Concepts of Risk in Nanomedicine Research

Linda F. Hogle

Risk is the most often cited reason for ethical concern about any medical science or technology, particularly those new technologies that are not yet well understood, or create unfamiliar conditions. In fact, while risk and risk-benefit analyses are but one aspect of ethical oversight, ethical review and risk assessment are sometimes taken to mean the same thing. This is not surprising, since both the Common Rule and Food and Drug Administration (FDA) foreground procedures for minimizing risk for human subjects and require local IRBs to engage in some sort of risk-benefit analysis in decisions to approve or deny proposed research.[1] Existing ethical review and oversight practices are based on the presumption that risk can be clearly identified within the planned activities of the protocol, that metrics can reasonably accurately predict potential hazards, and that mitigation measures can be taken to deal with unintended, harmful, or catastrophic events.

There is a great deal more to the ethics of nanomedicine than how best to assess risk, but for the purpose of this article, I problematize the concepts of risk that have been central to discussions about the topic, which have focused on the material characteristics and emerging properties of nanoscale entities themselves. I highlight some less discussed yet important aspects of risk, namely, that it is contingent on many factors outside the technical aspects of research, is perceived differently by different participants in new technology development, and may be operationalized for particular purposes. That is, the question of which kinds of potential harms become visible and the manner in which attempts are made to contain risk (or not) have distinct political and economic outcomes. There are ethical implications for the way societies make such decisions. As John Adams has put it, "Risk management decisions are moral decisions made in the face of uncertainty."[2] In this article, I contextualize concepts of risk within contemporary social and political environments influencing the rapid growth of nanotechnologies, in particular, nanodiagnostics and therapeutics. Ethical analyses undertaken in the project producing this symposium, "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and

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Oversight,"[3] have occurred in a historical moment in which translational medicine, evidence-based practice, debates about regulatory and health care reform, and awareness of prior incidents of harm from medical innovations collide in the question of how best to govern potentially high-risk, high-benefit technologies. At the same time, a superabundance of new data produced by and about nanomaterials threatens to overload existing frameworks to manage the safe introduction of new products while creating a need for new kinds of expertise.

been less discussed. The examples I use support two of the major recommendations of the project's recommendations article, namely, to convene an interagency working group facilitating communication of information across agencies and organizations, and to create a Secretary's advisory group on human subjects research in nanomedicine, with heterogeneous composition and public transparency.[4]

In the area of nanodiagnostics and therapeutics, there have been calls for extreme regulation on the one hand and on the other, a belief that existing over-

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Risk has been conceptualized differently over time, across societies and across professional and disciplinary groups, but it has taken on considerable cultural significance. Risk has become a predominant ordering concept in contemporary society, a phenomenon which is best understood sociologically and historically. First, I briefly outline key concepts and background necessary for putting risk concepts into perspective. I then deal with potential harms of relevance to nanomedicine and how uncertainty is managed. While other authors in this symposium have effectively described a number of technical risks, that is, those related to the material properties, physical or chemical interactions, and protocols, I discuss additional sources of potential harms of a social nature, which have salience but have

sight systems are fully sufficient for the review of any novel entity.[5] Conflicts over the best way to define and handle risks to date have resulted in an absence of coherent or consensual agreements about acceptability or tolerance of specific kinds of risk. As a result, oversight and regulation may evolve in a patchwork manner. There are implications beyond the issue of protecting human subjects in clinical trials. Rather, science is a social enterprise, and if research practice is not properly handled, there is the additional risk of compromising science as a social good.[6]

Risk as an Object of Study

A quick search for the terms "risk and nanomedicine" found 386 citations in 2006, 2,410 in 2011, and 1,780 for the first half of 2012, each year increasing in proportion to all articles on "nanomedicine."[7] Why is risk showing up more as a topic, given that nanomedicine techniques have been used for some time and there have been no major incidents of adverse effects (or at least, not widely reported if they exist)? Are more potential risks being uncovered by new data? Is concern over certain kinds of harms increasing? Is the enhanced discussion intended to stimulate or preempt changes in oversight? Or is attention to risks in nanomedicine part and parcel of the intensifying focus on risk in society at large? More fundamentally, what

do we mean when we as scientists, social theorists, bioethicists, and experts in law and policy use the term?

