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Building an Ethical Foundation for First-in-Human Nanotrials

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The biomedical literature and popular media are full of upbeat reports about the health benefits we can expect from medical innovations using nanotechnology. Some particularly enthusiastic reports portray nanotechnology as one of the innovations that will lead to a significantly extended human life span. Extreme enthusiasts predict that nanotechnology "will ultimately enable us to redesign and rebuild, molecule by molecule, our bodies and brains …."[1]

Nanomaterials have special characteristics that could contribute to improved patient care. But the same characteristics that make nanotechnology promising also present risks to humans exposed to nanomaterials. A failure to appreciate these risks could jeopardize the research effort. As others have pointed out, if nanomedical interventions produce unexpected human harm, a loss of public and government support for nanomedicine is likely to follow.[2]

Like other forms of medical innovation, novel nanomedical interventions require human testing to evaluate their safety and effectiveness. In this article, I consider ethical issues raised by the earliest stage of nanomedical testing, first-in-human (FIH) trials. Early-phase nanotrials raise many of the same ethical concerns that are raised by early-phase trials of other innovations. But certain nanotechnology features heighten the ethical challenges in conducting FIH nanotrials.

Nanomedical interventions present a higher level of uncertainty than do more conventional biomedical interventions; the level of uncertainty in the early phase of human testing is also higher than it is in later-phase human trials. Nanotechnology's recent emergence means that many innovations have not yet undergone the animal and other laboratory testing necessary to establish a proper evidentiary basis for human trials. At this point, it is also uncertain whether the traditional laboratory approaches to safety evaluation will supply adequate information on nanotechnology risks to human subjects.[3] Nanomedical products could present risks to "bystanders," too, including manufacturing workers, clinicians, and families of study participants. Much nanotechnology research and development is occurring in the private sector, where sponsors may be reluctant to publicize laboratory and other data that could help other investigators protect subjects in FIH nanotrials.[4] And the hype surrounding nanomedicine could promote unrealistic expectations among patients asked to participate in nanomedicine trials.

For all these reasons, researchers and regulatory officials should take a cautious approach in planning for FIH nanotrials. In this paper, I examine the ethical considerations relevant to FIH nanotrials, with a special focus on the preclinical research base needed to justify such trials. Although other ethical considerations are also relevant to this form of early-phase human research, the most salient concern at this stage is the relative lack of data on risks and potential benefits of investigational nanomedical interventions.

Potential Benefits and Harms

Nanotechnology enthusiasts hail the special properties of this new biomedical tool. Diagnostic systems using nanotechnology could be more sensitive and selective than are existing diagnostic approaches, supplying quicker and better information about serious diseases like cancer and heart disease.[5] Such systems could also give doctors quicker and more accurate feedback on treatment effects than existing monitoring approaches can provide.[6] Drugs delivered by nanocarriers could breach certain biological barriers in the human body more successfully than do existing methods of drug delivery. Drugs incorporating nanomaterials could succeed in reaching targets like cancer cells with greater accuracy and precision, producing fewer unwanted side effects and improved effectiveness.[7] Nanotechnology applications could assist researchers seeking to regenerate organs and tissue to replace ones damaged by illness or injury.[8] Nanotechnology might also be useful in creating better vectors for gene transfer efforts.[9]

But nanotechnology is a two-edged sword. The very features that make it so attractive for biomedical innovation create distinct human health risks. Nanomaterials easily travel into and through the body, eluding its ordinary defenses. As three Australian scientists put it, "the unique physiochemical properties of nanomaterials also mean that they may have unique bioavailabilities and other characteristics that make them potentially toxic to humans."[10] This creates the possibility of unanticipated harm to individuals receiving nanomedical interventions. It also creates worries about unintended exposure in people making nanomedicine products and others coming into contact with the products and product recipients.[11]

Scientists say that nanomaterials could have several harmful effects. Nanomaterials could travel to places other than their intended targets, entering the brain, liver, and other organs.[12] They could affect cell function in undesired ways, altering an individual's DNA[13] or producing detrimental effects like "inflammation, immunoreaction, or cancer."[14] Long-term effects are a major concern, for some nanomaterials are not eliminated by the body as efficiently as are the materials used in conventional medicine.[15]

Animal and other preclinical data on nanomaterial safety are scant, but the data that exist supply some cause for concern.[16] Researchers studying animals exposed to nanomaterials report inflammation and pulmonary fibrosis among test animals.[17] Others have found tissue damage in study animals.[18] A 2009 review of animal studies of carbon nanotubes, one of the most popular nanomedical innovations, found that animal testing had not produced sufficient evidence on this product's potential toxicity:

> An overall conclusion from these studies is the absence of acute or other adverse reactions between one week and three months following nanotube administration. However, none of these studies were designed with a toxicology model or specific mechanism under consideration. This [approach] is needed to determine the overall toxicity profile of carbon nanotubes — particularly in comparison with known toxins and other nanoparticle types ….[19]

