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Recommendations for Nanomedicine Human Subjects Research Oversight: An Evolutionary Approach for an Emerging Field

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Abstract

The nanomedicine field is fast evolving toward complex, “active,” and interactive formulations. Like many emerging technologies, nanomedicine raises questions of how human subjects research (HSR) should be conducted and the adequacy of current oversight, as well as how to integrate concerns over occupational, bystander, and environmental exposures. The history of oversight for HSR investigating emerging technologies is a patchwork quilt without systematic justification of when ordinary oversight for HSR is enough *versus* when added oversight is warranted. Nanomedicine HSR provides an occasion to think systematically about appropriate oversight, especially early in the evolution of a technology, when hazard and risk information may remain incomplete. This paper presents the consensus recommendations of a multidisciplinary, NIH-funded project group, to ensure a science-based and ethically informed approach to HSR issues in nanomedicine, and integrate HSR analysis with analysis of occupational, bystander, and environmental concerns. We recommend creating two bodies, an interagency Human Subjects Research in Nanomedicine (HSR/N) Working Group and a Secretary’s Advisory Committee on Nanomedicine (SAC/N). HSR/N and SAC/N should perform 3 primary functions: (1) analysis of the attributes and subsets of nanomedicine interventions that raise HSR challenges and current gaps in oversight; (2) providing advice to relevant agencies and institutional bodies on the HSR issues, as well as federal and federal-institutional coordination; and (3) gathering and analyzing information on HSR issues as they emerge in nanomedicine. HSR/N and SAC/N will create a home for HSR analysis and coordination in DHHS (the key agency for relevant HSR oversight), optimize federal and institutional approaches, and allow HSR review to evolve with greater knowledge about nanomedicine interventions and greater clarity about attributes of concern.

Keywords

Nanomedicine; nanotherapeutics; nanodiagnostics; nanotechnology; human subjects research; research oversight; research ethics

Introduction

Nanomedicine is yielding new and improved treatments and diagnostics for a range of diseases and disorders. Nanomedicine applications incorporate materials and components with nanoscale dimensions (often defined as 1-100nm, but sometimes defined to include dimensions up to 1000nm, as discussed further below) where novel physiochemical properties emerge as a result of size-dependent phenomena and high surface-to-mass ratio.² Nanotherapeutics and *in vivo* nanodiagnostics are a subset of nanomedicine products that enter the human body. These include drugs, biological products (biologics), implantable medical devices, and combination products that are designed to function in the body in ways unachievable at larger scales. Nanotherapeutics and *in vivo* nanodiagnostics incorporate materials that are engineered at the nanoscale to express novel properties that are medicinally useful. These nanomedicine applications can also contain nanomaterials that are biologically active, producing interactions that depend on biological triggers. Examples include nanoscale formulations of insoluble drugs to improve bioavailability and pharmacokinetics, drugs encapsulated in hollow nanoparticles with the ability to target and cross cellular and tissue membranes (including the blood-brain barrier) and to release their payload at a specific time or location, imaging agents that demonstrate novel optical properties to aid in locating micro-metastases, and antimicrobial and drug-eluting components or coatings of implantable medical devices such as stents.

As a group, nanomedicine products are not new. Some have been in use for years.³ However, over the last decade, products using active and interactive nanoparticles (rather than passive nanoparticles) have entered the development pipeline with testing in human subjects. A search of the literature in 2010, and since updated using search engines that track human trials, found 247 confirmed or likely nanomedicine products that were in human testing or had already gone through the HSR process.⁴

Nanomedicine interventions that are undergoing testing in human beings are already subject to federal and institutional rules and oversight, as codified in the Food and Drug Administration's (FDA's) human subjects protection rules⁵ and the similar, but not identical, Department of Health and Human Services (DHHS) Common Rule,⁶ subscribed to by multiple federal agencies. These rules guide Institutional Review Boards (IRBs), which are generally but not always housed at individual research institutions, in evaluating the ethical concerns posed by a research protocol, approving the adequacy of the protocol in addressing those concerns, and overseeing the research over time. Under these rules, IRBs assess factors including: minimization of risks to participants; reasonableness of risk to participants in relation to anticipated benefits, if any, to the participant and the importance of knowledge reasonably expected to result from the research; informed consent; and adequacy of data-monitoring.⁷

Virtually all HSR on nanotherapeutics and *in vivo* nanodiagnostics is subject to the FDA's authority to regulate human subjects research on drugs, devices, biologics, and combination products under the Federal Food, Drug, and Cosmetic Act.⁸ The FDA ensures that HSR on products requiring FDA approval for marketing complies with FDA regulations.⁹ A considerable portion of nanomedicine HSR is also subject to the Common Rule, which applies to all research conducted or funded by DHHS, including the National Institutes of Health (NIH), or any of the other agencies that have adopted the Rule.¹⁰ The Common Rule also applies to research conducted at institutions rendering a broad Federalwide Assurance (FWA) by committing to compliance with the Rule for a wider set of research projects conducted by those institutions.¹¹ The Office for Human Research Protections (OHRP), a body that reports to the Office of the Assistant Secretary for Health (OASH) in the DHHS Office of the Secretary,¹² provides additional guidance on HSR.

Under both the FDA and Common Rule regimes, IRBs function as the key body at the institutional level that is responsible for considering whether a protocol comports with the rules governing HSR. Under those rules, IRBs focus on protection of human participants, rather than evaluating the scientific soundness of a protocol, except as is necessary to determine whether the research has sufficient scientific merit to justify subjecting human participants to risk.¹³ Other review processes at both the FDA and NIH focus on evaluating scientific soundness. However, the FDA in particular also has extensive processes at the federal level for considering risks posed and the adequacy of proposed safeguards.

At the FDA, nanotherapeutics and *in vivo* nanodiagnostics must undergo premarket testing and approval under either the New Drug Application (NDA) process for drugs¹⁴ or the Premarket Approval (PMA) process for medical devices.¹⁵ Product manufacturers must submit an Investigational New Drug (IND) application for drugs¹⁶ or Investigational Device Exemption (IDE) application for devices.¹⁷ For devices, requirements differ according to whether the study poses a "significant risk" or "nonsignificant risk."¹⁸ The FDA also has the authority to require the submission of additional data necessary to evaluate the safety of both INDs and IDEs. The FDA Nanotechnology Task Force notes that this "provides FDA with the ability to...assess the safety and, as applicable, effectiveness of products, including relevant effects of nanoscale materials."¹⁹

For research that is subject to the Common Rule, NIH requires that protocols undergo scientific peer review by a Scientific Review Group (SRG) before being submitted to an IRB for review.²⁰ An SRG assesses the scientific soundness of a protocol, including consideration of "the adequacy of the proposed protection for humans, animals, and the environment, to the extent they may be adversely affected by the project proposed in the application."²¹

These FDA and Common Rule regimes constitute **baseline federal oversight** for HSR, with IRBs providing the **baseline oversight at the institutional level**. (States may have additional rules; we focus here on federal rules, the national system for protection of human subjects.) Some research activities conducted in the course of HSR, such as disposal of hazardous materials and laboratory practices, may also be subject to Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA)

regulations at the federal level, as well as state and locally imposed occupational and environmental requirements. (Again, we focus here on federal requirements.) Institutions have occupational and environmental oversight bodies to review research protocols and ensure compliance with federal, state, and local rules. These occupational and environmental oversight processes typically occur in parallel to IRB review and may not significantly influence IRB decisions. The baseline system of federal and institutional oversight for HSR, as well as the system for federal and institutional oversight for environmental and occupational protection in HSR, is depicted in Figure 1.

There is little specific guidance as yet on oversight for nanomedicine HSR protocols. NIH and OHRP have yet to issue guidance specific to SRG or IRB review of nanomedicine HSR, even though nanomedicine HSR is under way and the Recombinant DNA Advisory Committee (RAC) at the Office of Biotechnology Activities (OBA) has already considered some human gene transfer research (often called “gene therapy”) protocols using nanotechnology.²³ The FDA has been more active. In 2007, FDA’s Nanotechnology Task Force took the position that existing FDA authority was sufficient to adequately regulate nanomedicine, but recommended that the agency take steps including “[e]valuate the adequacy of current testing approaches”; “[i]ssue guidance to sponsors” on a number of topics; “[w]hen warranted, issue a call for data”; and “[a]ddress on a case-by-case basis whether labeling must or may contain information on the use of nanoscale materials.”²⁴ In 2010, FDA’s Center for Drug Evaluation Research (CDER) issued an addition to its Manual of Policies and Procedures (MAPP) requiring reviewers to verify accurate and complete documentation of particle type, size, agglomeration, solubility, and surface properties for all applications involving nanomaterials.²⁵ The FDA has also issued guidance for industry, such as a draft 2011 guidance on determining whether an FDA-regulated product involves nanotechnology for the purposes of FDA deliberations on whether additional nanomedicine oversight is required.²⁶ Despite FDA activity on nanomedicine submissions generally, the FDA has not issued guidance specifically on human subjects research challenges in nanomedicine. Similarly, while EPA and NIOSH have issued regulations and guidance on nanotechnology generally, they have not addressed nanomedicine HSR.²⁷

Even at the White House level, extensive attention to nanotechnology has not yielded guidance on nanomedicine HSR. The White House Office of Science and Technology Policy (OSTP) oversees an active set of bodies considering nanotechnology issues, yet none of these has addressed the emerging human subjects research issues. Under OSTP, the National Science and Technology Council’s (NSTC) Committee on Technology oversees the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee. NSET is supported by the National Nanotechnology Coordination Office (NNCO) as part of the multi-agency National Nanotechnology Initiative (NNI). NSET in turn has established four Working Groups on: Global Issues in Nanotechnology; Nanotechnology Environmental and Health Implications; Nanomanufacturing, Industry Liaison & Innovation; and Nanotechnology Public Engagement & Communications. In 2011, the OSTP, together with the Office of Management and Budget (OMB) and the U.S. Trade Representative (USTR), called for yet another working group, to focus on developing an approach to “choice of terminology relevant to the regulation and oversight of nanomaterials,” as well as to facilitate interagency coordination and involvement in nanotechnology research.²⁸ The lack

of a working group to focus on HSR issues in nanomedicine highlights a significant gap in governmental oversight for nanomedicine, a gap that this article addresses.

Our group recommends creation of two complementary oversight bodies under DHHS: a Secretary's Advisory Committee on Nanomedicine (SAC/N) to capture multiple stakeholder viewpoints and non-governmental expertise on nanomedicine in a public forum, and a Human Subjects Research in Nanomedicine (HSR/N) Working Group to facilitate coordination among regulating agencies, offices, and centers, taking into consideration SAC/N's advice. Nanomedicine is a complex field and significant expertise lies outside of the government, suggesting use of a Secretary's Advisory Committee. Additionally, nanomedicine HSR may raise public concerns that would be appropriately addressed by having a public forum for discussion and transparency to engender public trust. However, consideration and utilization of SAC/N recommendations call for a structure that can react to and implement changes, such as an HSR/N Working Group. Placement of HSR/N within DHHS is appropriate given that the Secretary oversees FDA, NIH, and NIOSH, the main components of the current HSR regulatory structure. The Secretary should also reach out to invite entities such as OSHA and EPA to participate in the working group.

Creation of the HSR/N Working Group and SAC/N would facilitate coordinated consideration of emerging challenges posed by some HSR on nanomedicine. The same nanomaterial characteristics that enable new and superior nanomedicine applications may also raise some concerns about nanomedicine research in humans. Recently, the National Research Council (NRC) of the National Academies released a report suggesting the importance of identifying environmental, health, and safety hazards of nanomaterials.²⁹ While not focused on HSR specifically, the report highlighted gaps in our understanding of potential human health and environmental reactions to complex nanoparticles. These gaps have implications for nanomedicine. They affect establishment of safe dosing levels of nanodrugs and the best animal models for testing particular types of nanomedicine products. Beyond highlighting gaps in technical knowledge about nanomaterials, the report also noted a need for a better approach to addressing nano properties and understanding "underlying biologic interactions that determine exposure and risk."³⁰ These findings were similar to the recommendations in a National Nanotechnology Initiative (NNI) 2011 report that also called for more research on the impact of nanomaterials on human health and the environment.³¹ The more recent PCAST assessment of NNI makes additional recommendations regarding efforts to consider human health issues.³²

It is important to note from the outset that no documented cases yet show harm resulting to human subjects from exposure to nano-materials in the course of nanomedicine HSR. However, the system of protection for human participants in research was designed beginning in the late 1970s in order to review proposed research protocols prophylactically to assess risk, decide whether risk is within acceptable limits, balance risk against expected benefits if any, ensure informed consent, and prevent harm.³³ The fact that we see no documented cases yet of harm to humans from nano-exposures in nanomedicine HSR stands to reason. Older forms of nanomedicine, such as the use of liposomes in drug delivery, have primarily used nanotechnology to create vehicles for drug transport in a "passive" use of this technology. Moreover, nanotoxicology and other means of assessing risk and hazard have

been in development. But the field of nanomedicine is evolving fast. More active, interactive, multi-modal uses of nanotechnology in medicinal and diagnostics are emerging. Considering now how best to anticipate nanomedicine HSR issues is entirely in line with the overarching preventive goals of HSR oversight.³⁴

Considering the hazards and potential risks posed by some nanomedicine interventions, including the more complex and active materials emerging, is warranted. Some of the great strengths and potential advantages of nanotherapeutics simultaneously pose challenges. Just as nanoscale size and properties can improve bioavailability and pharmacokinetics, they may also play a role in the toxicity and tissue distribution of nanoparticles.³⁵ These characteristics can also stimulate or suppress immune responses in the body³⁶ or cause increased, decreased, or abnormal function of tissues and organs.³⁷ Some studies suggest that particular nanomaterials may also have adverse reproductive effects, including effects on the gametes.³⁸ Furthermore, studies have shown that some nanomaterials introduced into the body may be susceptible to horizontal transmission to bystanders and movement into the environment through biological shedding and waste excretion,³⁹ and that manufacturing and handling of nanomedicine products or intermediates could expose researchers and lab workers to inhalation or dermal absorption of nanoparticles.⁴⁰

These sources of concern are, of course, merely the starting point for the kind of analysis that should be spearheaded by the HSR/N Working Group and SAC/N that we suggest. FDA regulations on HSR and the Common Rule make no mention of the distinction between hazard (a source of potential risk) and actual risk. The HSR/N Working Group and SAC/N should strive to conduct a science-based analysis of nanomedicine HSR issues, make this distinction, and then progress to the questions of how much risk is posed, of what kind, what data support these conclusions, and what HSR protections are needed. The data needed are currently still in development. Complicating the picture further, there remains a lack of consensus within the toxicology community on the degree of accuracy with which conventional animal and *in vitro* toxicology models can assess the potential risks of some engineered nanomaterials, especially active and complex nanomaterials.⁴¹ Further disagreement exists on whether these methods are able to assess long-term metabolic fate and predict the potential for unintentional secondary interactions, as well as delayed immunological, inflammatory, and carcinogenic effects.⁴² Complicating the picture further still, nanomedicine research in humans may raise concerns about hazard and risk not only to research participants, but also to researchers and workers, bystanders (such as family members and close contacts) who may be exposed to nanomaterials in the course of HSR, and the environment.