There are a number of subtle aspects to risk as a concept, and it is used in various ways across disciplines. As David Garland put it:

> Today's accounts of risk are remarkable for their multiplicity and for the variety of senses they give to the term. Risk is a calculation. Risk is a commodity. Risk is a capital. Risk is a technique of government. Risk is objective and scientifically knowable. Risk is subjective and socially constructed. Risk is a problem, a threat, a source of insecurity. Risk is a pleasure, a thrill, a source of profit and freedom. Risk is the means whereby we colonize and control the future. 'Risk society' is our late modern world spinning out of control.[8]

Risk, as compared to an actual incident of harm, conveys randomness and chance — something that may or may not occur and only to some people. But professional and disciplinary groups define and use the term differently: in health and civil safety fields, risk is associated with hazards and danger of harm, whereas in business and finance it means volatility and can imply the potential for either loss or opportunity and profit.[9] Risk assessment professionals think in terms of objective risks, that is, statistical correlations that can be made about phenomena, while many social theorists counter that definitions, measurements, and experiences of risk are always socially and historically situated. François Ewald suggests that risk is a way of treating phenomena: "Nothing is a risk in itself; there is no risk in reality. But anything can be a risk; it all depends on how one analyzes the danger, considers the event."[10] A probability of a phenomenon can be calculated to try to make an objective account on which to base decisions, but the statistical calculations themselves are placed within framings which may affect whether and to what extent something rises to the level of risk.

For purposes of this article, it is less important to create a precise definition of risk, assumed to be universally understood, than to examine the phenomena that make some things come to be viewed as risky (or not), which risks are rendered more visible than others, and why. I begin with a brief review of works that have theorized risk.

Social theorists Ulrich Beck, Anthony Giddens, and Nikolas Luhmann have argued that risk has become the predominant concept through which to view contemporary social life.[11] That is, the feature which most characterizes modernity is that risk discourse has become the basis of making decisions about economic and social life, and the lens through which individuals view their lives and social interactions. In their account, risk resides in the socio-technological systems in which we are engaged in everyday life rather than in natural phenomena alone. The technologies and institutions humans have created to benefit society are embedded in everyday life, but unintended, negative consequences are created in the process. The very institutions that produce risks (e.g., science, industry, governments) then create new institutions to measure potential dangers in an attempt to control or mitigate them.

A different take on risk analyzes it in terms of the practices, techniques, and rationalities which are used to regulate social life towards specific ends. In this account, more concerned with governmentality, social problems are now understood and ordered by specialized, professional experts who determine the acceptability and proper handling of risk events. Risk becomes "a way — or rather, a set of ways — of ordering reality or rendering it into calculable form."[12] Structures for governing societies are cast in terms of risk calculation and prediction, creating a sense of constant precaution. An entire industry has arisen to perform risk assessment (identification, quantification, and characterization) and risk management (decision-making based on assessments of "acceptable risk," and communication of strategies for risk mitigation), which then counsels governments, enterprise, and citizens on how to proceed with life and work.[13]

Although the state has legal and moral responsibility for the physical safety of its citizens, the capability of authorities to control risk has come into question. Whether responding to highly visible disasters (such as the tsunami and subsequent Fukushima reactor explosion and Hurricane Katrina, in which the devastating effects of natural disasters were amplified by human failures) or preventing dangers from new technologies, people feel they cannot trust authorities to protect them.

Parallel to the rise of risk analysts and managers is the rise of scholars who argue that concepts of risk must be understood culturally and politically, and that policy decisions based on risk analyses are not value-neutral.[14] Mary Douglas and Aaron Wildavsky argued that risk has a social function; that is, the definition of particular hazards as risks (or not) has implications for the regulation of social order.[15] Drawing on their work, others have demonstrated the various ways that risk may be politicized: it can be used to label groups or activities as being associated with risk (people "at risk" of carrying a genetic disorder or infectious disease), or to exclude groups from participating in activ-

ities in the name of protection (as in refusing employment to those seen to be "at risk" of contracting illness in certain jobs).

Douglas makes an explicit link between risk and morality, asserting that value judgments made about the acceptability of the risk and tolerability of harmful outcomes (should they occur) are always moral assessments. They may take into account scientific findings and facts believed to be objective, but they are made within particular economic, social, and political contexts.[16] Understanding the values embedded in concepts of risk is thus important for policy purposes. Moral communities and governmental authorities can be authorized to deal with danger in particular ways (or not, depending on how it is framed), but their decisions will not affect all equally. In the balancing of societal needs (for protections, security, economic well-being, benefits from scientific discoveries), some interests may gain and others lose. There will also always be those who are more vulnerable to the effects of decisions, particularly if they have little say in public policy decisions.[17]

Some would argue that contemporary societies now operate with an ethical imperative of risk aversion — that is, efforts to prevent risks from ever being taken.[18] One could ask: have we come to expect a no-risk society? Jesse Goodman, chief scientist at the FDA, suggested that there is a new intolerance for risk when he told the agency's Science Board that "uncertainty is not a concept that seems to be a part of our culture right now, except in celebrity marriages."[19] A society intolerant of risk would require policies that would require elaborate institutional infrastructures and constant surveillance to pre-detect circumstances which may or may not ultimately be dangers. Even then, such a society could not eliminate the uncertainties that exist in contemporary scientific medicine. The next section discusses risk as it applies to medicine and provides some historical basis for how it has been assessed and managed.

