risk minimization, management, and communication in clinical trials involving nanomedicine. Although these concerns about risk minimization, management, and communication routinely arise in the testing of new medical products, the application of nanotechnology to medicine may exacerbate these perennial problems and create a sense of urgency to proposals for reforming current regulations.[50],[51] Lack of knowledge about the potential risks of nanomaterials to human beings is currently the most significant issue pertaining to clinical trials involving the application of nanotechnology to medicine. Additional research focused on the physicochemical properties of nanomaterials and their potential impact on humans and the environment will be critical to the responsible development of nanomedicine.

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