The concerns about human safety also draw on existing knowledge about the health effects of ultrafine particles in the environment. These include naturally occurring particles like volcanic ash, as well as the many industrial byproducts associated with modern air pollution. Epidemiological research links ultrafine particles with cardiovascular and respiratory risks. Moreover, although natural selection may have given humans some protective mechanisms against naturally occurring particles, these mechanisms may be less effective against novel nanomaterials.[20]

The dearth of preclinical data means that nanomaterials may have risks that remain undiscovered. Adding to the uncertainty, nanomaterials have novel properties that can lead them to behave in unexpected ways. In its 2007 report on nanotechnology, a Food and Drug Administration (FDA) Task Force warned, "Biological interactions influenced by the particular chemistry and physical configuration of [a] nanoscale material might … occur in ways that are unpredictable without specific test data for the material."[21]

At this point, it is also unclear whether the conventional laboratory tests used to predict the biological reactivity of agents and materials used in new medical products will have the same level of accuracy in evaluating nanoscale materials.[22] As one public health expert put it, "the properties of nanoparticles can be sufficiently different from other chemical and physical agents so that standard regulatory approaches … may not be protective of human health or the environment."[23] For a number of reasons, he writes, human health effects may not be detected through standard testing. Routine assumptions governing such testing, such as the relation of dosage to harmful effects, may be inapplicable in the context of nanoparticles. Much more research will be needed before we have an accurate "big-picture" view of the general risks nanomedical interventions present to humans.

Recommendations for Preclinical Research

Scientists and advisory groups describe several specific actions that are needed to generate adequate preclinical information about safety risks presented by nanomedical interventions. One major task is to determine whether existing toxicity tests are adequate to evaluate materials on the nanoscale.[24] Officials must determine, too, what preclinical data are needed to evaluate the potential long-term toxicity of nanomaterials. More information is also needed on the potential toxic effects of novel nanomaterial properties.[25] A particularly pressing — yet daunting — challenge is to develop a better sense of the risks nanomedical interventions could present to bystanders. Some environmental health experts warn that if researchers and regulators neglect bystander risks, nanomaterials could become the "asbestos of the 21st century."[26]

Many commentators call for a more systematic approach to evaluating nanotechnology interventions. National and international regulators should establish a common research framework for evaluating nanomaterials. They should adopt standard protocols for testing nanomaterials[27] and consistent data reporting parameters that allow data from different laboratories to be compared. According to the FDA Task Force, "many of the studies published in the literature have been conducted with nanoscale materials that are either poorly characterized or not characterized."[28] For this reason, their findings may be inaccurate or inapplicable in other contexts.[29] Mandatory data reporting would be another element of an adequate risk assessment program.[30] In 2010, as part of an effort to standardize regulatory reporting, the FDA issued a required reporting format for sponsors seeking approval of nanomaterial-containing drugs.[31] Experts say that multidisciplinary collaboration among toxicologists, scientists, and doctors will be necessary to establish a rigorous approach to assessing nanomedicine safety.[32]

A "Business as Usual" Response

Many groups and individuals have made specific recommendations for developing an adequate safety testing system for nanomedical materials.[33] Though there is no shortage of recommendations for a cautious approach, authorities have yet to respond in kind. Indeed, the appearance of yet another report endorsing better risk assessment provoked the following complaint from the *Nature Nanomedicine* editorial board: "Another panel of experts in the UK has published another report calling for more research into the effects of nanomaterials on health and the environment. Will anyone listen this time?"[34]

So far, policymakers have failed to translate the calls for caution into formal policy. Nanomedical product development is apparently proceeding on an *ad hoc* basis, with agencies considering new medical products case by case. This is consistent with the FDA Task Force's general conclusion that the existing system governing premarket review of drugs and devices incorporates an acceptable framework for evaluating nanomedical products.[35]

The FDA has already approved nanomedical products for marketing, though critics have questioned whether the products received adequate regulatory scrutiny.[36] Most nanoproducts have apparently been approved based partly or entirely on data from studies of large-particle versions of their active ingredients. This is disturbing, for this approach ignores substantial study data indicating that the "FDA's presumption of bioequivalence is scientifically flawed."[37] And policymakers in other countries appear to share the FDA Task Force's judgment that current regulatory approaches are adequate to oversee nanomedical product development, including oversight of human trials evaluating safety and effectiveness.[38]

Preclinical Data and FIH Trials

Adequate preclinical data are an ethical and regulatory requirement for FIH nanotrials. Such data are necessary to fulfill the ethical and regulatory mandate to minimize risks to human subjects in research. They are necessary as well to evaluate the risks and expected benefits an FIH trial presents.[39] Without solid preclinical evidence, reviewers cannot determine whether the benefits a trial is expected to produce are sufficient to justify the anticipated risks to FIH trial participants.[40]

The current state of nanotechnology research presents two major problems for scientists, officials, and Institutional Review Board (IRB) members considering FIH trials. One is the lack of high-quality preclinical data I described earlier. The other is the general difficulty in predicting human effects from nonhuman animal and other laboratory findings, a problem that is present in all FIH trial situations.[41] In this situation, "How should we define a 'good guess' of study safety?"[42] And how should we decide whether FIH trials are likely to generate a benefit sufficient to justify the risks they present to human participants?

