Nanomedicine First-in-Human Research: Challenges for Informed Consent

Nancy M. P. King

Introduction

First-in-human (FIH) research has several characteristics that require special attention with respect to ethics and human subjects protections. At least some nanomedical technologies may also have characteristics that merit special attention in clinical research, as other papers in this symposium show. This paper considers how to address these characteristics in the consent form and process for FIH nanomedicine research, focusing principally on experimental nanotherapeutic interventions but also considering nanodiagnostic interventions.

It is essential, as a starting point, to recognize that the consent form and process are by no means the primary protectors of human subjects (although they are sometimes so regarded). Instead, consideration of the form and content of informed consent becomes relevant only after a clinical trial has been reviewed and deemed scientifically and ethically acceptable.[1]

Two convergent types of challenges to informed consent are posed by nanomedicine FIH research. First, some issues appear generally applicable to FIH research, but have specific nanomedicine implications. Second, some issues appear specific to nanomedicine research, but also arise in other FIH trials. Both types of challenges potentially implicate two varieties of issues: those that are genuinely novel, and those that have enduring significance but have, to date, been inadequately addressed. Thus, an inquiry into informed consent in FIH nanomedicine research should ask the following questions:

Question 1: What is really new, and what have we been ignoring for a while?

Question 2: What is actually worth worrying about?

Informed Consent: The Basics

The federal Common Rule,[2] that is, the set of regulations for the protection of human subjects in NIH-funded research that appears at 45 CFR Part 46, addresses informed consent by enumerating its "basic" and "additional" elements. An initial consideration, then, is how FIH nanomedicine research con-

Nancy M. P. King, J.D., *is Professor, Department of Social Sciences and Health Policy and Wake Forest Institute for Regenerative Medicine, Wake Forest School of Medicine. She is also Co-Director of the Center for Bioethics, Health, and Society and the Master of Arts in Bioethics Program at Wake Forest University. Her scholarship addresses a range of research ethics issues, including: informed consent; benefit and uncertainty; preclinical and animal research; international and cross-cultural questions; ethical issues in large-scale genetic research and biobanking, gene transfer research, and regenerative medicine; and connections between science, ethics, design, and policy in biotechnology research.*

sent forms and processes should address the basic elements of informed consent.

45CFR46.116(a) sets forth the basic elements of informed consent. The following are of particular relevance for FIH nanomedicine research:

> "[I]n seeking informed consent the following information shall be provided to each subject:
> (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
> (2) A description of any reasonably foreseeable risks or discomforts to the subject;
> (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
> (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject...."

Do current FIH research consent forms/processes address these basics well?

Study Purpose and Procedures

When consent forms provide "an explanation of the purposes of the research and a description of the procedures to be followed," the study purpose usually appears at or near the beginning of the consent form. In this way it provides essential context for the rest of the information about the study procedures and the experimental intervention. In FIH and other early-phase research, it is essential to distinguish the purposes of the particular study from the purposes of the entire line of research. If this distinction is not made, then the goal of the line of research — usually to identify a new treatment for the disease or condition of interest – can easily be conflated with the necessarily more limited goals of the trial under consideration.

Thus, the consent form and process in FIH nanomedicine research must explicitly describe the study purposes in terms appropriate for the study phase. This is a general issue for virtually all research, but it is especially important for FIH trials.[3] Although research involving novel biotechnologies, such as nanomedical interventions, does not necessarily fit the traditional clinical trial phases that characterize drug development, FIH trials always have safety as their primary or exclusive goal. Thus, the consent form and process should place emphasis on the purposes of safety testing and identification of risks of harm. In some studies, proof of principle and/or the identification of very preliminary efficacy signals may serve as secondary goals. The potential for direct clinical benefit should never be primary in FIH nanomedicine research.

Naming It Nano?