These are potential concerns for many emerging technologies.⁴³ Addressing these concerns in nanomedicine HSR is a chance to do a better job than in the past to address HSR concerns raised by emerging technologies. Wolf and Jones detail the somewhat chaotic history of responses to the HSR challenges raised by new domains of science and technology.⁴⁴ A wide range of regimes have been created to provide extra or “exceptional” review for HSR. It is difficult to discern an overarching rhyme or reason. Moreover, the preexisting system of “baseline” human subjects review in this country is already widely recognized to be stressed and in need of repair.⁴⁵ This article deliberately avoids creating yet another ad hoc regime of

extra review. Instead, we take the more cautious and incremental step of creating complementary oversight groups to coordinate analysis and data-gathering in order to ultimately devise an approach to human subjects research oversight in nanomedicine that is well grounded in both the ethics of human subjects review and the science of nanomedicine. This comports with the recent call for “a balanced, science-based approach to regulating nanomaterials...in a manner that protects human health, safety, and the environment without prejudging new technologies or creating unnecessary barriers to...innovation.”⁴⁶

We are not the first to consider nanomedicine HSR challenges. As Wolf and Jones have documented, a literature has begun to address the need for analysis and potential oversight for nanomedicine HSR.⁴⁷ However, the HSR proposals to date have generally focused on narrow aspects of the problem, such as the role of the FDA or the need for additional risk data (see Figure 2). In 2008, the President’s Council on Bioethics considered whether to launch analysis of nanotechnology issues, but ultimately declined. They explained that nanotechnology may indeed raise significant safety and other issues, but they were limiting their work to issues of “human dignity”: “[I]n order to begin...an investigation [by the President’s Council], the technology under question must... affect human dignity. Nanotechnologies that are currently available.... might make people sick, and they might harm the natural environment..., but their current manifestations do not risk altering the very nature of being human..... [N]ew, more concrete advances might justify its reengaging the topic.”⁴⁸

Nanomedicine HSR oversight requires a system that can carefully differentiate interventions raising concerns that may not be adequately addressed by baseline HSR oversight, from interventions that raise no such concerns. Different types of nanotherapeutics and *in vivo* nanodiagnosics present different environmental, health, and safety (EHS) risks of differing magnitudes, depending on a broad range of factors, including the type, size, shape, and complexity of the nanomaterial, the route of administration, and the biological elements with which the nanomaterial interacts once administered. For example, while some nanomedicine applications contain passive nanomaterials with fixed properties and functionalities, others contain active nanostructures with complex properties and functions that can be triggered or changed by environmental stimuli.⁴⁹ Consequently, while some nanomedicine applications are well characterized and understood and require no extra analysis or oversight, others may present risks that are currently difficult to identify, challenging to assess, and potentially merit extra attention beyond the current baseline.

Ensuring adequate HSR oversight for nanotherapeutics and *in vivo* nanodiagnosics is important to protect the rights and welfare of research participants, researchers and lab workers, bystanders, and the environment, as well as to promote public confidence in nanomedicine research and development.⁵⁰ It can also provide a starting point for the broader task of improving HSR oversight for sophisticated and emerging technologies. We find no ethical issues that are entirely unique to nanomedicine human subjects research; other cutting-edge domains of HSR pose similar problems. It is precisely for this reason that nanomedicine HSR can serve as a model for improvement in analysis and oversight of HSR issues. The challenges in developing such oversight are (1) to avoid the creation of unnecessary regulatory hurdles that can stifle research and innovation, and (2) to create a

system that can handle the current level of uncertainty surrounding some types of nanomedicine and adapt, as that level of uncertainty changes over time.

Our recommendations consider the ethics of nanomedicine HSR and protections for human subjects, as well as occupational, bystander, and environment safeguards. We break new ground by offering recommendations for a coordinated approach to federal and institutional oversight of nanomedicine HSR that addresses this full range of concerns. We accomplish this in six ways:

1. We recognize that not all categories of nanomedicine research pose the same type and seriousness of safety and ethical concerns. Our recommendations provide an oversight approach that differentiates among nanomedicine interventions in order to avoid the creation of unnecessary regulatory hurdles.
2. We focus both on strengthening the existing system of oversight and on addressing areas where new oversight may be needed. Our approach avoids proposing new requirements unless found to be necessary. We suggest a way to ascertain the need for new requirements over time.
3. We go beyond safety and ethical concerns for the human subject to address occupational, bystander, and environmental concerns. The existing system of HSR oversight focuses on the human subject. Our recommendations broaden the scope of oversight to include consideration of other potentially affected parties and environmental concerns.
4. We anticipate the increasing complexity of nanomedicine applications over time. While many nanomedicine applications today incorporate passive nanomaterials with fixed functionalities and more easily characterized properties, we recognize that nanomedicine innovation is moving in the direction of active nanosystems with more complex properties and functions. While passive nanomaterials can raise HSR issues, the more active and advanced forms of nanomedicine are likely to present new safety and ethical concerns with greater levels of uncertainty.
5. We provide recommendations for coordinated oversight across federal and institutional oversight bodies. Nanomedicine HSR protection, including protection for researchers and lab workers, bystanders, and the environment, spans the jurisdiction and authority of multiple oversight bodies, both at the federal and institutional levels. Coordination among these bodies is critical for reducing the cost and burden on individual agencies, avoiding the risk of duplication or gaps in oversight, and maximizing the amount of data and information available to each body.
6. We provide an adaptive and flexible approach to oversight through creation of an HSR/N Working Group and SAC/N. As new data and knowledge about nanomaterial risks become available over time and as increasingly complex nanomedicine applications are developed, it may become necessary to ratchet up or down oversight for nanomedicine HSR. Our approach provides an ongoing process of data-gathering and deliberation designed to allow oversight to evolve.

Part I of this paper provides our recommendation for an approach to identifying “nanomedicine” interventions for the purposes of developing HSR oversight. In **Part II**, we describe the characteristics of some nanomedicine HSR that may give rise to safety and ethical challenges potentially meriting additional oversight beyond the current baseline system, and suggest how to address those concerns. In **Part III**, we provide our recommendations for a flexible and evolutionary approach to nanomedicine human subjects oversight, including creation of an HSR/N Working Group and SAC/N advisory body.

Methods

This paper grows out of a 2-year project on “Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight,” funded by an ARRA Challenge grant from the National Human Genome Research Institute (NHGRI) at NIH. The project convened a multidisciplinary Working Group of academic and industry experts on nanomedicine, drug and device development, human gene transfer, HSR, and research oversight. The project analyzed challenges to HSR ethics and oversight posed by nanotherapeutics and nanodiagnostics by integrating empirical, normative, and policy approaches. Investigators and Research Assistants (RAs) researched whether and to what extent federal authorities and funders, key research institutions, researchers, and professional societies relevant to nanomedicine are addressing questions of HSR ethics in nanomedicine. Investigators and RAs also conducted an assessment of federal research oversight through review of the scientific, medical, legal, and bioethics literature on current FDA, NIH, and other federal oversight approaches germane to nanomedicine research; reviewed relevant statutes, regulations, guidance documents, and interpretive documents issued by FDA, NIH, and other relevant legal sources; and reviewed FDA, NIH, and other relevant websites for publicly-available materials relevant to human trials of nanodiagnostics and nanotherapeutics.

Over the course of the project, we held 5 Working Group meetings to discuss project findings and to deliberate on these recommendations. Our Working Group also formed four “small groups” focusing on issues identified as needing further and deeper consideration: (1) core risks posed by some nanomaterials, (2) challenges posed by first-in-human trials in nanomedicine, (3) protection of human subjects in nanomedicine trials; and (4) nanomedicine HSR issues beyond the purview of the Common Rule (occupational, bystander, and environmental risks and safeguards). In September 2011, we hosted a day-long national conference in Minneapolis, during which we presented our recommendations to an audience of invited stakeholders and experts, plus academics, policymakers, regulators, and members of the public, in order to elicit feedback. We then revised our recommendations in light of that feedback. Final revisions were negotiated by e-mail. While the analysis and recommendations below are the product of the consensus process undertaken by this multidisciplinary author group, individual co-authors may not fully endorse each and every recommendation. However, all authors have signed off on this article as a statement of our group’s conclusions.

Part I. Defining or Describing Nanomedicine for Human Subjects Research Oversight

One of the most vexing issues in nanotechnology oversight generally has been how to define or describe what is meant by “nanotechnology.” We begin our discussion there, to indicate what we mean by nanomedicine. Developing effective HSR guidance and oversight for nanomedicine protocols will require that all stakeholders know what area of HSR is being referenced. This does not mean that the entire domain of “nanomedicine” should be treated the same from an HSR perspective; it should not, as we acknowledge repeatedly below.

“Nanotechnology” has proven challenging to define. While agencies have created various definitions based upon a mix of criteria regarding particle size and properties, we may not yet know enough about the mix of particle characteristics that actually raise concerns to create a strict definition.⁵¹ The concern over any definition that focuses on particle size is that it shifts attention away from nanomaterial characteristics, such as reactivity, that are more relevant to risk calculation;⁵² the characteristics that raise concerns are not size itself, but properties demonstrated by certain nanoparticles. There is considerable debate over whether the best and most science-sensitive approach may ultimately be to forego a definition of “nanotechnology,” in favor of specifying those attributes of a product or material that raise well-founded concerns.⁵³

The task of defining nanotechnology has thus far rested largely with the National Nanotechnology Initiative (NNI), an important federal program overseen by the cabinet-level National Science and Technology Council (NSTC), which is guided by the Office of Science and Technology Policy (OSTP) at the White House. NNI was established in 2000 to coordinate the nanotechnology-related activities of 25 federal departments and agencies, including FDA, NIH, EPA, and OSHA.⁵⁴ Coordination and strategic planning of NNI activities is the responsibility of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of NSTC’s Committee on Technology, with membership from each of the NNI participating departments and agencies.⁵⁵ The current NNI definition of nanotechnology is “the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications.”⁵⁶ This definition has been the dominant one at the federal level, but it is not the only federal approach, as indicated in Figure 3.

The diversity of approaches evident in Figure 3 may reflect the reality that different agencies are searching for a definition or approach for different regulatory and oversight purposes. Much of nanotechnology research in fields such as materials science and chemistry focuses on exploiting the novel physiochemical properties (e.g., mechanical, optical, and thermal properties) of nanoscale materials used in products that are intended to interact with biological systems.⁵⁷ Because these novel properties are often seen at the 1 to 100 nanometer scale, the NNI definition may make sense for these areas of research. Yet, because nanomedicine specifically involves the interaction between nanomaterials and human physiology, *in vivo* therapeutic and diagnostic applications can operate at somewhat larger scales.⁵⁸

A significant challenge that regulatory agencies face in defining “nanomedicine” for oversight purposes is that some drugs that are not regarded as raising nanotechnology

challenges actually contain nanoscale particles or target the body's own nanoscale structures.⁵⁹ For example, an aspirin molecule is⁶⁰ approximately 0.75 nm in diameter, and a molecule of the common beta-blocker propranolol can fit inside a receptor with an area between 0.53 and 0.64 square nms.⁶¹ However, research involving *in vivo* nanotherapeutics differs from research involving these conventional drugs. Conventional drug research focuses on the chemical interaction between drugs and target cells, receptors, or proteins (i.e., pharmacokinetics and pharmacodynamics), and conventional device research focuses on the mechanical interaction between devices and target tissues, organs, and systems. Nanotherapeutics, however, can operate both chemically and mechanically.⁶² Consider, for example, a hollow nanoshell impregnated with a chemotherapy drug that is designed to break open and release its payload when exposed to infrared light administered externally. Such an application acts both mechanically (the breaking open of the nanoshell) and chemically (the action of the chemotherapy drug when released). Such an application has a broader set of therapeutic functions, as well as potential associated risks, than conventional drugs.