Jonathan Kimmelman's 2009 volume, *Gene Transfer and the Ethics of First-in Human Research*[43] offers good advice on how to answer these questions. Although he focuses on FIH trials in gene transfer research, FIH nanomedical trials present similar ethical challenges. Below I describe briefly Kimmelman's contribution, but readers should consult the volume itself for a full account of his elegant and insightful proposals.

Kimmelman argues that reviewers should require FIH studies of novel interventions to meet a condition he calls "modest translational distance."[44] This condition is not a mathematical formula, but a normative concept like clinical equipoise, incorporating study-by-study evaluation and judgments of the expert scientific community.[45] To meet the modest translational distance requirement, investigators must make a convincing case that a proposed FIH study relies on good preclinical evidence, as opposed to hunches and speculation. When the modest translational distance condition is met, preclinical data on anticipated human risks are solid enough to supply a reasonable basis for human risk estimates. First-in-human trials crossing a modest translational distance have adequate scientific value to justify risks to subjects, too.

Kimmelman argues that the preclinical evidence for an FIH trial of a novel intervention should be evaluated according to four criteria. First is the internal validity of the preclinical research, which depends on its use of rigorous methodological techniques like

randomization and blinding. Many animal studies fail to adopt these techniques, and this reduces the predictive value of their results.[46] Second is the external validity of the preclinical evidence, which depends on how closely the preclinical and human studies are related. A major factor here is the extent to which the animal models used in preclinical studies actually mimic the human response to an investigational intervention. Unfortunately, animal models often fail to predict human effects.[47] A third consideration is whether the proposed human trial incorporates methods and objectives that resemble those used in preclinical studies. Surprisingly, FIH studies sometimes include substantially revised endpoints and other experimental features that seriously diminish the relevance of the animal studies preceding them.[48] The fourth criterion concerns the credibility of claims that a body of preclinical evidence is adequate to support an FIH trial. Their personal and financial investments in scientific projects can lead researchers to make inflated claims about the quality and significance of the preclinical evidence supporting their FIH proposals. Kimmelman suggests several actions that can help study reviewers ascertain whether investigators proposing FIH trials are presenting too positive a picture of their preclinical evidence.

Besides demanding solid data on human risks, the modest translational distance requirement addresses the justification for FIH trials. Early-stage human trials are not designed to influence clinical practice in the way that phase III clinical trials are expected to do. Instead, FIH trials are designed to produce scientific information to guide planning for later-stage human trials. Kimmelman favors a broad approach to assessing the value of FIH trials, contending that an FIH trial can contribute in the following three ways: “by motivating further preclinical studies of an intervention (‘reciprocal value’), by prompting modification of human translational trials of a particular agent (‘iterative value’), or by informing other areas of loosely related research practice (‘collateral value’).”[49] The demand that FIH trials cross a modest translational distance from the preclinical evidence base increases the chance that those trials will be valuable in at least one of these ways, pointing to the best next steps for investigating a human health problem.

Researchers and reviewers would be wise to apply the modest translational distance requirement to FIH nanotrials. Such a move would be consistent with ethical and regulatory standards and would be in the field’s self-interest, too. A nanotrial disaster would threaten the entire field, just as Jesse Gelsinger’s death set back the gene transfer endeavor.[50]

It is true that demanding a high-quality science base for FIH nanotrials could slow the move from laboratory to human research. Yet setting a high standard is likely to make the field more productive in the long run. There is wide agreement that too many interventions that appear promising in the laboratory later prove ineffective in humans.[51] One explanation for this situation is that human trials are going forward without adequate preclinical support.[52] By setting high demands for the science underlying FIH nanotrials, nanotrial sponsors could increase the overall productivity of nanomedical research.

Nanomedicine Hype and FIH Trials

First-in-human trials involving individuals with serious and untreatable conditions raise additional ethical questions. Several features of this trial situation can compromise subjects’ decisions to participate in FIH trials.[53] Enthusiasm about nanomedicine could complicate efforts to promote informed and voluntary consent to early-phase nanotrials.