Risk and Human Medical Experimentation

The concept of risk as applied to human medical experimentation is relatively recent. Until the 20th century, there was not an organizational separation of experimentation from therapy in humans. As historians Sydney Halpern, Susan Lederer, and Harry Marks have shown, experimentation had previously been done within the bounds of medical practice, using a doctrine of "lesser harms."[20] Physicians judged what sort of interventions, including experimental treatments, were appropriate for their patients, and relied on persuasion to get them to participate. The rise of scientific medicine and changes in the organization of medicine in the late 19th century created conditions for more systematic experimentation on humans and drove the development of formalized clinical trials. Scientific theories about disease causation had to be confirmed in humans, and treatments had to be tested in controlled ways in humans to prove their efficacy.[21]

The increasing use of patients in trials changed the relationship of physicians to those who trusted them with their care. As more healthy volunteers became involved, a different set of responsibilities was also required to deal with humans-as-subjects who may not have had a relationship with the clinician-investigator. While historical evidence suggests that consent was obtained from patients for procedures, there was considerable resistance to a uniform code of protections by physician researchers, who insisted that testing concepts in humans was critical to medical knowledge. Informing patients of risks was not a systematic practice, and it was not formalized by professional associations or governmental authorities in the U.S. until the American Medical Association's voluntary guidelines for clinical investigators using humans in research in the 1916 Code of Ethics.[22] Benevolent deception and nondisclosure were still practiced, in the belief that providing too much information about potential harms might be detrimental to the patient — and to their relationship with their physician.[23]

The idea of tying benefits of a medical treatment to a probabilistic way of thinking about risks came as early as the 18th century, for example, in experimenting with smallpox vaccines. The disease was deadly for individuals, and there was the grave possibility of spreading it to others, but the vaccine itself could also harm or kill. How could it be known whether the potential great benefits were worth the potential great cost of life and loss of trust in physicians? Thomas Nettleton, credited with linking the notion of benefits and risks to probabilistic thinking, suggested that a numerical argument could be made to weigh costs against benefits using the new practice of collecting population-based vital statistics.[24] The logic of weighing risks of such experimentation against possible benefits came more into public discourse in the second half of the 19th century, particularly with interventions that required healthy volunteers rather than ill patients. Halpern illustrated this shift in her history of vaccine development.[25] The vaccine was a novel innovation with tremendous therapeutic potential, but little could be anticipated concerning dangers. Employing techniques of probability theory and statistical methods emerging at the time enabled the calculation of risk, created a tool with which to persuade people to accept immunization, and began to move decisions about harms and benefits into the realm of separate nonmedical experts. By the

mid-20th century, clinical research activities became more formalized, with the advent of randomized clinical trials and increasingly standardized procedures for conducting experiments. The changes in the organization of medical experimentation shifted concepts of protection and responsibility for taking on risk to the patient, with a focus on autonomy, individual rights, and entitlements — elements that had not traditionally been a part of medical practice.

The approach to managing risks began to shift from physician judgement to procedural means for containment of ill effects, primarily through the use of consent documents, and the formalization of protocols and guidelines administered through federal-level oversight organizations. While such formalized procedures certainly help to standardize practices, provide control, and codify expectations of ethical conduct, Halpern suggests that the irony was that having such systems in place actually enabled higher-risk experiments to take place, because of the belief that the procedures and rules would capture and manage risk.[26]

This history is important to keep in mind when considering novel technologies such as nanomedicine, not only because of the ongoing tension between protecting human subjects and fostering science to find better treatments for them, but also because of what can be learned from observing responses to such dilemmas within specific particular social, historical, and political conditions. The development of particular kinds of institutional responses and ways of thinking about humans-as-subjects was rooted in broader social and scientific phenomena at a particular historical moment, yet we persist in using essentially the same approaches today. Care of the subject has come to be framed primarily in terms of possible risks and benefits — as determined by mediating experts such as bioethicists and risk assessors — as much as general well-being.[27] Also, while concepts of risk are collective and population-based, responsibility for risks is largely on individuals. The tensions between differences in advocates for the value of population-based science and advocates for the rights and protections of individuals are simultaneously technical, ethical, and political. This is an old and continuing debate about normative ways of examining risk, but what is still often omitted in the bioethics and risk literature is consideration of patients within the context of their everyday lives, not reduced to statistical subjects or idealized as rational decision-makers.

This brings the discussion back to the question of who takes on responsibility for risk and risk mitigation, and who is obligated in case something goes wrong. Although discussions of trial sponsor responsibility and reparations exist, they are often within the framework of liability or corporate social responsibility. What has not been sufficiently studied in the bioethics and risk literature is the interaction between medical and business (or market) risk assessments. As stated previously, decisions about risk are valued-based: beyond specific harms and benefits residing within a product, judgments about the release of new products and protection of human subjects involves the interplay of potential market, cost, and public accountability issues.