The FDA has begun to grapple with the need to develop a more deliberate approach to nano-products. In 2010, FDA's Center for Drug Evaluation Research (CDER) issued an addition to its Manual of Policies and Procedures (MAPP) requiring chemistry, manufacturing, and controls (CMC) reviews to verify accurate and complete documentation of particle type, size, agglomeration, solubility, and surface properties for all applications involving nanomaterials, defined as "any material with at least one dimension smaller than 1,000 [nanometers]."⁶³ The MAPP definition is for the purposes of gathering data on nanomaterials to inform future deliberations on whether additional guidance or regulation is necessary for nano-products.⁶⁴ In addition, FDA issued a 2011 draft guidance for comment, stating that:

In the absence of a bright line as to where an upper [dimensional] limit should be set, the agency considers that an upper bound of one micrometer (i.e., 1,000 nm) would serve as a reasonable parameter for screening materials with dimensions beyond the nanoscale range for further examination to determine whether these materials exhibit properties or phenomena attributable to their dimension(s) and relevant to nanotechnology. The agency believes that the one micrometer upper limit...serves both to (1) exclude macro-scaled materials that may have properties attributable to their dimension(s) but are not likely relevant to nanotechnology; and (2) include those materials (such as aggregates, agglomerates, or coated, functionalized, or hierarchically assembled structures) with dimension(s) above 100 nm that may exhibit dimension-dependent properties or phenomena relevant to nanotechnology and distinct from those of macro-scaled materials.⁶⁵

Thus, the FDA has suggested a broader definition of "nanotechnology" in the context of nanomedicine review to capture more data potentially relevant to development of effective oversight. This wider net is particularly appropriate in the context of an oversight system to protect human subjects.

As noted above, use of a size parameter is not without controversy. The recent National Research Council report refrained from using size to define nanoengineered materials,

arguing that focus on “particle size may highlight issues that are not relevant while shifting attention from such properties as reactivity that may be more relevant to determining risks.”⁶⁶ This approach seems consistent with Maynard’s call for identifying nine to ten “attributes (including size and surface area) for which certain values trigger action.”⁶⁷

After considerable debate, our project recommends a 2-step approach, involving initial use of a size parameter until more is known about nanoparticle properties and an attribute-based approach can be established. Determining the exact cutoff point for the initial size-based definition is a difficult issue. While the recent FDA approach uses 1000nm to attempt to capture any and all substances with potential nano effects, such a high cutoff point captures many extraneous products. NNI and early FDA definition approaches that use 100nm exclude many nano-products that show unique physiochemical effects at somewhat larger scales.⁶⁸ For example, cancer research protocols include 150nm investigative gold nanoshells for thermal cancer therapy.⁶⁹ In addition, bioavailability may be increased by larger nano-particles, with liposomes of 150-200nm remaining in the blood stream longer than those of 70nm in size.⁷⁰ There is a distinct clustering of nano-product size in the 1 to 200nm range and a significant number of investigational and commercial nano-components have the size of 200 to 300nms, including a number of liposomes.⁷¹ Etheridge and colleagues use a cutoff of 300nm to encompass the unique properties of current nanomedicine applications while accounting for bioavailability and other nano-specific physiological behavior. A cutoff of 300nm allows for the inclusion of particles smaller than 100nm while not eliminating large nanoparticles demonstrating unique nano-related characteristics at 200nm or slightly larger.

One of the first tasks that should be undertaken by our proposed HSR/N Working Group is coordination of a harmonized approach to the definition or description of nanomedicine that is both science-based and sensitive to the goals of human subjects research review and oversight. The working group created by the June 2011 memo issued by OSTP, OMB, and USTR may be a great help, as a core task envisioned for that body is coordinating interagency work on terminology.⁷² That memo shows sensitivity to the pitfalls of formulating a categorical definition of nanotechnology with a size cut-off, suggesting that as scientific knowledge advances, what may ultimately prove more useful is a “focus on novel properties and phenomena observed in nanomaterials.”⁷³

Yet the efforts of the new OSTP/OMB/USTR working group to develop a sound approach to the terminology surrounding “nanotechnology” generally requires input on the special concerns surrounding human subjects research in nanomedicine. Our proposed SAC/N and HSR/N groups can gather and coordinate that input among the agencies and offices involved in human subjects research and its oversight. The bodies we propose can also bring the goals of human subjects research oversight to bear in accepting or suggesting modification of the OSTP/OMB/USTR working group’s terminology, much as FDA has found it necessary to cast a wider definitional net than the NNI definition might suggest, in order to gather data on nanomedicine products. Thus, we propose:

1. HSR/N and SAC/N in coordination with other federal authorities involved in nanomedicine HSR should develop an approach to the definition or description of

nanomedicine products that will serve the goals of human subjects research oversight.

2. While the science is developing to support identification of attributes that should trigger regulatory concern at certain values, it may be necessary to rely in part on an approximate size cut-off. We see work at FDA and NIH (two of the lead agencies on human subjects research) that would suggest temporary use a dimensional criterion, which could be 100nm, 300nm, or 1000nm. Because the goal in reviewing nanotherapeutics and *in vivo* diagnostics is in part protection of human subjects in research, we suggest casting a wide definitional net for now in information-gathering and analysis. This argues for an inclusive dimensional criterion, such as the 1000nm cutoff that the FDA MAPP document has used for information-gathering.
3. Thus, nanomedicine would include drugs, devices, and biologics with one dimension roughly at the chosen nanometer size or smaller that exhibit either physiological properties (including shape dispersibility, surface charge, and surface reactivity) or biological interactions (including protein adsorption, barrier penetration, cellular uptake, aggregation, degradation, and pathway signaling) emerging at this scale.
4. However, we suggest that this approach using a size cutoff should be temporary, with the goal of moving toward a more attribute-based approach, as the science develops to support that and the OSTP/OMB/USTR working group terminology effort progresses.

Part II. Safety and Ethical Challenges of Nanomedicine Human Subjects Research

Under FDA rules on HSR and the Common Rule, protocols for nanomedicine HSR must receive approval from an IRB based on criteria including:

- minimization of risks to subjects;
- reasonable risk to subjects in relation to anticipated benefits, if any, and the importance of knowledge reasonably expected to result from the research;
- informed consent from the subject;
- adequate data-monitoring; and
- protection of subjects' privacy and the confidentiality of data.

IRB approval based on these criteria constitutes a key part of the baseline system for HSR oversight depicted in Figure 1. Baseline IRB review is effective for evaluating most HSR protocols, but has two key limitations that challenge its adequacy for some areas of research. First, IRBs need enough reliable information about a protocol's risks to be able to decide whether those risks are acceptable and minimized. This means that an IRB must have enough information, including data from bench and animal trials, to identify the types of risks posed, their potential severity, and their likelihood of occurring, in order to evaluate whether the risks are minimized and reasonable in relation to anticipated benefits if any.⁷⁴ The second limitation is that IRBs typically focus on the acceptability of a protocol for the

human subject, but do not provide robust consideration of occupational, bystander, or environmental concerns. This narrow focus is supported by commentators who argue that IRBs lack the time, resources, and expertise, as well as the statutory authority to address issues beyond the human subject and that these concerns are generally addressed adequately by other oversight mechanisms such as EPA and OSHA regulations.⁷⁵ However, concerns for workers, bystanders, and the environment often factor into societal acceptability of scientific research even when the research could produce valuable outcomes.

As a consequence of these limitations, some domains of HSR that present uncertain or difficult-to-assess risks to human subjects and concerns about occupational, bystander, and environmental risks (such as human gene transfer research involving recombinant DNA) have been identified as requiring “exceptional” HSR oversight – oversight involving additional substantive and procedural rules designed to deal with the inadequacies of the baseline system.⁷⁶ Protocols for HSR on human gene transfer research, for example, are subject to the basic oversight depicted in Figure 1, as well as additional exceptional oversight depicted in Figure 4. As Figure 4 depicts, such protocols require FDA and IRB approval, and must also be registered with the NIH’s Office of Biotechnology Activities (OBA). They are reviewed by OBA’s Recombinant DNA Advisory Committee (RAC), which assesses whether the protocol raises “important scientific, medical, ethical, or social issues that warrant in-depth discussion at the RAC’s quarterly public meetings.”⁷⁷ The RAC also advises OBA and the Office of the Director at NIH about oversight needs it has identified in the course of its reviews. NIH guidelines further require that these gene therapy protocols receive institutional review by an Institutional Biosafety Committee (IBC), including consideration of occupational, bystander, and environmental concerns.⁷⁸ Figure 5 identifies this and other categories of HSR receiving exceptional oversight.

Some nanomedicine research, such as research on non-viral nano-vectors for human gene transfer, already falls under an existing area of exceptional oversight and, as a result, receives additional oversight now. However, other areas of nanomedicine research may also present similar challenges to basic HSR oversight, but are not covered by any existing exceptional oversight regime. In this section, we identify safety and ethical concerns that some nanomedicine applications may pose for HSR oversight and provide recommendations for how these challenges can be addressed by federal and institutional oversight bodies. We first provide a more detailed overview of why some nanomedicine applications may present additional risk-related challenges for HSR oversight. We then discuss how these specific challenges may affect IRB consideration of first-in-human (FIH) research and risk-benefit analysis, informed consent, and data monitoring. Finally, we discuss how some nanomedicine HSR can present occupational, bystander, and environmental concerns meriting oversight beyond the basic FDA rules and Common Rule.

A. Nanomedicine Risks—To evaluate what kind of challenge nanomedicine is presenting to HSR oversight, Etheridge and colleagues from our project group conducted a search and analysis of the relevant nanomedicine and nanotoxicology literature, including inventorying all nanomedicine applications that are currently in or have already completed HSR.⁸⁰ This research revealed more than 247 confirmed or likely nanomedicine products that are in human subjects research or approved for market use. (Note that this analysis used

a dimensional cutoff of 300nm for the biological and physiological reasons discussed above in Part I, though the paper separately analyzes “nanomedicine” claims up to 2000 nm.) The authors further found that 4 of the 5 most prevalent types of investigational and approved nanomedicine applications involve direct human exposure, most often through injection or implantation. Additionally, they found that the most significant portion of nanomedicine research and commercialization is in the area of cancer therapy and other drug delivery. There are two likely reasons for this. First, a significant portion of conventional drugs, most notably chemotherapy drugs, demonstrate poor solubility and, as a result, poor bioavailability and dose response.⁸¹ Second, many of these same drugs, including chemotherapy drugs, produce significant side effects in patients associated with their broad distribution in the body and toxic effects on healthy tissues.⁸² Consequently, many researchers developing new drugs are looking to nanotechnology to improve the bioavailability and targeting of these drugs. Etheridge et al. also found that there is considerable research in the area of multi-functional nanomedicine applications which serve multiple therapeutic or diagnostic functions or that change functionalities in response to biological or external triggers.

Identifying hazard and ultimately risk characteristics associated with these applications is a challenging task. The nano-components in these applications include a great variety of materials and structures, some of which are passive with fixed functionality and others that are active with functionalities that are triggered or changed by internal or environmental stimuli.⁸³ The hazards and risks associated with these different types of interventions and materials can further depend on the characteristics of the nanoparticles themselves (e.g., size, composition, surface chemistry), the behaviors of the nanoparticles in biological systems (e.g., protein adsorption, barrier penetration, cellular uptake, aggregation, degradation, pathway signaling, and toxicity), and the route through which the nanoparticles are introduced into the body (e.g., oral ingestion, parenteral administration, topical application, and implantation). Indeed, for many individual types of nanomedicine applications there is a considerable literature dealing with potential EHS risks. In many instances, hazard and risk characteristics result from the same properties that make a nanomedicine application beneficial because (1) the very purposes of using nanoscale components is to exploit the ability of these components to access otherwise impenetrable areas of the body or to exploit the novel physiochemical properties that emerge at the nanoscale, and (2) these same nanoscale functionalities also present toxicological and environmental fate and transport hazards and risks that are widely recognized though, in many instances, poorly understood.

While size, composition, and surface chemistry enable improved pharmacokinetics and bioavailability, they can also play a role in the toxicity of nanoparticles.⁸⁴ Although a number of reports have elucidated interactions with cells *in vitro* and tissues and organs *in vivo*,⁸⁵ the clinical significance of these effects remain uncertain. It remains particularly difficult to assess long-term biological consequences of these particles in the body and to predict the potential for unintentional secondary interactions or immunological, inflammatory, or carcinogenic effects, which may take months or years to appear.⁸⁶ High nanoparticle content in biological wastes excreted by research subjects also has been cited as

a source of concern because of potential exposure to bystanders and the environment.⁸⁷ Yet clearly, at least the acute side effects of existing nanoparticulate agents such as Doxil™ (e.g., complement activation) have been characterized and dealt with through the usual preclinical and clinical trial evaluation methodologies. For these earlier versions of nanomaterials in clinical use, few deleterious consequences have been uncovered.