At this point, cancer is the most active nanomedical research area. Nanotrials have already involved subjects with untreatable cancer[54] and many trials are ongoing.[55] The National Cancer Institute (NCI) is an ardent nanotechnology supporter. The agency has created an “Alliance for Nanotechnology” whose aim is “to increase the visibility and availability of

nanomaterials and nanoscale devices to allow investigators … to do what they do best — discover and invent new tools to fight cancer."[56]

This positive attitude is surely useful in public relations and budget negotiations, but some of the agency's promotional assertions are inconsistent with the scientific literature. For example, in their document discussing nanotechnology safety, NCI officials affirm the need for careful study of nanomaterials, but downplay the risks. According to this document, "most engineered nanoparticles are far less toxic than household cleaning products, insecticides used on family pets, and over-the-counter dandruff remedies. Certainly, the nanoparticles used as drug carriers for chemotherapeutics are much less toxic than the drugs they carry…."[57] Assertions like these seem premature in light of the concerns expressed by many scientists and environmental health experts.

Excessive enthusiasm about nanomedicine could lead to unwarranted decisions to move forward with FIH nanotrials. It could also complicate the effort to give prospective participants a clear picture of the risks and uncertainties accompanying early-phase nanotrials. Individuals entering the research discussion with a distorted impression of nanotechnology's clinical promise might tune out information about a trial's limits and dangers. These are general problems in early-phase research involving patients with serious illness, but nanotechnology's rosy public image make them particularly worrisome in the context of FIH nanotrials.

Strengthening FIH Nanotrial Oversight

In the current climate, nanomedical product developers and regulatory officials are betting that these products will prove to be reasonably safe and effective. They are also betting that such products fail to present dangers and uncertainties meriting a departure from the customary approach to risk assessment. These may prove to be winning bets, but if they are not, trial subjects, patients, and bystanders will bear the heaviest burdens of the loss.

Without regulatory intervention, the level of risk assessment is likely to remain unchanged. As one interdisciplinary research group observed, "Research into understanding and preventing risk often has a low priority in the competitive worlds of intellectual property, research funding, and technology development."[58] Nanomedical researchers and industry sponsors would benefit from taking a cautious approach to risk assessment, but we should not count on them to do so voluntarily.

Taking action in four areas could go a long way toward improving decisions about FIH nanotechnology trials. One is to create a trial registry covering all phase I nanotrials. Researchers should be required to submit to the registry potentially relevant safety data from both preclinical studies and early human trials of nanomedicine. Industry sponsors will probably object to such data sharing on the grounds that the data are proprietary information, but it would be possible to report safety data without divulging confidential material on product research and development.[59] A narrow reform would be to collect such data in a secure database, with access limited to FDA and other regulatory officials.[60] A more expansive approach would be to establish a database open to anyone seeking information on potential hazards to subjects in FIH nanotrials. Ideally, the database would include FIH studies in all settings, whether or not the studies were intended as support for FDA approval. Access to such information would give those planning and reviewing FIH studies a better evidentiary basis for evaluating risks to FIH subjects and the justification for proposed studies.

Improved decisions would also come with efforts to enhance the quality of scientific and ethical review of FIH nanotrials. Analysts make several recommendations that could achieve

this goal. The FDA could enhance its oversight by developing better preclinical tests to evaluate the safety of nanoscale materials; the agency could also require research sponsors to submit data from such tests when they seek permission to conduct FIH nanotrials.[61] Some analysts call for the creation of a national nanomedicine research oversight body with duties similar to the NIH Recombinant DNA Advisory Committee.[62] Alternatively, the NIH could collect review materials from IRBs evaluating FIH nanotrials and make them available to other IRBs considering similar trials.[63] Academic health centers could take the ethical high road by posting on websites their IRB proceedings regarding FIH nanotrials.[64]

Bystander risks should be another target of policy action. Although FIH trials will expose few bystanders to nanomedical product risks, large-scale production and use of such products would expose many people to such risks. Potential adverse effects to bystanders should be addressed at an early point, to avoid harm to others and to avoid the waste of resources that occurs when harmful products are permitted to enter the market.[65] In the past, oversight groups have evaluated bystander risks presented by other forms of early-phase human research, including research involving gene transfer, xenografts, and the nuclear-powered artificial heart.[66] Officials could establish a nanoproduct oversight group to examine bystander risks and determine whether additional research is needed to develop an adequate understanding of the nature and severity of such risks.

Toning down the public rhetoric about nanomedicine could improve the situation, too. Investigators and research sponsors should openly acknowledge that nanomedicine's potential benefits might not materialize, and that unanticipated harms might materialize. Truth-telling about nanomedicine could produce better decisions about when to go forward with FIH nanotrials and also give prospective subjects a more accurate picture of study risks and potential benefits. As a relatively novel area of inquiry, nanomedicine has an opportunity to establish the high standards that could make the field an ethical and productive human research endeavor.

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