A key additional component of describing the purpose and procedures of the study is of vital current importance in nanomedicine research: describing the nature of the experimental intervention. Whether, and if so, when, to use the term "nano"-anything has been widely discussed since the advent of nanotechnology. Many different size-based definitions of nanomaterials have been promulgated by many different oversight bodies.[4] As a result, deciding when to describe an experimental intervention as an experimental "nanomedical" intervention is critical to informed consent. Should disclosure be based on size, or on the attributes of the intervention and its effects? Nanosize may have no significance in the body in some cases; in other cases, nanosized materials have been in use as nanomedicines for long enough to predate the term, yet new research involving substantially similar nanosized materials may be expected to use the term. Thus,

The consent form and process in FIH nanomedicine research must explicitly describe the study purposes in terms appropriate for the study phase. This is a general issue for virtually all research, but it is especially important for FIH trials. Although research involving novel biotechnologies, such as nanomedical interventions, does not necessarily fit the traditional clinical trial phases that characterize drug development, FIH trials always have safety as their primary or exclusive goal. Thus, the consent form and process should place emphasis on the purposes of safety testing and identification of risks of harm.

the question arises: Is it necessary to say "nano"? Or is it acceptable to instead simply describe the characteristics of interest, for example: "The intervention uses materials of very small size that because of their size may have unique effects in the body."?[5]

As with gene transfer research interventions, the characteristics of investigational nanomedicine products that create optimism about direct benefit are the same that pose unique risks of harm. And as with gene transfer interventions, the term "nano" itself may be viewed as a necessary component of adequate disclosure precisely because it represents potentially alarming technology, such that its omission might be considered deceptive. In this respect, perhaps the question whether to use the term should be distinguished, for the purposes of informed consent, from the obligation to provide a clear and particularized description of the potential effects of nanosize in the body in the study at issue. Where the relevant science already uses "nano" terminology, this language should be included in the consent form and process. However, when the relevant science does not use "nano" terminology, it is no less important to fully and accurately describe the intervention, its risks of harm, and potential benefits, if any.[6]

Where the relevant science already uses "nano" terminology, this language should be included in the consent form and process. However, when the relevant science does not use "nano" terminology, it is no less important to fully and accurately describe the intervention, its risks of harm, and potential benefits, if any.

Risks of Harm

Determining what risks of harm are reasonably foreseeable, and therefore should be disclosed and described to potential subjects, is an ubiquitous challenge in informed consent. Risk disclosure and description are arguably even more challenging in FIH research involving novel interventions like nanomedicines, simply because the available information is limited and is usually derived not from prior experience in humans, but from laboratory and animal studies, and sometimes from similar but not identical interventions.[7]

A considerable and growing literature addresses the risks of harm arising from nanotechnology; however, most of this literature is focused on environmental effects,[8] with little attention as yet given to nanomedical interventions and the risks of harm to research subjects. This literature is instructive nonetheless, both because it reflects a particular framework of societal concerns about risks of harm, including so-called bystander risks and the precautionary principle,[9] and because it highlights the context in which the risks of harm from nanomedicines are likely to be viewed by potential subjects: that fact that many nanomaterials are already in use outside the body.

Notwithstanding this general context, in every clinical trial, and thus in all nanomedicine research, the risks of harm are necessarily intervention-specific. When the experimental intervention is made up in whole or part of nanomaterials, the risks of harm could be similar to but less than the risks of harm posed by larger particles of the same material, because smaller size means less toxicity. In contrast, there might be additional or greater harms derived specifically from the nanosize of the materials. Nanomaterials may pose risks of harm that are more pervasive in the body, and/or more permanent, than the risks of harm posed by larger particles, because smaller particles are distributed more widely and/or are more difficult to remove. There may also be effects of nanosize that are unanticipated and unknown. Whatever the case, anticipated harms should be thoroughly and clearly described, and the basis for expectations of harm should be explained. Expectations of harm may be theoretical only; or they may be based on preclinical evidence from laboratory and animal models, or analogized from similar but not identical research. Nanomedicine-specific risks of harm meriting disclosure are likely to include bioaccumulation and its implications; the potential for long-term persistence of effects and for delayed adverse effects; and thus, the need for long-term monitoring of subjects.[10] Specific risks arising from nanodiagnostic research include (1) the possibility that a false positive finding could lead to more invasive confirmatory diagnostics, and (2) the possibility that novel diagnostic interventions could uncover unrelated information of potential significance, usually referred to as "incidental findings,"[11] which are of unproven reliability but merit follow-up.