Still, the need to fully consider acute and chronic side effects of novel nanostructures is mandated by FDA guidance, as it is for all new interventions. However, there is a lack of consensus in the toxicology community as to the accuracy of conventional toxicological tests applied to nanoscale materials.⁸⁸ Several reports have highlighted this lack of certainty regarding nanomaterial risks⁸⁹ and have suggested that traditional risk management frameworks need to have a mechanism for incorporating new toxicological data when making decisions.⁹⁰ Specifically, some scholars report that animal models used to assess risks in humans may not be effective for nanomaterials because of differences in how nanomaterials are absorbed, distributed, metabolized, and excreted by humans and animals.⁹¹ Similar concerns exist regarding *in vitro* assays and general mechanisms for identifying exposure routes and effects of nanomaterials in the human body and environment.⁹² These problems have given rise to a branch of toxicology devoted to nanotoxicology that is concerned with nanoscale risk attributes that differ from those at the macroscale.⁹³ In addition, and perhaps not surprising given the nascence of the field, there is almost no literature on the long-term effects of nanomaterials in humans.⁹⁴ All of these problems make it hard for an IRB to evaluate whether risks to subjects are reasonable and minimized. If IRB members use their knowledge of risk assessment at larger scales, they may miss the special challenges involved in making nano risk evaluations.⁹⁵

B. First-in-Human Research and Risk-Benefit Considerations—First-in-human (FIH) trials test new medical products in humans for the first time following preclinical bench and animal studies. The goal of these early FIH trials is not to demonstrate medical benefits, but to produce additional safety and efficacy data in a small population of human subjects. These additional data are used to support subsequent trials in larger populations. A sponsor seeking to conduct a FIH trial of a product ultimately requiring FDA approval, will need both FDA approval of an IND and IRB approval. In reviewing a proposal for FIH research, both the FDA and an IRB must first ask whether initiation of research on human subjects is acceptable. They then evaluate the risks and benefits of the protocol. In this section, we combine our discussion of FIH and risk-benefit considerations for nanomedicine HSR because of their significant interrelation and because both are affected by the same central challenge of some nanomedicine applications—uncertainty of risks and need for risk data.

The safe and ethical conduct of FIH and early phase trials is important not only to protect the rights and welfare of human subjects, but also to protect research and innovation. A study or product may face significant setbacks if it produces serious adverse effects (SAEs) or poorly received outcomes during an FIH or early phase drug trial.⁹⁶ The FDA requires drug trials that proceed in phases, with each requiring IRB approval. Traditionally, sponsors have been expected to conduct Phase I, II, III, and sometimes post-market Phase IV studies (though these phases are sometimes combined, as in Phase II/III trials).⁹⁷ FDA determines

whether to approve the drug for market based on these Phase III findings and may require sponsors to conduct Phase IV studies, post-market studies, to gather data about adverse effects. In 2006, the FDA added Phase 0 trials to the Phase I-IV scheme.⁹⁸ In Phase 0 trials a single small dose of the intervention under study is administered to a small pool of healthy subjects to determine whether its effects in humans matches the effects anticipated from preclinical studies.⁹⁹ These Phase 0 trials present the greatest uncertainty to human subjects in terms of risk.¹⁰⁰ Thus, both Phase 0 trials (when used) and Phase I trials may be the context for launching FIH studies.

The FDA and IRBs face protocols for FIH trials of nanomedicine as new products are developed incorporating more advanced, complex, and active nanostructures. The ability of both oversight entities to evaluate the acceptability of proposed FIH trials will be challenged by the current uncertainty as to the accuracy of preclinical animal and bench data in predicting human effects for some nanomaterials. Necessary data sets that assist in setting proper health and safety guidelines are still lacking for many nanomaterials, including reliable *in vitro* and *in vivo* assays that accurately predict human responses and full documentation of nanoparticle interactions within the human body, including how particles are transported, metabolized, and excreted, and how they interaction with human organs and human biological systems.¹⁰¹ Some analysts argue that the applicability of animal risk data to humans is limited at best, given the possibility of significant differences in how humans and animals metabolize some nanomaterials.¹⁰² This is especially true for nanomaterials that produce an immunogenic response, which may be considerably different in animals than in humans.¹⁰³ For some nanomedicine applications for cancer treatment, the limitations of animal models may be even greater because the use of non-tumor-bearing animals in these studies ignores the ability of tumors to disrupt the blood-brain barrier, allowing easier penetration by nanomaterials.¹⁰⁴ The limited duration of animal studies of nanomaterials may hamper assessment of long-term risks to humans, such as carcinogenicity, and animal studies delivering high doses in a short timeframe may not produce results reflecting the effects of smaller doses over a longer time in humans.¹⁰⁵ Further criticisms of the utility of animal studies to predict effects in HSR generally may be especially problematic in the context of some nanomedicine research. One such criticism is that, because of their small sample size and limited duration, animal studies only reveal the fastest, most pervasive, and most easily detectible adverse effects.¹⁰⁶ Differences may exist between animals and humans regarding how nanoparticles are processed through bodily systems or excreted; in mice larger nanoparticles may tend to agglomerate, whereas the same particles could pass quickly through human systems.¹⁰⁷ Some nanoparticles may produce significantly delayed unintended secondary effects or immunologic, inflammatory, or carcinogenic effects as a result of the body retaining nanoparticles for a long period of time and breaking them down more slowly than large particles.¹⁰⁸ Animal studies may not detect these effects.

These FIH issues blend into the larger issue of how the FDA and IRBs can reliably assess risks. While some nanomedicine protocols will use familiar and well understood nano-components (such as liposomes, dendrimers, micelles, and proteins), others will use novel and complex nanomaterials with poorly understood risks. The range and complexity of benefits, risks, and uncertainties are likely to increase in the future, as more applications

incorporate active nanomaterials with properties that change through biological interactions and in response to environmental triggers.

Uncertainty surrounding the risks posed by some nanomedicine trials may raise additional ethical and oversight challenges. Informed consent may be difficult to get, as explanations of nanomedicine risks that are based on uncertain preclinical data may not do a good job of communicating the real risks. Uncertainty about risks may also militate in favor of long-term monitoring of subjects, especially for nanomedicine applications with a potential risk of bioaccumulation or delayed or long-term effects. Yet long-term monitoring requires extended cooperation from research participants, thus raising more ethical complexities.

One approach to assist the FDA and IRBs in addressing uncertainty in FIH trials and in risk-benefit evaluation more generally is to establish a set of criteria to use in assessing the acceptability of risk. This approach has been used in HSR oversight for human gene transfer trials.¹⁰⁹ NIH established *Guidelines* for investigators and oversight bodies.¹¹⁰ Appendix M of these *Guidelines*, entitled “Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One of More Human Research Participants,” provides a set of questions that investigators must answer and federal and institutional oversight bodies can use to guide evaluation of protocols. Appendix M and the associated *NIH Guidelines* articulate criteria to guide evaluation of a proposed protocol, include criteria pertaining to safety reporting, research design, anticipated risks and benefits, preclinical and risk assessment studies, selection of human subjects, informed consent procedures and documents, and long-term follow-up.¹¹¹

Some commentators suggest that the *NIH Guidelines* have the potential to serve as a model for oversight in other areas of emerging research with uncertain benefits and risks.¹¹² Our research team found several aspects of this model potentially useful for oversight of nanomedicine HSR, especially the Appendix M Points-to-Consider. Consequently, this model significantly influences our recommendations for the development of a nanomedicine points-to-consider document, explained in Part III.

We offer the following recommendations for how HSR oversight can address FIH trials and risk-benefit determinations in the context of nanomedicine:

1. In evaluating a proposed nanomedicine protocol, especially for an FIH trial, the FDA and relevant IRB should consider the adequacy of the preclinical data offered to support the appropriateness of undertaking human trials. They should consider the variety of animal and *in vitro* models used to assess risk, and whether they show consistent risk findings using different assessment methods; the potential for immunogenic and other biological reactions that may occur in humans but not in animals; small sample size and short duration in animal studies, that may result in difficulty in detecting rare or delayed adverse effects; the use of disproportionate dosing in animals to simulate long-term exposure effects; and whether the animal studies were randomized or blinded. They should also consider how closely preclinical studies match the proposed human protocol with respect to the composition of the intervention, the mode of administration, and other relevant variables.

2. Where the reliability of preclinical studies is uncertain in predicting human risks, the FDA and IRBs should ask investigators to articulate the limitations of their preclinical models and to provide what data they have that support the reliability of the preclinical studies.
3. The FDA and IRBs should carefully analyze protocols using nanomaterials with the potential to cause long-term or delayed adverse effects and potentially requiring ongoing monitoring. If such risks exist or if the potential for such risks is uncertain, researchers should be asked to disclose and address them in their informed consent documents.

C. Informed Consent Considerations—As we have suggested, some nanomedicine HSR presents challenges for informed consent. The FDA rules on HSR and the Common Rule establish both general requirements for informed consent and additional features that IRBs may require. The general requirements include explanations of foreseeable risks and benefits to the subject.¹¹³ Additional elements of informed consent that may be required include a “statement that the...[intervention] may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable”; anticipated situations where the subject’s participation may be terminated by the researchers; and 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.”¹¹⁴ These additional elements of informed consent may well prove germane to those nanomedicine trials investigating fundamentally new interventions in FIH or Phase 0 or 1 trials. Indeed, findings that some nanomaterial may bioaccumulate in the gonads or demonstrate cytotoxicity in gametes¹¹⁵ demonstrate the potential importance of considering whether a subject may become pregnant or a subject’s gametes may be used to conceive.

An additional challenge to informed consent in the context of some nanomedicine research may be the therapeutic misconception, a widely recognized problem that occurs when human subjects believe that they are receiving clinical care and fail to appreciate that they are participating in research with risks and potentially no therapeutic benefit.¹¹⁶ Studies indicate that the therapeutic misconception is pervasive in clinical trials;¹¹⁷ the current informed consent process may not consistently ensure that human subjects understand the nature of their participation in research.¹¹⁸ Some nanomedicine HSR may heighten risk of the therapeutic misconception. When nanomedicine applications entering FIH and early-phase trials with varying levels of uncertainty as to potential risks to human subjects and the adequacy of preclinical data to predict such risks, subjects may have difficulty grasping the dimensions of the risks they are assuming.¹¹⁹ In addition, a significant portion of nanomedicine applications entering human trials focus on treating cancer, especially late-stage cancer or cancer that is difficult to treat using conventional therapeutics. Subjects afflicted with serious or life-threatening conditions may cling to hope that participating in research will benefit them; this can result in the therapeutic misconception plus a willingness to accept high levels of risk.¹²⁰

Finally, some commentators have raised the question of whether informed consent documents in nanomedicine HSR should include disclosure that the intervention contains “nanoscale” components.¹²¹ The question of whether to use “nano-” in the informed consent process leads to consideration of how the public views nanotechnology.¹²² Public opinion seems to range from concern over the lack of specific regulations for nano-products to support for greater investment in nanotechnology research and innovation.¹²³ One meta-analysis found that more members of the public associated nanotechnology with benefits than with risks, but that a sizeable minority was unsure.¹²⁴ One scholar argues that the public is likely to embrace nanomedicine products, based on evidence of positive public opinion toward biomedicine more generally.¹²⁵ However, others argue that if the public cannot tell whether a medical product contains nanomaterials, this will raise concerns about nanomedicine and result in negative public opinion.¹²⁶

The question of what to disclose in the informed consent process in the context of human subjects research is somewhat different than the more general question of labeling “nano” in products for consumers. In the context of HSR, the informed consent process is supposed to serve a crucial ethical function. Disclosure must be robust in order to allow individuals to determine as an exercise of their autonomy whether to agree to undertake the risks and burdens of participation. Withholding information or terminology that might lead individuals to decline participation is difficult to defend.

Because informed consent plays such a crucial function in HSR, we conclude that the informed consent process and document in nanomedicine HSR should indeed disclose that a study involves nanomaterials. Implementing this recommendation is challenging, given that defining “nano” remains a subject of debate,¹²⁷ and not all sponsors using nanomaterials in their products state that. We suggest that at the very least, where the relevant documents (such as the research protocol) already use “nano” terminology, this should not be withheld from participants and should be included in the informed consent process and documents. Disclosure is important to engendering public confidence in nanomedicine research and to ensuring that, in the event of a serious adverse event in a nanomedicine trial, the public does not feel deceived by researchers and does not react against nanomedicine research. However, when the relevant documents do NOT use “nano” terminology, what is likely to be most important ethically is to fully and accurately describe the intervention, its risks, and potential benefits, if any. This terminology issue in the informed consent process reinforces the importance of a coordinated, federally led process to clarify terminology and what is embraced by “nanomedicine,” as we discussed above.

We thus offer the following recommendations for addressing informed consent challenges raised by some nanomedicine research:

1. Informed consent processes and documents should state when “nanoscale” interventions are to be used in a protocol (at least when the relevant documents associated with the proposed trial use such “nano” terminology) and should describe the relevant attributes of the intervention. Effectuating this recommendation will be aided by the work of the OSTP/OMB/USTR working

group on terminology and our proposed HSR/N Working Group and SAC/N specifically on human subjects research issues.

2. IRBs should be aware of the risk of the therapeutic misconception in some nanomedicine research. When reviewing nanomedicine protocols, IRBs should scrutinize the proposed informed consent documents and procedures and, where necessary, recommend changes to ensure clear communication that the protocol constitutes research not clinical care, accurate description of risks, and appropriately cautious description of potential benefits, if any.
3. IRBs should determine whether individual nanomedicine protocols call for additional elements of informed consent, as set forth in the FDA rules on HSR and the Common Rule, such as a statement that the protocol involves some risks that are unforeseeable (to the subject or embryo or fetus if the subject becomes pregnant or the subject's gametes are used to conceive).
4. IRBs should determine whether the informed consent processes and documents for individual nanomedicine protocols include adequate language on potential risks and implications of bioaccumulation, long-term permanence, delayed adverse effects, and need for long-term monitoring of subjects.