An instructive case showing how medical risk assessment can be explicitly tied to potential markets is Interleukin-2 (IL-2, marketed as Proleukin), an anticancer drug. Developed by Cetus, IL-2 was touted as a breakthrough drug and evidence of the potential of the new, rapidly growing biotechnology industry sector in the 1980s and 1990s. At the time, several related trends were coming together: increased public demand for new medicines, media coverage hyping the potential of biotech drugs, a strong entrepreneurial environment with flows of investment capital into a burgeoning new industry, but also, greater public scrutiny of regulatory decisions. Using data from FDA advisory committee meetings, Arthur Daemmrich shows how risk contexts changed over time and in interaction with external factors beyond risk calculations themselves. Considerations included the following: the interplay between conflicting concerns about severe adverse effects appearing in trials and insufficient expertise of physicians with the new modality, market pressures to have successful biotech products, public pressures to approve risk-free products, and concerns about access to expensive drugs (even though price was not supposed to be a factor in approval decisions).[28] Initially, the drug was not approved due to severe side effects, but in negotiations with the sponsor, changes were made in the target population, data analysis techniques, and more. After several years, despite persistently clear evidence of a high risk of adverse effects with little proof of efficacy, the FDA allowed IL2 to be used in specific populations, but required the sponsor to conduct long-term monitoring. Daemmrich argues that the shift in attitude toward risk shown in advisory committee minutes included an explicit accommodation of market needs.[29]

Daemmrich goes on to compare the politics of risk assessment of IL-2 in Germany, which had quite different historical and social risk contexts related to human subjects protections, physician roles and responsibilities, public awareness of clinical trials, different regulatory processes, and a conservative economic environment. In the context of broad social concern about all genetic modifications, EuroCetus emphasized the "natural" biological activity which

would pose no special risks whereas in the U.S. the emphasis was more on patient need and the growth of new markets trumping necessary risks.[30] Even though there was general concern about genetic technologies, specific drug trials were not generally publicly visible, and decisions remained more in the hands of physicians. This resulted in a much easier integration into regular therapeutic practice than in the U.S. It is not that IL-2 had any fewer substantive potential harms, but rather there were significant differences in the way the two environments dealt with risk. More comparative work such as this would provide a more nuanced understanding of risk and medical innovation.[31]

in preclinical studies or may be surmised from analogy to other known phenomena, but if a harm has not yet been observed in ways that are deemed relevant (especially for humans), it must be identified and labeled as such to provoke a response from scientific or policy communities. Such decisions always involve value judgments. Which harms are deemed to be relevant, relevant for whom, and who is involved in judging?

Enormous investments have gone into devising formulas and procedures to identify, predict, and manage risk, thus making risk a major industry in the 21st century. The work of "taming chance" done by risk experts is about detecting, quantifying, and characterizing

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Locating and Containing Risk

If risk is culturally contingent on historical, political, and social conditions, then it follows that some things that may be considered risky in one set of circumstances may not be considered risky in another. Niklas Luhmann argued that the experience of risk is not just about the potential physical harm itself; rather, it results from processes by which groups and individuals create interpretations of risk.[32] He further suggests that risk events, whether theoretical or real, will not have an impact unless humans observe them and communicate the experience to others. Essentially, this is a question of what comes to count as risks worth worrying about in societies, and what choices are made as a result, based on some calculus of probability and magnitude of harm. For example, with known risks and proven harms after Fukushima and other nuclear disasters, some countries abandon nuclear energy technologies and others proceed. With mixed interpretations of potential harms from genetically modified crops, European countries had much greater public attention and hence, regulatory scrutiny, than the U.S.

In judging the relevance of risks from an emerging technology such as nanomedicine, much depends on observations of harm; physical injury may be observed

likelihoods and vulnerabilities.[33] But managing uncertainty entails more than identifying potential risks and informing those who may be affected. Where risk cannot be quantified, attempts are made to deal with uncertainty by creating rules, procedures, and categorizations with which to guide decisions. Diane Vaughn calls these ways of directing work practices and surveillance for anomalies "technologies of control."[34] These become ways of trying to transform uncertainty and randomness into certainty and regularity.

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subject research which are often omitted in discussions about protections, that is, the humans themselves.

Managing Uncertainty

Standardized procedures provide control, promise to contain risk, and establish a lingua franca among a diversity of research and regulatory communities. As such, they serve as an important guide for decision making as well as coordinating information.

In human subjects research, bioethics has perhaps become overly preoccupied with procedural matters. Emphasis is on what goes into the consent form and process, what is or is not disclosed (should subjects be told that this investigational intervention is a nanotherapy?), and the clarity of the information given to trial subjects. These issues are critically important, but an over-reliance on informed consent for protecting subjects puts considerable burden on individuals to take on risk, despite the fact that risk is estimated for populations, not that individual. Individuals are put in the position of having to take responsibility for their own understanding of the risks of nanomedicine, which are complicated even for experts to understand, and much of the information provided to individuals to make a decision is filtered through experts with particular positions on the research.[35] What also may be missed by focusing primarily on procedures are the broader questions of how risk might be differently interpreted by participants (e.g., subjects, researchers, review committees, regulators) and who is responsible for ameliorating risk.