One of the challenges in risk disclosure, which is especially acute in all early-phase research, is avoiding over-disclosure in the consent form and process. Clear and thorough description may become so detailed that not only potential subjects, but also oversight bodies and investigators, can fall prey to "information seduc-

tion" — whereby the sheer amount of information provides a false reassurance against the possibility of the unpredictable and the unknown. Under-disclosure is not a solution to this problem; it merely perpetuates uninformative "boilerplate." Instead, open acknowledgment of uncertainty should be coupled not with excessively detailed descriptions of all potential harms regardless of magnitude or likelihood, but rather with information that is clear, brief, and meaningful, the promise to minimize risks of harm, and a description of the procedures that have been instituted to protect and monitor subjects and to respond rapidly if and when harms materialize.[12]

Potential for Benefit

Determining whether any potential benefits may reasonably be expected, and therefore should be disclosed and described to potential subjects, is a second pervasive and significant informed consent challenge, one which is extremely important and especially difficult in FIH research.[13] When the available information about potential benefit is limited at best, but the goal of the line of research is to demonstrate clinical benefit, and the potential subjects in FIH trials are patients with the disease or condition that the experimental intervention is ultimately intended to treat, clarity about potential benefit can easily be outweighed by excessive expectations.[14] Yet the discussion of potential benefit in research consent forms and processes — particularly in early-phase research — is most often vague, stereotypical, uninformative at best, and misleading at worst.[15]

In every clinical trial, and thus in all nanomedicine research, the potential for direct benefit arising from the experimental intervention is intervention-specific. When the experimental intervention is made up in whole or part of nanomaterials, the potential benefits could resemble those arising from larger particles of the same material, or they could be completely different in nature, magnitude, and likelihood as a result of the size effect. Nanomaterials may have effects that are anticipated to be more pervasive or more permanent. There may also be effects of nanosize that are unanticipated and unknown. Whatever the case, anticipated benefits should be thoroughly and clearly described, and the basis for expectations of harm should be explained. The potential for direct benefit may be nonexistent, or theoretical only, or possible but unlikely, based on preclinical evidence from laboratory and animal models or analogized from similar but not identical research.

Several components of the discussion of potential benefit are particularly important in FIH research, including nanomedicine research. First, it is essential to distinguish direct, inclusion, and societal benefits. Direct benefits are clinically meaningful benefits arising from the experimental intervention; these are the benefits of greatest significance for most patient-subjects. Inclusion benefits arise from simply participating in the research, whether or not one receives the experimental intervention or is directly benefited by it. Inclusion benefits, provided to all subjects as inducements to participate, might be a free physical examination, medical testing and monitoring beyond what is required by the research, or other nonmonetary benefit. Finally, societal benefits stem not from research participation but from the outcomes of the line of research. For these reasons, it is necessary to use language very carefully and deliberately: "You may benefit from being in this study" is different from "You may benefit from getting the experimental intervention" — the former referring to inclusion benefits and the latter to direct benefits. Similarly, "The purpose of this study is to find out if the experimental intervention is safe. We also want to see if subjects can benefit from getting the experimental intervention" is different from "The purpose of this research is to develop a new treatment for X disease" — the former being specific to the study at hand, while the latter confuses the line of research with the study at hand.[16]

Second, discussion of the potential for direct benefit must be more specific and detailed than the all-too-common boilerplate statement, "You may or may not benefit." Direct benefit can and should be described in terms that resemble description of risks of harm: the nature of the benefit, its magnitude (that is, its size and duration — a change in laboratory values, which may or may not be linkable to clinical benefit? a reduction of symptoms? a cure? a temporary or permanent effect?), and its likelihood. In FIH research, especially FIH research with levels of uncertainty as high as in nanomedicine research, these dimensions of direct benefit may be exceedingly difficult to quantify; nonetheless, addressing them, even when precision is impossible, at least signals to potential subjects that there is more to the potential for benefit than "Either I will benefit or I won't."[17] What would count as a good description of reasonably expectable direct benefit in FIH nanomedicine research remains to be seen, but that is, of course, the goal.