D. Data-Monitoring Considerations—The Common Rule and FDA rules on IRB review of proposed HSR require that “[w]hen appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.”¹²⁸ Evaluating the adequacy of such monitoring plans is a challenge for IRBs whenever there is uncertainty as to the type of risks that need monitoring. Yet monitoring is important when there is uncertainty about the types and degree of risk to human subjects. Given the potential for such uncertainty in some nanomedicine HSR, especially uncertainty about potential long-term or delayed adverse effects, data-monitoring is important. Because of the fast-evolving nature of nanomedicine and the paucity of data on long-term risks as well as risks associated with more complex and active materials, data-monitoring is a significant tool to ensure that the lessons of early trials guide the design and review of later trials.

While IRBs play an important role in assessing the need for and the adequacy of monitoring plans, Data and Safety Monitoring Boards (DSMBs) often perform this monitoring function. FDA regulations require data-monitoring for all clinical trials of drugs, biologics, and devices requiring IND or IDA approval.¹²⁹ DSMBs provide advice to sponsors about the ongoing safety of their clinical trials.¹³⁰ For both drugs and devices, sponsors must immediately terminate studies when data-monitoring reveals an “unreasonable risk to subjects.”¹³¹ DSMBs are typically only required for “large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer.”¹³² Early-phase clinical trials are generally not required to use DSMBs.¹³³

NIH requires DSMBs for all NIH-supported or conducted Phase III clinical trials and (where appropriate) for Phase I and II clinical trials that are multi-site, blinded, or involving high-risk interventions or vulnerable populations.¹³⁴ “The method and degree of monitoring

needed is related to the degree of risk involved.”¹³⁵ DSMBs can make recommendations for halting or modifying a trial because of risk concerns.¹³⁶

Because current practice does not require the use of DSMBs for early-phase clinical trials, many nanomedicine trials at that stage may not use these data-monitoring bodies. However, the use of DSMBs or other institutionally established committees with similar responsibilities can be a useful tool for gathering data on uncertain risks in nanomedicine HSR trials. For example, a DSMB could monitor liver function data to assess bioaccumulation risks or inflammatory markers to identify an immunologic response. Performing such monitoring during the early trial phases can help ensure that subsequent trials are designed to minimize these risks. Such data can also provide valuable input for IRBs as they review the adequacy of a protocol’s research design, as well the need to revise informed consent documents and inform human subjects about new findings of risk.

Consequently, we recommend the following:

1. FDA should recommend the use of DSMBs or another data-monitoring body with similar functions for those nanomedicine trials that present uncertain or particularly significant risks, including for bioaccumulation and delayed adverse effects. Data and findings from monitoring should be used not only to inform investigator and sponsor decisions, but also to inform FDA, NIH, and IRB approval processes.
2. In reviewing a nanomedicine protocol’s data-monitoring plans, IRBs and DSMBs should consider the adequacy of the plan to detect potential long-term or delayed adverse reactions.
3. IRBs should consider whether a particular nanomedicine protocol requires more frequent data-reporting to a DSMB to ensure that risks and harms are quickly identified.
4. IRBs and DSMBs should ensure that nanomedicine protocols that present significantly uncertain or serious risks to subjects provide clear triggers and procedures for halting research in the event of serious adverse effects (SAEs).
5. IRBs and DSMBs should ensure that protocol procedures include appropriate provisions for prompt reporting of any unexpected serious adverse effects (SAEs) or research findings revealing a new significant risk to research participants.

E. Considerations Beyond the Common Rule—Much remains to be understood about occupational, bystander, and environmental risks of nanomaterials. Research detailing health and environmental effects is limited.¹³⁷ For instance, it remains unclear whether certain classes of nanomaterials pose a greater risk to workers, and whether nanomaterials in certain states (e.g., liquid or solid) pose greater risks of accidental exposure.¹³⁸ After nanomaterials are shed by subjects, how persistent are they in the community and environment? If a nanomaterial enters an ecosystem, what are the effects on organisms, populations, and the ecosystem itself? Such gaps in our knowledge are highlighted in the recent NRC report.¹³⁹ Some nanomedicine HSR raises occupational exposure concerns for researchers and lab workers who may inhale nanoparticles or absorb them through their skin

in the course of manufacturing, handling, or administering nanomedicine interventions.¹⁴⁰ Bystanders (including family members and close contacts of human subjects) may also be potentially exposed to nanomaterials excreted or otherwise shed by subjects. Laboratory disposal practices, as well as excretion and shedding, can also release nanomaterials into the environment. Increasing our understanding and control of workplace and environmental exposures is a significant goal of recent government strategies for nanomaterial risk management.¹⁴¹

Consideration of occupational, bystander, and environmental effects is beyond the traditional scope of IRB deliberation, as IRBs focus on the protection of human subjects themselves.¹⁴² Some commentators argue that consideration of these issues exceeds IRBs' expertise and would overburden them.¹⁴³ Because the HSR regulations do not provide guidance on these issues,¹⁴⁴ some have argued that IRBs are not the right bodies to consider them.¹⁴⁵ In the case of bystander risks, for example, the argument is that protection of bystanders is a public issue that should be addressed by a policy-making body, not a review body such as an IRB.¹⁴⁶ Yet bystander risks are important in deciding whether HSR is ethical.¹⁴⁷ Indeed, some argue that investigators conducting HSR have an obligation to consider effects on bystanders.¹⁴⁸

While IRBs are not tasked to oversee occupational, bystander, and environmental risks, there are other federal and institutional authorities that do provide relevant oversight. The occupational safety of lab workers and scientists, for example, is subject to oversight by OSHA, plus the Centers for Disease Control and Prevention (CDC) and NIH, who have issued a joint Biosafety in Microbiological and Biomedical Laboratories (BMBL) manual.¹⁴⁹ The BMBL manual provides guidance on laboratory practices, safety equipment, and facility design, as well as information on specific microbiological agents relevant to lab worker safety.¹⁵⁰ Under OSHA regulations, research institutions also convene laboratory safety committees (LSCs) responsible for ensuring the adequacy of safety training and the compliance of lab procedures with OSHA.¹⁵¹ These occupational safety oversight mechanisms consider concerns raised by HSR, among many other activities. The CDC and NIH have already issued requirements that are specific to the use of nanomaterials in laboratories.¹⁵² OSHA too has addressed nanotechnology, indicating on its website that nanotechnology is subject to general OSHA standards.¹⁵³ NIOSH (an office under the CDC) is also already involved in nanotechnology-related occupational risk and safety assessment. In addition to identifying 10 critical topic areas in nanotechnology for the purpose of "addressing knowledge gaps, developing strategies, and providing recommendations,"¹⁵⁴ NIOSH has produced a number of guidance documents on safe handling and monitoring of nanomaterials in the workplace.¹⁵⁵ NIOSH has also developed a Nanotechnology Information Library (NIL), an online database with information about nanomaterial properties and characterization.¹⁵⁶ Despite all of this work, some urge the need for additional oversight.¹⁵⁷

Environmental health and safety is subject to oversight from the EPA. While EPA is already involved in the oversight of nanotechnology and nanomaterials, it plays a limited role with respect to environmental issues raised by HSR. Under 21 C.F.R. part 25, approval of clinical trials qualifies as a federal action requiring compliance with the National Environmental

Policy Act (NEPA),¹⁵⁸ which requires preparation of an environmental impact statement with a finding of no significant environmental impact or the applicability of one of several categorical exclusions. These exclusions apply broadly to almost all drug, device, biologic, and combination product approvals and are not written with any consideration for the hazard and risks that may be posed by some nanomaterials. Indeed, a categorical exclusion applies so long as the risk assessment concludes that the expected environmental concentration of a drug will be less than 1 part per billion.¹⁵⁹ Given that nanomaterials may be more reactive than non-nano materials at smaller scales, this exclusion deserves scrutiny.

EPA does have direct involvement in overseeing certain HSR. EPA plays an active oversight role for human subjects research involving intentional dosing with pesticides.¹⁶⁰ EPA has created a Human Studies Review Board (HSRB) “to provide independent advice and recommendations to EPA on issues related to the scientific and ethical review of research involving human subjects.”¹⁶¹

Despite the involvement of these federal occupational and environmental oversight bodies in the area of nanotechnology and EPA’s involvement in some HSR, there has been little effort to integrate EHS analyses with HSR oversight generally, or in the domain of nanomedicine. However, one area of HSR oversight in which there is considerable integration of human subject concerns and occupational and environmental considerations is rDNA research. Under the *NIH Guidelines* for rDNA research, protocols for HSR must be reviewed not only by an IRB, but also by a locally established Institutional Biosafety Committee (IBC) responsible for evaluating occupational, population, and environmental risks associated with the research.¹⁶² Some institutions have expanded the mandate of their IBCs to include other areas posing biosafety concerns.¹⁶³

IBCs are one candidate for a local body to take on the broader mission of considering those nanomedicine research protocols found to raise safety concerns beyond human subjects themselves. IBCs can work with IRBs to integrate human subjects and broader concerns and to assess whether the risks of a protocol are acceptable. However, tasking IBCs to consider some nanomedicine protocols would require new guidance. IBCs are governed by the *NIH Guidelines*, which address only rDNA research and offer only NIH guidance. To effectively address nanomedicine, IBCs would require nano-specific guidance analogous to that provided by the *NIH Guidelines* for rDNA research. Moreover, integration of NIH, FDA, EPA, and OSHA guidance would help coordinate consideration of the full range of issues.

We recommend creation of guidance and resources to allow IBCs (or equivalent local committees) to consider occupational, bystander, and environmental concerns raised by nanomedicine protocols, in coordination with IRBs and other local committees with relevant jurisdiction (such as lab safety committees). However, not all nanomedicine research poses occupational, bystander, and environmental concerns. Consequently, we recommend that currently existing institutional committees trigger IBC review only for nanomedicine protocols that are identified as presenting significant uncertainty or concern with respect to occupational, bystander, or environmental issues. Identification of these cases of potential concern will be assisted by efforts, such as those of the National Research Council, to improve toxicological studies on engineered nanomaterials.

Consequently, we recommend that:

1. Nanomedicine protocols submitted to IRBs should include data supporting the safety of HSR to workers, bystanders, and the environment. Protocols should include descriptions of clinical and laboratory practices for nanomaterial handling, containment, and disposal, including disposal of biowastes containing nanomaterials.
2. IBCs or equivalent committees should review those nanomedicine protocols that are identified by HSR approval bodies as presenting occupational, bystander, or environmental risks or significant uncertainty with respect to these concerns. Such review should include consideration of the adequacy of data supporting occupational, bystander, and environmental safety and the adequacy of clinical and laboratory practices proposed.
3. Review by an IBC or equivalent committee should take place concurrently with or before IRB review, to aid coordinated consideration of whether nanomedicine research protocols should move forward.
4. IBCs or equivalent committees should also provide their review findings to DSMBs to inform safety and monitoring decisions.
5. Where risks to family members and close contacts exist, IRBs should ensure that protocols provide adequate procedures for informing subjects of these risks, should consider whether bystanders should be informed of risks, and should consider how subjects and bystanders will be provided with information and training to minimize risks.

Part III. A Flexible, Evolutionary Approach to Oversight

As more information becomes available about hazards and risks associated with specific nanomedicine interventions, it may become necessary to increase or decrease oversight for different types of nanomedicine HSR. Protecting human subjects is a priority in HSR oversight. At the same time, avoiding significant costs and barriers to innovation should be a priority as well. Consequently, we recommend a flexible, evolutionary approach to oversight that:

1. Recognizes that not all nanomedicine interventions present the same risks and concerns for human subjects research protection;
2. Establishes criteria for identifying those nanomedicine protocols that raise heightened concerns, potentially requiring additional analysis;
3. Enables **adaptive oversight that can evolve** (both ratchet up and ratchet down) as knowledge, data, and experience with nanomedicine interventions grow over time and the science and technology evolve; and
4. **Provides a coordinated framework** for analysis and development of oversight mechanisms, as well as for sharing of knowledge and information across federal agencies and offices, as well as institutional oversight bodies.

Instead of creating new regulation, this flexible approach establishes a process for identifying nanomedicine HSR protocols that may require additional analysis and oversight. Where a need for additional oversight is identified, our approach can provide a coordinated approach across agencies and offices. As new knowledge and data emerge about nanotherapeutics and *in vivo* nanodiagnostics, this can be used to inform the further evolution of oversight.

We have recommended above that the linchpin of this evolutionary and adaptive approach to nanomedicine HSR oversight be two complementary committees—an HSR/N Working Group for inter-agency coordination, advised by a SAC/N public committee of experts and other stakeholders. We recommend that they be placed in DHHS, where FDA, NIH, and OHRP--key oversight entities for HSR generally--reside. Membership in HSR/N should include representatives from agencies and offices including OHRP, NIH, FDA, NIOSH, EPA, and OSHA. Concurrently with the formation of HSR/N, the Secretary of DHHS should create SAC/N and assemble experts and stakeholders in nanomedicine to advise the Secretary and HSR/N.