In nanomedicine, technologies of control include taxonomies based on various properties of nanomaterials or their mode of action. The sorting of products or materials into discrete categories is meant to provide a way to make decisions about when and how to act, both prophylactically and post-event. While size is the obvious criterion for identifying nanotechnology, many writers have debated if this should be the criterion for signaling and then estimating risk, and if so, what the size cutoff should be. Steffen Hansen et al. advocate instead using a combination of properties and the location of the nanostructure in systems to trigger risk assessment (differentiating bulk products, those with nanostructures on the surface, and nanoparticles, with nanoparticles being further subdivided by shape and form).[36] Taxonomies are useful for making review processes more expedient and may help with recognizing what might trigger the need for greater oversight. Still, phenomena at the nanoscale — particularly in interaction with human biology — may escape tidy boundaries. Even categories based on nuanced understanding of emergent properties and interactions at the nanoscale tend to assume that risk is measurable and can be neatly correlated with material properties and attributes, which may not be the case. Risk is fluid, not static, as many models presume, and is largely influenced by the way it is framed within particular social environments.

Risk-aversion strategies may focus so intensely on technical aspects that they are blind to other non-technical issues, which may ultimately create more significant dangers because they are less obvious and may be ignored. There are several "non-technical" sources of risk in any enterprise, especially potentially high-risk, high-profile areas such as nanomedicine. These include the local organizational and institutional contexts in which science proceeds, including the way organizations deal with anomalies and respond to external influences. Scientific and sociological literatures alike are rife with examples of risk classifications that misdirect information-gathering efforts or miss unexpected potential threats. A classic example is bioterrorism preparedness systems focused on sophisticated high-tech systems (such as missile systems), when the actual threat comes from sources using low technologies (such as shoe bombs). More insidiously, typologies, routines, and procedures, for all their value, may foster a false sense of security. When everything is categorized as high- or low-risk, with rules in a guidebook somewhere for how to proceed, there is a mirage of everything being under control. Certainly many safety problems can be handled if everyone knows what they are supposed to do. Yet having procedures in place may create complacency, may under- or over-emphasize some factors at the expense of others, and may not deal with other types of risk, such as the many kinds of organizational or other systemic errors that may create harms. Charles Perrow, for example, has warned against the tendency to ignore "normal accidents." These are the small events which are viewed as a routine, unavoidable part of scientific processes.[37] He argued that large-scale, high-impact accidents are rarely the result of a single technological cause; rather, they result from organizational, technical, and contextual phenomena acting together. In the famed example of the Challenger launch decision, for example, Diane Vaughn found that when no serious consequences resulted from early episodes of problems such as O ring seal failure, such events were accepted as normal, unavoidable, and thus nothing to worry about. She termed the phenomenon of becoming accustomed to such events as the "normalization of deviance."[38]

What compounded the Challenger problem was unclear authority for responsibility and miscommunication between engineering teams and management. More than a lack of "safety culture," Vaughn argues

that external pressures to speed innovation in the face of resource scarcity, including a competitive environment and the need to justify high-risk outcome research utilizing large federal funding, contributed to accepting anomalies as normal and failing to see warning signs.

In Vaughn's examples of aerospace and traffic control, workers look for anomalies in a relatively standardized institutional context. Scientific practices in nanotechnology, though, are still evolving, and often take place in small start-up firms. Work practices may not have become stable enough to recognize anomalies, and the science itself still has many "unknown unknowns." What is the "normal" against which one can identify an anomaly?

Like space exploration, the nanotechnology environment includes the need to demonstrate progress in light of significant federal and private investments. Like any new area, there is steep competition for funding and intellectual property, so developers of nanoscale products are protective of their knowledge. Data sharing, particularly regarding findings about dangers or problems arising in research at any stage (e.g., information beyond what might be contained in clinicaltrials.gov or other open sources), could contribute to an early warning system. Yet resistance to sharing information due to competitiveness, or perhaps simply a lack of incentive, constrains attempts to create such a system. The inter-agency working group proposed by Fatehi et al. in this issue would aid recognition of problems across regulatory domains,[39] but can only go so far without researchers' willingness to be open about potential problems.