Just as with risks of harm, a significant challenge in discussing potential benefit, especially in early-phase research, is avoiding over-disclosure in the consent form and process. "Information seduction" in the context of potential benefit provides a false assurance that clinical benefit will materialize, and under-disclosure does not correct the problem. Instead, as is the case for risk disclosure, open acknowledgment of uncertainty

about benefit is essential. This acknowledgment should be coupled with the promise to minimize risks of harm and the reminder that benefit cannot be promised.

The Therapeutic Misconception

The therapeutic misconception (TM), widely seen and discussed in clinical research enrolling patients as subjects, is the tendency to view research as treatment, to blur the distinction between research and treatment, or to have unreasonably high expectations of direct benefit from receiving the experimental intervention. First identified by Paul Appelbaum and colleagues some 30 years ago,[18] TM is most often attributed to patient-subjects, but it is also common in investigators and oversight bodies. TM is of concern because it may adversely affect understanding about the nature of the research and the likelihood that the experimental intervention will be beneficial for subjects. TM thus might compromise decision making by patient-subjects; it might also influence how investigators describe the research to potential subjects in the informed consent process, as well as how oversight bodies like IRBs view the research.[19]

Although TM may influence decision making at any stage of clinical research, it may be more likely in FIH research enrolling patients as subjects. Traditionally, the patients approached for participation in FIH trials are usually those with severe or advanced disease, for whom there are no good treatment choices available (either because all standard treatments have failed or because no good standard treatment exists). This is the approach to subject selection that is most often employed in oncology research. It has had significant influence on subject selection in FIH research involving novel technologies, including gene transfer and nanomedicine, in large part because many nanomedical and gene transfer interventions are employed in oncology research.[20]

In such cases, all stakeholders are hoping that a new, untried intervention will offer some benefit that standard treatment cannot provide. Although this hope is understandable, the resulting TM may have more significant distorting effects on decision making in FIH research than in later-phase clinical trials, because FIH research brings with it fewer data and more unknowns.

There is no agreement in the bioethics literature on how best to identify TM and assess its effects on decision making in clinical research.[21] However, several things are clear. First, the likelihood of TM in subjects enrolled in FIH research can be considerably reduced if it is addressed and reduced in investigators and IRBs, so that the consent form and process provide clear, accurate, and realistic information about the potential for direct benefit.[22] Second, TM should not be viewed as an automatic disqualifying factor for potential subjects, particularly when vague or misleading information has contributed to potential subjects' views.[23] Finally, hope for benefit is not always TM. It is normal to hope for benefit even if it is not expected. A subject who says, for example, "I know that the likelihood that anyone in this trial will experience any meaningful benefit is 1 in 100, but I'm confident that I will be that one!" may well be expressing a degree of optimism that is unproblematic in context.[24]

Alternatives to Participation

In much FIH research, including nanomedical research, the alternatives available to patient-subjects are often inadequate. Standard treatments may be directed toward symptomatic relief only; may be accompanied by significant toxicities; may have temporary or partial rather than permanent or curative effects; and/or may have a low likelihood of success. All of these characteristics of alternatives to research participation are important to disclose, as they are likely to be important in the decision making of potential subjects. This may be especially true for FIH nanomedical research because the mechanisms of action and the anticipated harm-benefit balance may be quite different in nanoscale interventions than in conventional medicine.

In addition, for nanomedicine research, the existence of nanocosmetics and other nanoproducts provides an important backdrop for disclosure and discussion. On the one hand, nanomedical interventions may be viewed as potentially more risky because of what is still unknown about the nanoscale. On the other hand, because many nanoproducts are already in common use, nanomedicine research may seem particularly safe. How specifically this context of available alternatives and in-use nanoproducts should be described and discussed depends on how likely public awareness of it may be to influence potential subjects' understanding and therefore assessment of the experimental intervention itself.