HSR/N and SAC/N will fill a gap in the current federal oversight structure for nanotechnology, by adding a capacity to consider the HSR issues. Both bodies should interact with the nanotechnology committees and offices that already exist. NSET is a subcommittee of the National Science and Technology Council's (NSTC) Committee on Technology. NSET and the National Nanotechnology Coordination Office (NNCO) are responsible for coordinating planning, budgeting, and program implementation for NNI, a major federal effort to coordinate approaches to nanotechnology issues across 25 federal agencies. Another body, the President's Council of Advisors on Science and Technology (PCAST), which reports at the Cabinet level, is responsible for evaluating the technical accomplishments of the NNI, recommending new goals and research areas, and suggesting budget changes. PCAST is also charged with issuing recommendations to the President about the NNI and broader nanotechnology policy. Indeed, PCAST issued a report in 2012 with recommendations to create unified strategies across agencies, promote information sharing, and increase contributions from experts outside the government.¹⁶⁴ As noted above, NSET currently has 4 Working Groups: Global Issues in Nanotechnology; Nanotechnology Environmental and Health Implications; Nanomanufacturing, Industry Liaison & Innovation; and Nanotechnology Public Engagement and Communications.

The approach we recommend creates a home for the consideration of nanomedicine HSR issues within DHHS, the federal agency that houses the FDA, NIH, and OHRP, which are the primary federal regulators and oversight entities for human subjects research. (See Figure 6.) We should note that in recommending creation of an HSR/N Working Group, we are mindful that "working group" is often used federally to apply to inter-agency committees, whereas "task force" usually signifies intra-agency membership.¹⁶⁵ There is a history of interagency working groups housed within DHHS, with participants across government.¹⁶⁶ The Working Group would have membership from FDA, NIH, NIOSH, OHRP, and other appropriate DHHS offices, and representatives from offices and agencies outside of DHHS, such as NSET, EPA, DOJ (OSHA), and NNI.

In addition to the creation of HSR/N, we recommend the creation of SAC/N, made up of experts and public representatives to provide substantive input on nanomedicine ethical issues. DHHS already has a Secretary's Advisory Committee on Human Research Protections (SACHRP).¹⁶⁸ SACHRP was formed in 2001 by then-Secretary Thompson;¹⁶⁹ the current Secretary of DHHS could order formation of SAC/N. SACHRP's current charter allows SACHRP to consider any issue, but with emphasis on stated areas, which do not include nanomedicine HSR.¹⁷⁰ This is why our group recommends an analogous committee, with membership providing nanomedicine HSR expertise. However, a subcommittee of SACHRP might suffice, so long as it has appropriately expert membership. Figure 7 depicts the organizational location of the two committees we recommend.

SAC/N should be created as a public advisory body under the Federal Advisory Committee Act (FACA).¹⁷¹ FACA governs committees, boards, commissions, councils, and similar groups established to advise officers and agencies within the federal government.¹⁷² FACA committees "are meant to provide independent, expert, and objective advice" on policy issues,¹⁷³ and work by engaging both government and non-government employees in a transparent, public forum.¹⁷⁴ Though controversy has occasionally erupted over FACA committee functioning, particularly regarding the requirement of balance in points of view represented,¹⁷⁵ a FACA committee would offer benefits for oversight of nanomedicine HSR. SAC/N would be subject to requirements in terms of membership, advance notice of meetings in the *Federal Register*, and meetings open to the public, unless statutorily allowed to be closed.¹⁷⁶ Nanomedicine continues to be a controversial emerging area of technology, so an open and transparent forum for debate is highly desirable. NNI has also highlighted the need integrate various shareholder views, in a way that promotes transparency.¹⁷⁷ Current mechanisms to solicit and act on non-governmental expert advice are inadequate.¹⁷⁸ FACA committees the needed transparency and incorporation of stakeholders. SAC/N would also create shared governance among governmental entities, experts, and the public.¹⁷⁹ SAC/N would bring to the table individuals well-versed on the science of nanomedicine. Nanomedicine is a quickly evolving field that demands involvement of top industry and academic experts to ensure the government is informed of new developments and trends with the science and within industry.

SAC/N is needed, but not enough to achieve nanomedicine HSR oversight that is effective. Simultaneous creation of an HSR/N Working Group will allow government officials to work behind closed doors and efficiently to evaluate regulatory recommendations and enact changes as necessary. HSR/N can also facilitate regulations and promote information-sharing mechanisms among agencies, offices, and centers, including on proprietary product information. HSR/N can facilitate the sharing of information from various government databases on nanoparticle toxicity; while such databases have proliferated, methods of data-sharing are underdeveloped.¹⁸⁰ Pairing a FACA committee with a regulatory working group or equivalent has been used elsewhere, such as in oversight of human gene transfer HSR, where the RAC has served as the FACA committee, while the FDA has housed regulatory decision-making.

HSR/N and SAC/N should initially serve 3 complementary functions with respect to nanomedicine HSR, with a possible fourth function to be added later (see Figure 8).

SAC/N's activities under each function are closely modeled on the responsibilities given to SACHRP under its charter (suggesting again that SAC/N might also exist as a subcommittee of SACHRP, as opposed to an independent entity.) These three initial functions should be ongoing and should evolve over time. **In performing the analytical function, HSR/N** should lead and coordinate identification and analysis of nanomedicine HSR issues. This should begin with consideration of how best to define or describe nanomedicine protocols of potential concern; we recommend the approach to definition/description presented in Part I of this paper. HSR/N may also benefit from interaction with the new OSTP/OMB/USTR working group established by memo dated June 2011, as discussed above.¹⁸¹ That working group "will coordinate an approach and choice of terminology relevant to the regulation and oversight of nanomaterials," will "develop this framework," and will "enable...agencies to...influence ongoing research into nanotechnology";¹⁸² this suggests that the new agency will spearhead the kind of scientific research needed to generate science-based regulation. Yet because this memo devotes no attention to human subjects research issues, the existence of HSR/N devoted to those issues creates an opportunity for fruitful interaction between the new working group and HSR/N on human subjects issues as well as EHS issues more generally. The analytical work of HSR/N and SAC/N should progress to how best to analyze and synthesize data. HSR/N should lead these evaluations in a coordinated way across agencies and offices and also identify and formulate plans for conducting analysis of different characteristics and categories of nanoproducts and research, whereas SAC/N should review the work of OHRP and other agencies regulating nanomedicine HSR. SAC/N also must serve as a forum to collect input from the public and other stakeholders outside of the government regarding nanomedicine regulation and help keep the public informed of its activities.

In performing the advisory function, HSR/N should coordinate development of an interagency document on "Points-to-Consider in the Design and Submission of Protocols for Research of Nanotherapeutics and *In Vivo* Nanodiagnostics in Human Research Participants," as well as provide advice to federal agencies as they develop regulations and oversight. This Points-to-Consider document should aim to generate data that will aid development of a science-based and ethical approach to nanomedicine HSR, while guiding and coordinating analysis by the federal and institutional bodies involved in HSR oversight. SAC/N should consult with and provide advice to the Secretary, through the Assistant Secretary for Health, on matters pertaining to continuance and improvement of functions regarding nanomedicine human subjects research. Each of the agencies participating in HSR/N work should bring to development of this document its concerns and informational needs. Relevant portions of this Points-to-Consider document should provide guidance to institutional review bodies such as IRBs, IBCs, and DSMBs as to issues they should consider in performing their reviews and approvals of nanomedicine research protocols. The document should also provide guidance to investigators as to the information they should supply to aid evaluation of the safety and ethics of nanomedicine HSR, in light of FDA and Common Rule HSR regulations.

Our recommendations for this Points-to-Consider document are influenced by Appendix M of the *NIH Guidelines*, created by the RAC to aid review of gene therapy and rDNA

protocols.¹⁸³ Appendix M, entitled “Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One of More Human Research Participants,” structures investigator applications for review, while the body of the *NIH Guidelines* provides guidance to both investigators and federal and institutional oversight bodies to aid analysis of proposed protocols for human gene transfer research. King has suggested that the RAC and associated *Guidelines* can indeed serve as a model for oversight of other areas of emerging research with uncertain benefits and risks.¹⁸⁴

Figure 9 identifies issues that the HSR/N Points-to-Consider document should address, at a minimum. Some of these issues are derived from the Points-to-Consider in Appendix M of the *NIH Guidelines*. Others derive from our analysis in this article.

The information review function means that HSR/N should serve as a forum for involved agencies to discuss and share new knowledge and trends of concern to nanomedicine HSR, including SAEs, that they have identified through their individual data-submission processes, research activities, and data-monitoring efforts. Additionally, as part of the information review process, HSR/N should facilitate cross-agency sharing of information about SAEs and other issues in nanomedicine research. Knowledge gained through this information review process should inform the plenary and guidance functions over time. SAC/N should review the work and plans of HSR/N pertaining to information review, and should monitor challenges that IRBs and their institutions face in reviewing and conducting nanomedicine research. In addition, SAC/N should also coordinate with NSET to gather new findings and information that might assist in completion of its analytical and advisory functions.

A fourth possible function may be added later if needed. **A protocol reviewing function** should only be established if, in the course of the other three functions, it is determined that some nanomedicine protocols present risks that are complex and significant enough to require additional protocol review beyond that available in baseline HSR review. HSR/N should determine if a protocol reviewing function is necessary and coordinate the formation of such a process. SAC/N would provide a forum for public discussion and input into the formation process. One possible model for such protocol review could be the RAC model for gene therapy research using rDNA.

The use of HSR/N to coordinate across agencies on nanomedicine and the use of SAC/N to ensure expert and stakeholder input should reap benefits for all of the agencies and offices involved in nanomedicine HSR and its oversights, across the federal government and individual institutions. This approach can thus reduce the burden on each federal oversight body to identify and analyze areas of concern in nanomedicine research and can coordinate the approaches of diverse agencies. This can reduce both the risk of duplication of efforts and the risk that some oversight needs go overlooked. Second, it can reduce the risk of shortsighted regulations that may add significant but potentially unnecessary financial and time hurdles to innovation. At the same time, HSR/N can advance coordination between federal and local institutional oversight bodies for HSR/N while keeping the public well informed of progress through SAC/N. The work of these bodies can increase the likelihood that federal and local bodies are operating in synchrony.

Finally, this flexible approach to oversight provides a potential model for oversight of other areas of HSR involving emerging science and technology. Instead of leaving thousands of local IRBs on their own to evaluate fast-evolving and challenging science and technology, our proposal creates a home for analysis and advice. Instead of leaving multiple federal agencies with overlapping responsibilities for overseeing HSR without means to coordinate, pool data, and resolve conflicting approaches, we suggest a pathway to harmonization. Instead of maintaining the fiction that the acceptability of an HSR protocol raises unrelated issues of participant, occupational, bystander, and environmental safety, we suggest how to face the reality that a protocol's acceptability depends on adequate safety and risk management on all four fronts. Finally, instead of suggesting that there is a bright line separating science whose HSR protocol's need only "baseline" review from science whose protocol's need "exceptional" review, we set up a flexible and evolutionary way to begin to distinguish individual protocols needing more intensive review. The goal is to set up an analytic process that is science-based, careful about the distinction between hazard and risk, capable of distinguishing individual protocols of concern, and thoroughly grounded in the established ethical standards guiding human subjects research in the United States.

Conclusion

Federal and institutional oversight bodies are already facing protocols for HSR involving nanotherapeutics and *in vivo* nanodiagnostics. Some of these nanomedicine protocols raise ethical and safety concerns for human subjects, workers, bystanders, and the environment. Many of these concerns are associated with the current lack of knowledge and certainty as to the risks of certain nanomaterials to humans, which can vary depending on the type of nanomedicine application in question. Consequently, HSR oversight of nanomedicine requires an approach that (1) differentiates between nanomedicine applications that present plausible, significant risks and those that do not, (2) provides adequate safety and ethical protections while avoiding unnecessary hurdles to innovation, and (3) is flexible and evolutionary, allowing for new knowledge and data about nanomedicine to inform analysis and oversight over time.

The most important feature of our recommendations is that we urge creation of a home for analysis of HSR issues in nanomedicine. Federal and private investment in nanotechnology is in the billions of dollars per year. The federal government has rightly created an impressive array of offices dedicated to analysis of nanotechnology issues and creation of sound policy, from NNI to NSET and its working groups. Yet nowhere in this structure or in any agency is there currently a central home for coordinating analysis of human subjects research issues. This should be fixed, with creation of an HSR/N Working Group and Secretary's Advisory Committee on Nanomedicine under DHHS. Progress in nanomedicine, with its enormous potential for human benefit, depends on the willingness of individuals to participate in human subjects research and their confidence that the ethics of human subjects research will be maintained, especially in the face of uncertainty and fast-moving science. Our nation's investment in nanotechnology and nanomedicine must be matched by investment in coordinated, sound, and effective oversight for the human subjects research essential to advance this burgeoning and high-impact field.