Converging Technologies and Disciplinary Constraints

One of the hallmarks of nanotechnologies is the trend toward so-called converging technologies, in which there are synthetic, biologic, and informatic components.[40] Nanomedical techniques require knowledge of systems biology and cell signaling, mathematical modeling, biophysics, and more. They utilize physical as much as chemical properties for intended effects, and may involve emergent properties (properties that may change once the material is at the intended site), which may be physical, biological, or both. For example, many nanotherapeutics build upon existing technologies using liposomes, micelles, and nanoparticles. Some researchers are striving for even greater specificity and control by designing modular devices with programmability features. To illustrate, one device being tested uses DNA origami techniques and is designed to act like a container, delivering a payload of a drug or other material that releases its cargo only in the presence of a particular set of molecules. The result is a three-dimensional DNA "box" that can be opened by using an aptamer as a key. The multiple, programmable activities, including the ability to recognize and activate signaling pathways in target cells, means the device is simultaneously a sensing, therapeutic, and computing device.[41] Several areas of physical and life sciences are brought together, but it is not yet clear that these professional communities speak to each other or read each other's literatures sufficiently to recognize when a problem may occur.

It would be difficult to say, then, that nanomedicine is a bounded field with its own safety and efficacy features. Nanoscale techniques are being used in gene editing and other genetic approaches to therapy, as well as in stem cell and tissue engineering approaches to regenerative medicine. For example, nano techniques are used to initiate cell signaling cascades to stimulate a regenerative effect within a host's body and to self-assemble nanofibers into blood vessel-like structures to promote angiogenesis.[42] This makes it difficult to classify activity that is nano-specific rather than product-specific. Further, the sheer complexity of some approaches to nanotherapeutics exceeds previously existing therapeutic agents. For example, a multi-stage, nested system is one proposed way to foil the body's natural barriers and still deliver a payload of drug to a targeted area.[43] Products containing sensing and data-collecting features constitute a completely different form of potential risk besides any physical or chemical effect in the body, including concerns about data use and privacy.[44] Existing definitions of toxicity and biocompatibility, based on much older biological and chemical techniques, become difficult to sustain with such products, especially those with properties designed to change once within a particular environment in the body. For example, Rebecca Hall et al. use the example of carbon nanotubes, which may be nontoxic, but may become toxic based on size and shape.[45] When regulators are accustomed to evaluating safety based on the way previous products have conventionally been reviewed, they may likely be sensitized to look for certain forms of risk while not considering others. Steffen Hansen et al., among others, argue, for example, that the current regulatory review paradigm centered on toxicity does not take into account the unique kinds of activity associated with nanotherapeutics and diagnostics that might cause an immune or other response in the body.[46] How should a chemical molecule that self-assembles into a machine-like entity or a drug delivery vehicle be categorized, much less evaluated?

Regulatory expertise is just catching up to many nascent fields, and some have argued that the FDA is

unprepared for new kinds of evaluation.[47] Product risk evaluation for regulatory purposes has conventionally been done based on whether the product of interest fits statutory definitions of a drug (seen as having primarily chemical properties), a device (with mechanical properties), or a biological (often derived from human or animal sources and having primarily biological properties). Each of these categories has a particular statutory history, disciplinary ties, and conventions for determining what comes to count as a valid safety concern. However, W. John Koolage and Ralph Hall argue that because more is now understood about underlying forces at the nanoscale that make materials behave as they do, there is little justification to conduct safety assessments based on conventional ways of evaluating chemistry, biological, or physical properties as required in existing statutes.[48] The ways in which nanodiagnostics and nanotherapeutics combine different technologies, as well as the diverse kinds of technical, disciplinary expertise involved, call for a rethinking of the basis for which any authority evaluating risk and safety — regulatory authorities in particular — makes determinations.

Lived Experimental Bodies

What gets tested in clinical trials is the discrete entity being injected or introduced, or metabolites from the intervention, not the body-in-action. Yet the lived experimental bodies of human subjects will alter the effects of an intervention, as well as interpretation of data produced by the body. While the implications extend to any kind of trial, there may be additional effects to consider in nano-based trials. Bodies move around, flex, strain, and exert interior bodily forces. Even subtle movements may create internal physical effects such as microabrasions or disruptions to cell membranes with some nanotherapeutic products, and exposure to various environments could potentially create additive effects, or the body itself may affect bystanders.

Beyond physical effects, humans in clinical trials are not passive experimental objects. They interact in the world and encounter different environments. The role of "human subject" is but one among all of the roles and experiences of their lives: they must continue to work or put their affairs in order, they must mother or sister their families, they must care for their bodies (which may mean balancing depression or hypertension or other conditions, in addition to the one in which they are engaging as a research partner). They must reconcile information given to them by clinical experts with information they know about what works for their bodies and for their ability to function in their everyday lives. They may then make their own work-arounds and adaptations to prescribed routines — including possibly modifying their own the clinical protocols or provisions such as quarantine or pre-trial immunosuppression that may be used in nanotherapy trials. While researchers must abide by procedural norms for consent and certainly are aware of individual physiological phenomena and differences among subjects, they rarely attend to such lived social conditions that may equally affect study outcomes. How can these less-visible elements of research be accounted for in risk assessments?