Informed Consent: Additional Elements

How should FIH nanomedicine research consent forms/processes address the additional elements of informed consent?

At 45CFR46.116(b), the Common Rule[25] sets forth additional elements of informed consent, to be provided "when appropriate." Of particular relevance to FIH nanomedicine research are the following:

> "(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or

may become pregnant) which are currently unforeseeable;
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;...
(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject...."

Do current FIH consent forms/processes address these additional elements well?

Uncertainties and Unknowns

FIH trials often present far more uncertainty than later-phase studies. A primary reason is that the translation from preclinical to clinical research represents a very large step. Even when animal models are available, it is well recognized that they are imperfect at best, and many conditions lack any reasonably good animal model. Thus, FIH trials may begin with high levels of uncertainty about the effects of the intervention in humans, including basic information like the dose-response relationship, biodistribution and bioaccumulation, and even basic pharmacokinetics.[27]

Certainly this lack of knowledge poses challenges for informed consent, particularly with regard to how best to describe and discuss what is uncertain and what is unknown. But to what extent is this really a problem of disclosure? How much of this problem should be addressed earlier — that is, in the IRB's consideration of whether a study is ready to move from preclinical to clinical trials? What goes into the consent form matters only when the research has been determined ready for human subjects; unfortunately, however, how to determine precisely this critical readiness is under-addressed, especially in novel biotechnologies wherein the characteristics that portend benefit are precisely those posing unknown risks of harm, and basic information is as yet unknown.

Once that prior essential determination has been made, the consent form and process should include information that potential subjects could find important in deciding whether or not to enroll in the research. But what is informative? How should what is uncertain and unknown be discussed?

Uncertainty and Harms to Others

It is one thing to address the possibility of unknown risks of harm to research subjects; it is something else entirely to consider the risks of transmitting harms vertically to offspring, or horizontally to close contacts (family members, researchers, health care providers, etc.). The production and dissemination of nanotechnological interventions has long raised

The production and dissemination of nanotechnological interventions has long raised concerns about risks of harm to third parties and to the environment. The extent to which nanomedical interventions pose similar risks of harm is as yet undetermined, but should be considered by investigators and included in the consent form and process, much as viral shedding has been of concern in gene transfer research.

Is There Life beyond Boilerplate?

The overwhelming majority of clinical research consent forms already address these and most other additional elements as set forth above. However, the standard language used almost never rises above the most routine boilerplate. For instance, everybody adds the following statement to the risk section: "Some risks of harm may be unforeseeable." Most consent forms also inform potential subjects that "you may be terminated from the study without your consent at any time, for example if you fail to follow instructions, if your condition worsens, or if the study is stopped." Some consent forms elaborate further: "If you leave the study we will ask you to allow us to continue monitoring you, for your own health." A few types of studies, such as gene transfer research, have long-term follow-up requirements that are imposed by NIH or FDA, and describe those requirements in the consent form.[26] And virtually all consent forms for studies of any duration include a promise to provide information relevant to participation: e.g., "You will be provided with any significant new information that might affect your decision to continue in the study." The question for FIH nanomedicine research is not whether to include boilerplate statements like these, but whether more detailed and study-specific information is called for.

concerns about risks of harm to third parties and to the environment.[28] The extent to which nanomedical interventions pose similar risks of harm is as yet undetermined, but should be considered by investigators and included in the consent form and process, much as viral shedding has been of concern in gene transfer research.[29] Some nanomaterial may bioaccumulate in the gonads or demonstrate cytotoxicity in gametes.[30] Thus, requiring contraception (for male as well as female subjects) may be important, and the consent form and process may include the request to follow any pregnancy that results during study participation. Analogous precautions have long been followed in gene transfer research, which raises similar concerns regarding both vertical and horizontal transmission of risks of harm.