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Appendix A

Glossary of Acronyms

BMBL	Biosafety in Microbiological and Biomedical Laboratories
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CMC	Chemistry, Manufacturing, and Controls
CT	Committee on Technology
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data Safety Monitor Board
EHS	Environmental, health, and safety
EPA	Environmental Protection Agency
ENM	Engineered nanomaterials
FACA	Federal Advisory Committee Act
FDA	Food and Drug Administration
FIH	First-in-human
FWA	Federalwide Assurance
HSRB	Human Studies Review Board
IBC	Institutional Biosafety Committee
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
GIN	Global Issues in Nanotechnology Working Group

HSR	Human subjects research
HSR/N	Human Subjects Research in Nanomedicine Working Group
LSC	Laboratory Safety Committee
MAPP	Manual of Policies and Procedures
NCI	National Cancer Institute
NDA	New Drug Application
NEHI	Nanotechnology Environmental and Health Implications Working Group
NEPA	National Environmental Policy Act
NHGRI	National Human Genome Research Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NILI	Nanomanufacturing, Industry Liaison, and Innovation Working Group
NIOSH	National Institute for Occupational Safety and Health
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NPEC	Nanotechnology Public Engagement and Communications Working Group
NRC	National Research Council
NSR	Nonsignificant risk
NSET	Nanoscale Science, Engineering, and Technology Subcommittee
NSTC	National Science and Technology Council
NTP	National Toxicology Program
OASH	Office of the Assistant Secretary for Health
OBA	Office of Biotechnology Activities
OHRP	Office for Human Research Protections
OMB	Office of Management and Budget
OSTP	Office of Science and Technology Policy
OSHA	Occupational Safety and Health Administration
PCAST	President's Council of Advisors on Science and Technology
PMA	Premarket approval
RAC	Recombinant DNA Advisory Committee
RDRC	Radioactive Drug Research Committee
SACHRP	Secretary's Advisory Committee on Human Research Protections

SAC/N	Secretary's Advisory Committee on Nanomedicine
SAE	Serious Adverse Event
SR	Significant risk
SRG	Scientific Review Group
USTR	U.S. Trade Representative

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Executive Summary

Nanotherapeutics and *in vivo* nanodiagnostics are a subset of nanomedicine applications that includes drugs, biological products, and implantable medical devices incorporating nanoscale materials. These nanomedicine products can enable new or improved treatments and diagnostics for many diseases and disorders. Human subjects research (HSR) on nanomedicine interventions is already under way, with a number of products already approved for use. Such research is subject to existing federal and institutional oversight rules and regulations, including Food and Drug Administration (FDA) rules on HSR for all FDA-regulated products and the Department of Health and Human Services (DHHS) Common Rule for HSR funded or conducted by NIH or any of the other signatory agencies. Both of these regimes require HSR protocols to obtain approval from an Institutional Review Board (IRB), based on assessment of the ethical appropriateness of research on human participants. However, some nanomedicine HSR may raise safety and ethics concerns that pose challenges to the existing system of oversight and that may merit consideration of additional oversight. The concerns that may warrant additional oversight include marked uncertainty about hazard and risk to human subjects and about occupational exposures of researchers and lab workers, exposures of bystanders such as family members, and environmental effects.

Concerns posed by some nanomedicine HSR reflect the emergence of increasingly complex, active, and interactive products. These concerns also reflect the limits of an HSR oversight system developed over 30 years ago, with widely recognized problems and limitations. We are not arguing that the ethical issues raised by nanomedicine HSR are unique to that field and arise in no other domain of HSR for emerging science and technology. To the contrary, our recommendations regarding nanomedicine HSR offer an opportunity to examine the larger issue of the adequacy of the current HSR oversight system in the face of increasingly sophisticated science and technologies.

This article presents the first published recommendations on how to comprehensively approach the challenges raised by nanomedicine research in human beings. While some nanomedicine HSR requires no extra oversight, we suggest an oversight approach that can identify research that may need extra oversight, that can structure that extra oversight in a targeted way, and that can evolve with greater knowledge about nanomedicine materials and interventions. We recommend the formation of two complementary bodies – an interagency group comprised of governmental officials, and a federal advisory committee comprised of outside experts and stakeholders who can offer advice in a public forum. Creation of both bodies ensures the administrative power to coordinate among agencies while also having a forum for all stakeholders.

- An interagency Humans Subjects Research in Nanomedicine (HSR/N) Working Group should be established to coordinate among federal agencies and offices addressing nanomedicine HSR oversight. We suggest that this HSR/N Working Group be housed within DHHS with member representatives from federal agencies and offices that are key to nanomedicine HSR.

- A Secretary's Advisory Committee on Nanomedicine (SAC/N) should additionally be established under the Federal Advisory Committee Act (FACA) to provide recommendations on sound approaches to nanomedicine human subjects research and a forum for public discussion. SAC/N may be created as a subcommittee of the Secretary's Advisory Committee on Human Research Protections (SACHRP) or as a separate body.
- HSR/N and SAC/N should initially serve (1) analytical, (2) advisory, and (3) information review functions. A fourth potential function, new federal protocol-by-protocol review (as was conducted in the past, for example, in the Recombinant DNA Advisory Committee's (RAC's) review of human gene transfer protocols), does not appear to be warranted at this time.
- For the purposes of nanomedicine HSR oversight and data collection, HSR/N and SAC/N in coordination with other nano-focused offices (including NSET and NNI) should consider how best to establish an interim definition of nanomedicine, which may ultimately lead to a different approach, based on identifying key attributes of concern. Federal definitions of "nanotechnology" in general have varied, though NNI's definition focusing on functionalities engineered to emerge at dimensions of up to 100nm has been most prominent. However, identifying "nanomedicine" products specifically for the purposes of HSR oversight raises somewhat different issues, calling for a more inclusive set of criteria in order to err on the side of capturing HSR concerns. It may be that any such definition should ultimately yield to a roster of relevant attributes of concern.¹ Yet the creation of a roster of attributes of concern is difficult at present, given the state of scientific and toxicological knowledge. HSR/N and SAC/N may thus need to start with a size-based definition, in keeping with the traditional commitment of HSR review to anticipating and preventing harm to human subjects.
- Upon considering the recommendations of SAC/N, HSR/N should facilitate cross-agency coordination on a Points-to-Consider document to help guide institutions and researchers crafting and overseeing protocols for nanomedicine HSR. This Points-to-Consider document should articulate what information is needed to facilitate sound, science-based analysis of ethical and safety questions. It should also provide guidance for information-gathering by institutional review bodies such as IRBs, Data Safety Monitoring Boards (DSMBs), and committees responsible for occupational and environmental review of research protocols.

Our recommendations avoid the creation of additional regulation for nanomedicine HSR as a class. Instead we recommend establishing a means to convene and coordinate federal oversight authorities for the purposes of setting priorities, collecting information, and building infrastructure for effective oversight of nanomedicine HSR, relying on inputs from top experts in the field and key stakeholders as nanomedicine progresses to more complex, active, and interactive interventions. HSR/N and SAC/N will provide governmental and public forums to address nanomedicine HSR issues as the science and

HSR challenges evolve. This flexible approach will reduce the burden on individual agencies and oversight bodies to independently develop their own analyses and datasets, by instead facilitating a coordinated process among relevant agencies, institutions, and centers. This will reduce duplication of effort, help avoid gaps in analysis and oversight, and will ensure a more science-based approach to HSR oversight, thus avoiding unnecessary impediments to innovation. This flexible and evolutionary approach to HSR oversight, including consideration of occupational, bystander, and environmental analysis, may provide a model for HSR oversight in other areas of emerging science and technology.

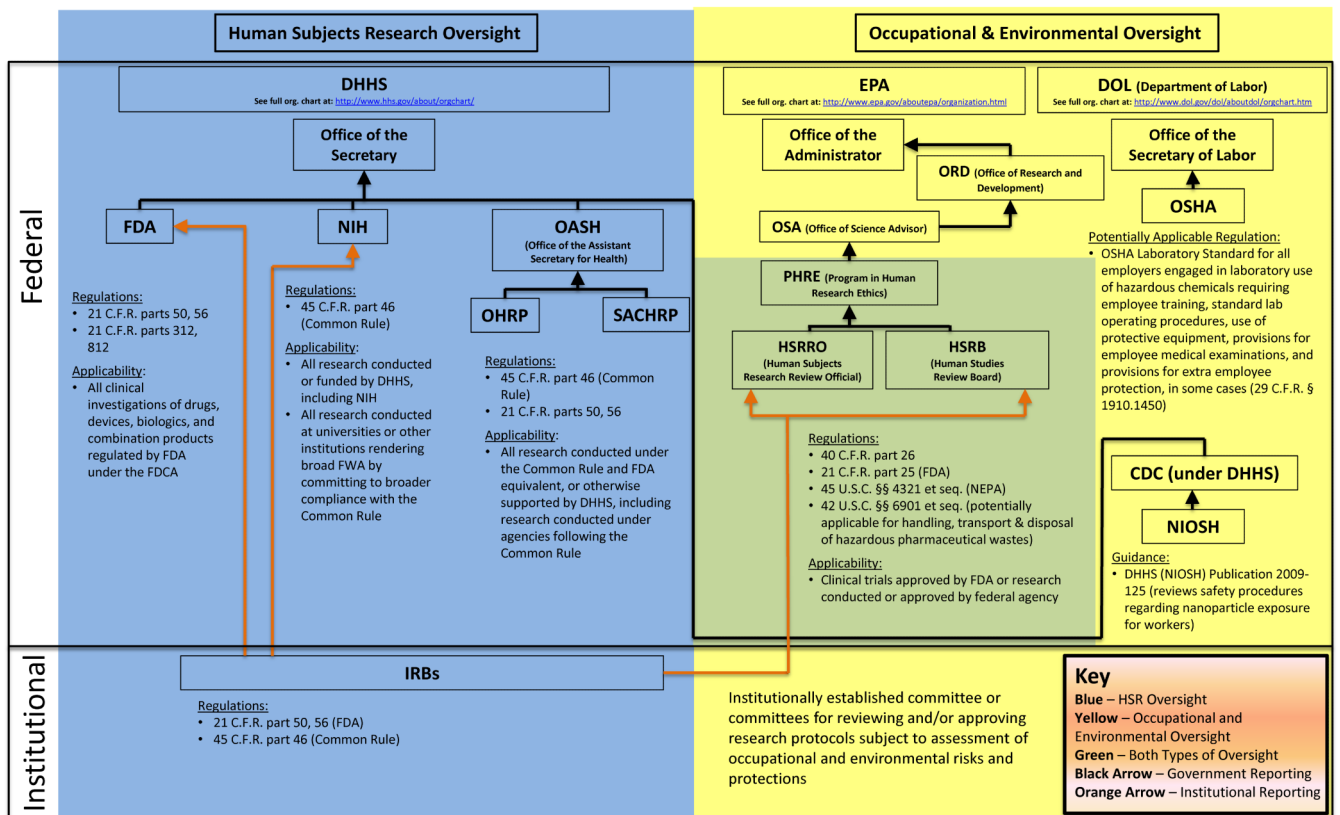


Figure 1. Baseline System of Federal and Institutional Oversight of Human Subjects Research²²

Year	Author/Proponent	Proposed Approach	Core Recommendations
2011	Timmermans, Zhao & van den Hoven ¹⁸⁶	Value Sensitive Design (VSD)	<ul style="list-style-type: none"> • Recommends when developing high-tech nanoproducts that social and ethical issues are taken into account, by using design framework that focuses on values and requirements of moral import. • Design framework helps to reconcile opposing value in engineering design, such as safety versus efficacy.
2011	Wolf & Jones ¹⁸⁷	Standing federal guidance body	<ul style="list-style-type: none"> • Recommends creation federal body or institution to provide guidance for nanomedicine research. • Body provides standing source of advice on nanomedicine when local IRB seek additional expertise for nanoproducts.
2010	Bawa ¹⁸⁸	New FDA center	<ul style="list-style-type: none"> • Recommends creation of a new center at FDA specifically for handling nanoproducts. • Along with a new Center, either new regulations or amended regulations should be created that take into account nano-specific properties.
2009	Fadecel & Garcia-Bennett ¹⁸⁹	Individual assessment of new nano-materials	<ul style="list-style-type: none"> • When a new nanomaterial is tested or a previously tested nanomaterial is altered in size, an individual assessment of the new particle should be conducted. • Recommends increased preclinical studies and studies that examine nano-effects, such as bioaccumulation.

2009	Harris ¹⁹⁰	Risk and characteristic-based regulation	<ul style="list-style-type: none"> • FDA currently faces difficulty classifying certain nano-products' primary mode of action, but nano risks result from unique characteristics displayed by particles. • Nanoproducts should be classified based on risks and nano-characteristics of products. • FDA should receive increased funding to ensure sufficient nano experts to review applications.
2009	Hoet et al. ¹⁹¹	Individual assessment of new nano-products	<ul style="list-style-type: none"> • Increasingly complex products justify a case-by-case approach to hazard identification, based on the unique characteristics of the material. • The risk assessment framework should be reformed to take account of heightened risks.
2008	Bawa & Johnson ¹⁹²	Expanded federal ethics guidance and oversight	<ul style="list-style-type: none"> • Recommends heightened requirements for <i>in vivo</i> and <i>ex vivo</i> research before clinical research is approved. • Emphasize unpredictable risks for newer materials in risk/benefit analysis. • Make sure that subjects receive all details of studies, including information on risks, benefits, and confidentiality.
2008	DeVill ¹⁹³	Central repository of nano-studies	<ul style="list-style-type: none"> • A central repository should be created, in which all medical uses of substances are documented and analyzed (registry studies). • Studies should be aimed at documenting harmful characteristics of nanoparticles.
2008	Staggers et al. ¹⁹⁴	Expanded federal ethical guidance	<ul style="list-style-type: none"> • Existing guidelines from other emergent technology areas such as genetics should be used as a basis for producing additional ethical guidelines. • Guidelines should be aimed at protecting human dignity and integrity in nano-research.
2008	Virdi ¹⁹⁵	Multi-criterion decision analysis	<ul style="list-style-type: none"> • Based on a model by Linkov et al., multi-criterion decision analysis involves assessing a product's risks, the relative riskiness of alternative therapies, and the effects of therapy in assessing the acceptability of studies.
2007	Lenk & Biller-Andorno ¹⁹⁶	Elevated testing standards for nanomaterials and expanded view of risks	<ul style="list-style-type: none"> • In animal studies, testing standards and results should be heightened. • Researchers should expand the roster of risks they consider when designing clinical trials to include (1) long-term outcomes, (2) toxicity, (3) new nano-effects, and (4) the probability of occasional but catastrophic events.