Much is at stake for investigators, who have considerable interests in protecting trial participants both as human subjects and as data sources. Not only do they have obligations to subjects, but they are obligated to produce the best data possible, or their work could be seen as ineffective, wasteful, or worse, could result in a loss of trust in the research enterprise overall. How can they best balance the real needs of acquiring "good" and sufficient data (especially in an era of evidence-based medicine) with the needs of the research subjects, who are both vulnerable humans and a cen-

Despite good pre-clinical data, the use of proper non-human models, and attempts to use computational predictive techniques, it is impossible to know what may happen in situ in the human (the "unknown unknowns"). The trial has to be thought of as a learning process: entirely new and unexpected questions and problems may arise in the process of collecting data, which arguably makes research on an emerging technology iterative in a somewhat different way than with other kinds of trials. This may not in and of itself make a trial riskier, but it means that the researcher, subject, and IRB may confront greater unpredictability.

tral part of knowledge production? As Ilana Löwy put it, patients' bodies are major instruments of the development and validation of medical knowledge.[49] Data produced by the body as a research instrument shapes medical knowledge and practices, particularly in a field still very much in development. With first-in-human trials of products involving novel mechanisms, such as nanomedicine, investigators are asking questions about what happens as it is happening; research questions are raised simultaneously with the production of knowledge. Despite good pre-clinical data, the use of proper non-human models, and attempts to use computational predictive techniques, it is impossible to know what may happen in situ in the human (the "unknown unknowns"). The trial has to be thought of as a learning process: entirely new and unexpected questions and problems may arise in the process of collecting data, which arguably makes research on an emerging technology iterative in a somewhat different way than with other kinds of trials. This may not in and of itself make a trial riskier, but it means that the researcher, subject, and IRB may confront greater unpredictability.

There are tensions, then, between the needs of learning, efficiency, and cost-effectiveness in expensive trials, and the need to protect humans as subjects. Compromises tipping either toward the protection of the persons or the data will inevitably cause conflict.

A Final Word about Risk Perception

Paul Slovic, a leader in psychosocial analyses of risk perception, argues that while dangers are real, there is no such thing as "objective" risk that is independent of culture. Rather, risk is always subjective. That is, even when estimated by experts, it is based on theoretical models whose structure is subjective and assumption-laden, and whose inputs are dependent on judgement.[50] Furthermore, while risk assessment and management techniques attempt to create certainty out of uncertainty, debates over risk can also be used to create uncertainties: by casting doubt on theories and facts, these debates can make "knowns" into "unknowns." This has happened in debates over global warming, for example. In the absence of absolute, definitive evidence of harm or safety, a policy choice may be to legislate permissively or restrictively, or to take no action at all, depending on the political and economic environment in which the choice is being made. Economic gains or costs, concern over the reactions of publics (including political constituencies), and other factors may affect the selective use and interpretation of evidence toward policy goals. A lack of definitive evidence often results by default in the conclusion that no oversight or intervention needed. This is consistent with a business-as-usual approach and with the contemporary emphasis on promoting translation of new drugs and treatments into the public domain.

The role of communications is central to some theories about risk perception. The way people observe and experience risks is influenced by institutional structures and norms, cultural framings, media coverage, affiliations with certain interest groups and more. Calls for increased regulation, litigation, or public attention communicate an intensified sense of risk. Silence or apathy may not necessarily suggest that risk is nonexistent, but rather, an assumption that existing technologies of control will suffice to deal with it.

Some risk perception theorists argue that people may either over- or underestimate risks, and may then over- or under-react.[51] Consistent with arguments about false security in procedures and protocols, some studies of technologies or regulations intended to protect people from risk, actually may cause riskier behavior, because they assume that the procedure or technology has taken care of it. For example, a study of taxi drivers using anti-lock brakes found that those drivers had far more accidents than a control group; they believed they were safer just from having the brakes installed, and possibly took more chances than they might have otherwise.[52]

Such studies have opened the way for behavioral economists to claim that while institutions may respond to public reactions over controversies, people are not good judges of risks, benefits, potential losses, or potential gains. In such a case, some argue that "worst case scenarios" should never be disclosed, as there might be costly analyses for unlikely events which would disturb people without cause.[53] Others argue that there is a right and a responsibility to disclose information to the public, no matter how remote a danger might be, in order to have broader participation in decision-making.[54] However, such stances ignore the vulnerability of some people who have no ability to reduce their risk exposure (such those dependent on a water supply despite chemical dumping into the water), and assume that only expert judgments matter.[55]

Brian Wynne elaborates the latter point, arguing that non-expert knowledge may add significant knowledge.[56] There are multiple ways of evaluating risks, and non-experts have unique knowledge that might aid in determining appropriate end-points of experiments, aspects of the context not visible to experts, and so forth. This is an argument in favor of the recommendation in the project group's article in this issue, suggesting a Secretary's advisory committee on human subject research in nanomedicine that

is comprised of a variety of members, including appropriate non-experts.[57]

It is important to emphasize that most of the risk perception literature focuses on lay perceptions. But experts, including scientists, regulators, and bioethicists, also receive information filtered through the same sources and may also be sensitized to the kinds of things previously designated as risky.