Long-Term Follow-Up

Understanding the role of patient-subject includes understanding why long-term follow-up (LTFU) is sought. But when subjects are lost to follow-up, most of the problem may not lie with the consent form and process. Investigators need to design good LTFU and incorporate it into their protocols; funding agencies need to support recommended LTFU – not recommend LTFU based on what they can afford to support. Protocols need to address the practicalities of LTFU: how it can be accomplished if patient-subjects are scattered around the country and the globe, after the intervention phase of the study has ended, and if unforeseen but common circumstances arise, such as if the principal investigator changes institutions. Making LTFU easier for patient-subjects helps underscore its importance and their role in knowledge production.

But none of this is specific to FIH nanomedicine research. Determining what follow-up is necessary, appropriate, and practical is a study-specific exercise, based on the nature of the nanomedicine intervention being studied and the information being sought. LTFU may be necessary in nanomedicine research in order to learn about patterns of bioaccumulation and their potential effects; what to look for, when and for how long to monitor, and where in the body to look will ordinarily be study-specific. Analogous considerations have long informed gene transfer research, where delayed development of cancer from insertional mutagenesis has been seen in some study subjects.[31] Describing what is expected of subjects in the consent form and process is simple and straightforward; structuring LTFU to maximize its ease and effectiveness is another matter.

Conclusions and Recommendations

FIH nanomedicine research raises the same informed consent issues as are regularly seen in other FIH research enrolling patients as research subjects. Investigators and IRBs should pay close attention to the need to devise study-specific disclosures relevant to potential subjects' decision making, including poorly understood risks of harm from bioaccumulation, the need for LTFU, and the likelihood that potential benefit will be overestimated. The IRB's task, in essence, is to assist the investigator in making a fair offer of research participation to potential subjects under conditions of uncertainty, where the goals are twofold: (1) to contribute to generalizable knowledge and (2) to keep subjects as safe as possible under the circumstances.

While there are surely some risks of harm that are too great to pose to human subjects, no matter how eager some patients might be to take great risks as research subjects, IRBs should not ignore the perspectives of patient-subjects. In FIH nanomedicine research, the consent form and process help to make clear the scientific nature of research goals and the provisional and iterative nature of research progress. The role of informed consent in clinical research promotes the autonomy of potential subjects and encourages critical reflection by investigators and potential subjects.[32] Thus, the consent form and process have important educational functions, yet they are not intended to serve as a primary means of protecting subjects from the harms posed by excessively risky research. Potential subjects should not be asked to consent or refuse to participate in research unless and until the IRB has decided that the risks of harm posed by the research are reasonable and have been minimized as far as possible.

In these key respects, informed consent in research serves as a powerful reminder of the relationship between science and society. Nanomedicine research opens up a broad vista of potentially profound scientific advances and at the same time exposes clearly how much we still need to know about its potential harms. The consent form and process thus function as vehicles for education and collaboration about FIH nanomedicine research, first between the investigators and IRBs who create the forms and processes, and later between the investigators and potential subjects who use them in decision making. This can only work, of course, when boilerplate is abandoned, study-specific information is conveyed with straightforward clarity, and uncertainty is acknowledged and placed in proper perspective.

Acknowledgements

Work on this paper was supported in part by NIH NHGRI ARRA Challenge grant #1-RC1-HG005338-01, "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight." The contents of this paper are solely the responsibility of the author and do not necessarily reflect the views of NIH or NHGRI. Thanks to Samantha Vaillancourt for research assistance.

References

1. E. Emanuel, D. Wendler, and C. Grady, "What Makes Clinical Research Ethical?" *JAMA* 283, no. 20 (2000): 2701-2711.
2. U.S. Department of Health and Human Services, "Common Rule, 45 CFR 46.101-124," *Federal Register* 56, no. 117 (June 18, 1991): 28012-28022.
3. N. M. P. King, G. E. Henderson, L. R. Churchill, A. M. Davis, S. C. Hull, and D. K. Nelson et al., "Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research," *IRB: Ethics & Human Subjects Research* 27, no. 1 (2005): 1-8.
4. L. Fatehi and S. M. Wolf et al., "Recommendations for Nanomedicine Human Subjects Research Oversight: An Evolutionary Approach for an Emerging Field," *Journal of Law, Medicine & Ethics* 40, no. 4 (2012): 716-750; D. B. Resnik and S. S. Tinkle, "Ethical Issues in Clinical Trials Involving Nanomedicine," *Contemporary Clinical Trials* 28, no. 4 (2007): 433-441.
5. A. D. Maynard, D. B. Warheit, and M. A. Philbert, "The New Toxicology of Sophisticated Materials: Nanotoxicology and Beyond," *Toxicological Sciences* 120, no. S1 (2011): S109-S129.
6. See Fatehi et al., *supra* note 4.
7. J. Kimmelman and A. J. London, "Predicting Harms and Benefits in Translational Trials: Ethics, Evidence, and Uncertainty," *PLoS Medicine* 8, no. 3 (2011): e1001010 (5 pages), *available at* <http://dx.doi.org/10.1371%2Fjournal.pmed.1001010> (last visited November 12, 2012); J. Kimmelman, "Recent Developments in Gene Transfer: Risk and Ethics," *BMJ* 330, no. 7482 (2005): 79-82.
8. R. McGinn, "Ethical Responsibilities of Nanotechnology Researchers: A Short Guide," *Nanoethics* 4, no. 1 (2010): 1-12; S. M. Wolf, G. Ramachandran, J. Kuzma, and J. Paradise, eds., "Symposium: Developing Oversight Approaches to Nanobiotechnology: The Lessons of History," *Journal of Law, Medicine & Ethics* 37, no. 4 (2009): 543-789.
9. J. Kimmelman, "Missing the Forest: Further Thoughts on the Ethics of Bystander Risk in Medical Research," *Cambridge Quarterly of Healthcare Ethics* 16, no. 4 (2007b): 483-90; J. Kimmelman, "Predicting Ethical and Safety Risks to Bystanders from Nanomedicine Research," *Journal of Law, Medicine & Ethics* 40, no. 4 (2012): 841-847; G. Marchant, Applying Prudent Precaution to Nanomedicine Clinical Trials, this symposium; G. Ramachandran, J. Howard, A. Maynard, and M. Philbert, "Handling Worker and Third-Party Exposures in Nanomedicine Research," *Journal of Law, Medicine & Ethics* 40, no. 4 (2012): 831-840.
10. M. E. McAuliffe and M. J. Perry, "Are Nanoparticles Potential Male Reproductive Toxicants? A Literature Review," *Nanotoxicology* 1, no. 3 (2007): 204-10; V. Wiwanitkit, A. Sereemaspun, and R. Rojanathanes, "Effect of Gold Nanoparticles on Spermatozoa: The First World Report," *Fertility and Sterility* 91, no. 1 (2009): e7-e8, *available at* <http://www.sciencedirect.com/science/article/B6T6K-4RB5BNR-2/2/33a12feb54d3316276cbabaa2d9492b0> (last visited November 12, 2012).
11. S. M. Wolf, J. Paradise, C. A. Nelson, J. P. Kahn, F. Lawrenz, "Symposium: Incidental Findings in Human Subjects Research: From Imaging to Genomics," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 216-383.
12. F. Jotterand and A. A. Alexander, "Managing the 'Known Unknowns': Theranostic Cancer Nanomedicine and Informed Consent," in *Biomedical Nanotechnology: Methods and Protocols* (New York: Springer-Verlag, 2011): at Chapter 26.
13. N. M. P. King, "Defining and Describing Benefit Appropriately in Clinical Trials," *Journal of Law, Medicine & Ethics* 28, no. 4 (2000): 332-343.