Conclusions

Perceptions and misperceptions of risk by policymakers, scientists, and members of the public alike play a significant role in decisions to allow technologies to go forward or not, and how best to mitigate any potential problems. Value judgments occur at every step of the process, from the way a technology is represented in various arenas (e.g., regulatory, political, investment), to determination of what criteria to use to measure effects, to determining who gets to decide which risks are acceptable, and how they are to be evaluated. Pragmatically, the question may not be how "real" the risks are, but rather, how they come to count in society, which in turn says a good deal about a society and its institutions of governance.

Some scientists, ethicists, and policymakers have been extremely vocal about the need to revisit risk review for nanotechnologies, citing multiple causes for concern. Others suggest that existing systems are sufficient and claim that current procedures already recognize and deal with dangers so that adding new layers of review will only slow the introduction of potentially enormously useful products.[58] Indecision about the best course of action will likely result in no increased oversight. However, to create new bodies for review or to institute new guidelines, procedures, and tests requires the political will to do so. In an era of pressure to see returns from national investment in research, this may not be likely. Nanotechnology is also situated in a historical moment in which broader issues of expertise, evidence, and capacity are being called into question. Calls for regulatory reform seek to reduce redundancies and make agencies more efficient, which may reduce some of the systematic error as described by Vaughn above, but could also potentially strip them of resources needed to analyze risk in novel products. Some would argue that agencies such as the FDA already lack the resources and expertise necessary to deal with the variety of novel entities submitted for review. Here is where the recommendation to create an inter-agency working group is most compelling: critical information may be available, but is simply not accessed effectively or equally across regulatory agencies and other relevant organizations, due to infrastructure weaknesses or some of the institutional or procedural issues as described above. An inter-agency working group could bridge gaps in knowledge and types of expertise, be better able to conduct more comprehensive and interdisciplinary analyses, and more readily flag potential problems.

Novel products are also entering review in the context of evidence-based medicine policies, which have a higher bar for demonstrating effectiveness and may affect risk-benefit analyses accordingly. Expertise at the local level of IRBs is at issue as well: can they be expected to bear most of the burden of recognizing relevant risks, and is there enough consistency among IRBs to be confident that human subject protections are commensurable across locations?

Perhaps what we should ask is not what is different about nanomedicine that might trigger new or different oversight mechanisms, but what (if anything) is changing in human subjects protection. Explorations into different ways of conducting pre-clinical trials, including the suggestion of introducing bioinformatics and predictive algorithms or cell-based, in vitro preclinicals with the addition of visualization techniques during and post-administration of nanomedicines may change analyses, or at least the way IRBs and agencies review risk data. Because of the sophistication of some technologies being tried in humans, IRBs have begun focusing more on the complex technical aspects of the science rather than the bigger clinical picture for trial subjects. If true, what is the impact on the well-being of patients? Jonathan Kimmelman argues that the purview of IRBs should be much broader than assessing risk alone, and that the context in which trials are conducted should be a primary consideration.[59]

Medical risk assessments performed by bioethicists, quantitative risk experts, and regulatory and other oversight authorities have not sufficiently considered the broader landscape of risk, including business and market risk assessments made by those translating concepts into products. Decisions made about novel products from this perspective — from clinical trial to market entry — are based on different assumptions and priorities than those used by bioethicists and regulators, yet there is a distinct interaction between the two decision-making processes.

One way to deal with risk might be to incentivize trial sponsors themselves to become more reflective about risk and risk practices. Stimulated by financial collapses as much as technological and natural disasters, many organizations have become aware of how greatly high-visibility disasters might affect the welfare of the organization for the near and long term.[60]

Certainly this has proven to be the case in some areas of medicine, such as gene transfer research.

What we may be seeing (or need to see) is the transformation of roles and institutions charged with the protection of human subjects, including those charged with protections as their primary duty (IRBs plus trial sponsors) and those for whom it has not been the primary task, such as the Environmental Protection Agency. Coordination and communication among all entities is critical in order to prevent assumptions from being concretized into practice and to assure an integrated, coherent reflection on review practices as a whole. If we accept that values are embedded in risk, risk interpretation, and amelioration, then adding to the oversight of nanomedicine human subjects research by creating an inter-agency working group and Secretary's advisory committee with heterogenous members representing different kinds of expertise and roles in society will be helpful in acknowledging and weighing the scientific, moral, and social elements of decisions about how best to proceed. The project recommendations published in this symposium[61] challenge the nanodiagnostics and therapeutics community to move forward by recommending these two mechanisms of coordination and a multiple stakeholder advisory body. They are an important step toward responsible innovation in nanomedicine.

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