14. R. Dresser, "First-in-Human Trial Participants: Not a Vulnerable Population, but Vulnerable Nonetheless," *Journal of Law, Medicine & Ethics* 37, no. 1 (2009): 38-50; N. M. P. King and O. Cohen-Haguenauer, "En Route to Ethical Recommendations for Gene Transfer Clinical Trials," *Molecular Therapy* 16, no. 3 (2008): 432-438.
15. N. Kass, H. Taylor, L. Fogarty, J. Sugarman, S. N. Goodman, A. Goodwin-Landher, M. Carducci, and H. Hurwitz, "Purpose and Benefits of Early Phase Cancer Trials: What Do Oncologists Say? What Do Patients Hear?" *Journal of Empirical Research on Human Research Ethics* 3, no. 3 (2008): 57-68; see King et al., *supra* note 3.
16. See King, *supra* note 13.
17. See King et al., *supra* note 3.
18. P. S. Appelbaum, L. H. Roth, and C. Lidz, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," *International Journal of Law and Psychiatry* 5, no. 3-4 (1982): 319-29.
19. L. R. Churchill, D. K. Nelson, G. E. Henderson, N. M. P. King, A. M. Davis, E. Leahey, and B. S. Wilfond, "Assessing Benefits in Clinical Research: Why Diversity in Benefit Assessment Can Be Risky," *IRB: Ethics & Human Research* 25, no. 3 (2003): 1-8; R. Dresser, "The Ubiquity and Utility of the Therapeutic Misconception," *Social Philosophy & Policy* 19, no. 2 (2002): 271-294; G. E. Henderson, M. M. Easter, and C. Zimmer et al., "Therapeutic Misconception in Early Phase Gene Transfer Trials," *Social Science and Medicine* 62, no. 1 (2006): 239-253; J. Kimmelman, "The Therapeutic Misconception at 25: Treatment, Research, and Confusion," *Hastings Center Report* 37, no. 6 (2007): 36-42.
20. See Dresser, *supra* note 14; King and Cohen-Haguenauer, *supra* note 14; King et al., *supra* note 3; Fatehi et al., *supra* note 4.
21. G. E. Henderson, L. R. Churchill, A. M. Davis, C. Grady, S. Joffe, and N. Kass et al., "Clinical Trials and Medical Care: Defining the Therapeutic Misconception," *PLoS Medicine* 4, no. 11 (2007): 1735-1738.
22. See Henderson et al., *supra* note 19; King et al., *supra* note 3.
23. L. R. Churchill, M. L. Collins, N. M. P. King, S. Pemberton, and K. Wailoo, "Genetic Research as Therapy: Implications of 'Gene Therapy' for Informed Consent," *Journal of Law Medicine & Ethics* 26, no. 1 (1998): 38-47.
23. See Kass et al., *supra* note 15; King et al., *supra* note 3.
24. S. Horng and C. Grady, "Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, and Therapeutic Optimism," *IRB: Ethics & Human Research* 25, no. 1 (2003): 11-16; D. P. Sulmasy, A. B. Astrow, M. K. He, D. M. Sells, N. J. Meropol, E. Micco, and K. P. Weinfurt, "The Culture of Faith and Hope: Patients' Justifications for Their High Estimates of Expected Therapeutic Benefit When Enrolling in Early Phase Oncology Trials," *Cancer* 116, no. 15 (2010): 3702-3711.
25. See Common Rule, *supra* note 2.
26. National Institutes of Health, "NIH Guidance on Informed Consent for Gene Transfer Research," *available at* <http://www4.od.nih.gov/oba/RAC/ic> (last visited November 12, 2012).
27. See Kimmelman, *supra* note 7; King and Cohen-Haguenauer, *supra* note 14.
28. See McGinn, *supra* note 8.
29. E. A. Schenk-Braat, M. M. van Mierlo, G. Wagemaker, C. H. Bangma, and L. C. Kaptein, "An Inventory of Shedding Data from Clinical Gene Therapy Trials," *Journal of Gene Medicine* 9, no. 10 (2007): 910-921; King and Cohen-Haguenauer, *supra* note 14.
30. See sources cited in *supra* note 10.
31. S. Hacein-Bey-Abina, C. Von Kalle, M. Schmidt, M. P. McCormack, N. Wulffraat, and P. Leboulch et al., "LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1," *Science* 302, no. 5645 (2003): 415-419.
32. A. Capron, "Informed Consent in Catastrophic Disease Research and Treatment," *University of Pennsylvania Law Review* 123, no. 2 (1974): 340-438.