2007	Resnik & Tinkle ¹⁹⁷	Additional safety requirements for nano-studies	<ul style="list-style-type: none"> • Data Safety Monitoring Boards (DSMBs) should be used to track adverse events, reactions, and unanticipated toxicity. • Physician should be required to report adverse events relevant to products, even after approval. • Additional long-term studies are needed, following clinical trials. • Communication with participants should be expanded if the study involves a material not well-studied. • Risk communication with the public is necessary during clinical trials.
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Figure 2. Inventory of Major Proposed Approaches to Oversight of Nanomedicine Human Subjects Research, 2007-11 (adapted from Wolf and Jones, 2011)¹⁸⁵

Agency	Definition/Approach
FDA	<p>In June 2011, FDA released for comment a draft guidance document indicating that: [W]hen considering whether an FDA-regulated product contains nanomaterials or otherwise involves the applications of nanotechnology, FDA will ask:</p> <ol style="list-style-type: none"> 1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or 2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.¹⁹⁸ <p>The FDA has stated that it “has not established its own formal definition, though the agency participated in the development of the NNI definition of ‘nanotechnology.’ Using that definition, nanotechnology relevant to the FDA might include research and technology development that both satisfies the NNI definition and relates to a product regulated by FDA.”¹⁹⁹</p> <p>FDA’s Center for Drug Evaluation Research (CDER) describes nanomaterials in its Manual of Policies and Procedures (MAPP) as “any material with at least one dimension smaller than 1,000 [nanometers].”²⁰⁰</p>

NIH	<p>NIH defines nanotechnology as “the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, a scale at which unique properties of materials emerge that can be used to develop novel technologies and products.”²⁰¹</p> <p>NIH’s National Cancer Institute (NCI) describes nanotechnology as “the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects.”²⁰²</p> <p>Beginning in 2004, NCI’s requests for grant applications for Centers of Cancer Nanotechnology Excellence and Cancer Nanotechnology Platform Partnerships have provided that qualifying research must involve “[d]evices or base materials . . . smaller than 1000 nm in size although the assembly, synthesis, and/or fabrication of components of these final structures at dimensions less than 300 nm should be demonstrated.”²⁰³</p> <p>According to the NIH’s National Institute of Environmental Health Sciences (NIEHS), “[n]anoscale materials are defined as a set of substances where at least one dimension is less than approximately 100 nanometers.”²⁰⁴</p>
EPA	<p>“While many definitions for nanotechnology exist, EPA uses the NNI definition. The NNI calls it ‘nanotechnology’ only if it involves all of the following:</p> <ol style="list-style-type: none"> 1. Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometer range. 2. Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size. 3. Ability to control or manipulate on the atomic scale.”²⁰⁵ <p>The Office of Pesticide Program’s working definition of “nanoscale materials” is “[a]n ingredient that contains particles that have been intentionally produced to have at least one dimension that measures between approximately 1 and 100 nanometers.”²⁰⁶</p>
OSHA	<p>OSHA defines nanotechnology as “the understanding, manipulation, and control of matter at dimensions of roughly 1 to 100 nanometers, which is near-atomic scale, to produce new materials, devices, and structures” and “engineered nanoscale materials or nanomaterials” as “materials that have been purposefully manufactured, synthesized, or manipulated to have a size with at least one dimension in the range of approximately 1 to 100 nanometers and that exhibit unique properties determined by their size.”²⁰⁷</p>
NIOSH	<p>NIOSH defines nanotechnology with reference to the NNI definition and further provides clarification on potential definitions for “nano-objects,” “ultrafine particles,” “engineered nanoparticles,” and “nanoaerosol,” all with reference to a dimensional scale of 1 to 100 nanometers.²⁰⁸</p>

NRC	<p>In lieu of an actual definition, the NRC identifies engineered nanomaterials (ENM) in reference to “principles that help to identify emergent, plausible, and severe risks resulting from designing and engineering materials at the nanoscale . . . The principles are built on three concepts: emergent risk, plausibility, and severity.”²⁰⁹</p>
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Figure 3. FDA, NIH, EPA, OSHA, and NIOSH Definitions of “Nanotechnology”

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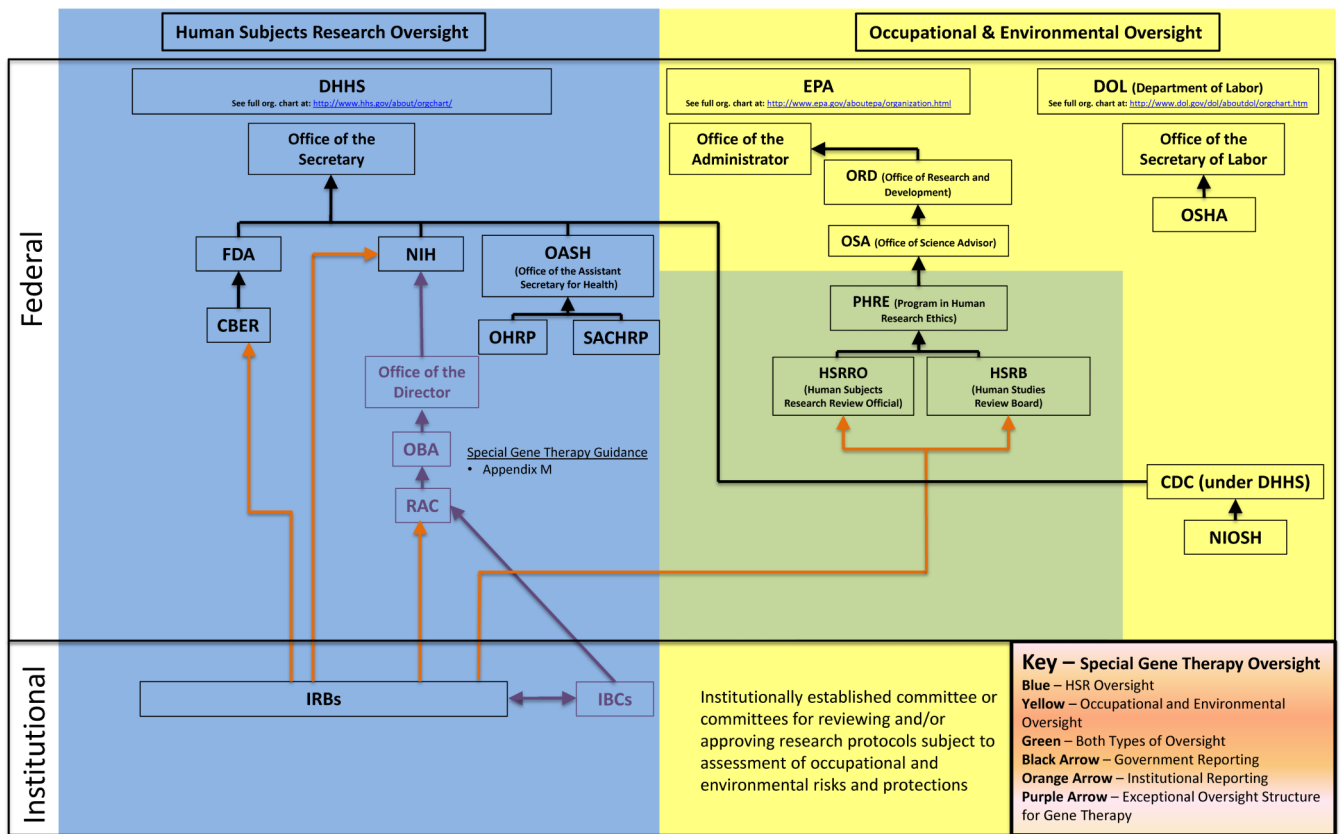


Figure 4. Baseline and Exception Oversight for the Example of Human Gene Transfer Research⁷⁹

Exceptional Category	Additional Oversight Required
Human Gene Transfer and Recombinant DNA Research	Local IRB review, plus review by the RAC at NIH and by CBER at FDA. NIH also requires review by an IBC.
Pediatric Research	Certain forms of pediatric research require review by federal 407 panels convened by OHRP under 45 C.F.R. §46.407.
Emergency Interventions	Research involving emergency interventions to which the human subject cannot consent in advance require application of special IRB rules, satisfaction of certain OHRP requirements, compliance with FDA rules on emergency research (if applicable), and establishment of an independent data safety monitoring board (DSMB).
Fetal Tissue Transplantation	Requires signed statement from woman terminating pregnancy, the physician performing the procedure, and the researcher under 42 U.S.C.S. §289g-1.
Intentional Dosing with Pesticides	Requires central review at EPA and use of an independent Human Studies Review Board (HSRB).
Dual-Use Concerns	Research raising dual-use concerns requires extra oversight by the Centers for Disease Control (CDC) and National Science Advisory Board for Biosecurity (NSABB).
Radioactive Drugs	Human research using a radioactive drug or biological product must receive approval from the FDA Radioactive Drug Research Committee (RDRC) under 21 C.F.R. §361.1. ²¹¹
Synthetic Biology	Both the RAC and NSABB have proposed additional requirements.

Figure 5. Categories of Human Subjects Research that Are Subject to Added Oversight (from Wolf and Jones, 2011)²¹⁰

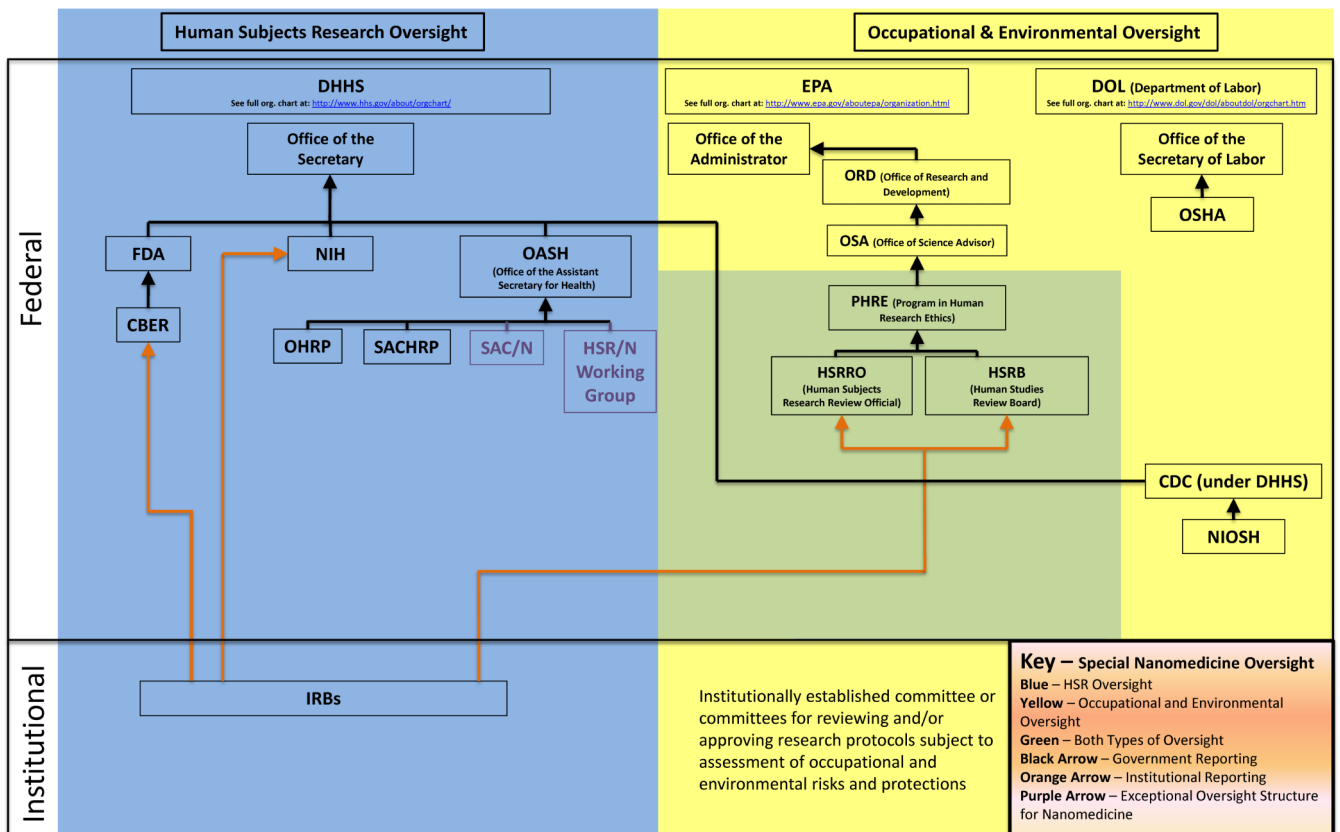


Figure 6. Recommended Baseline and Exceptional Oversight for Nanomedicine¹⁶⁷

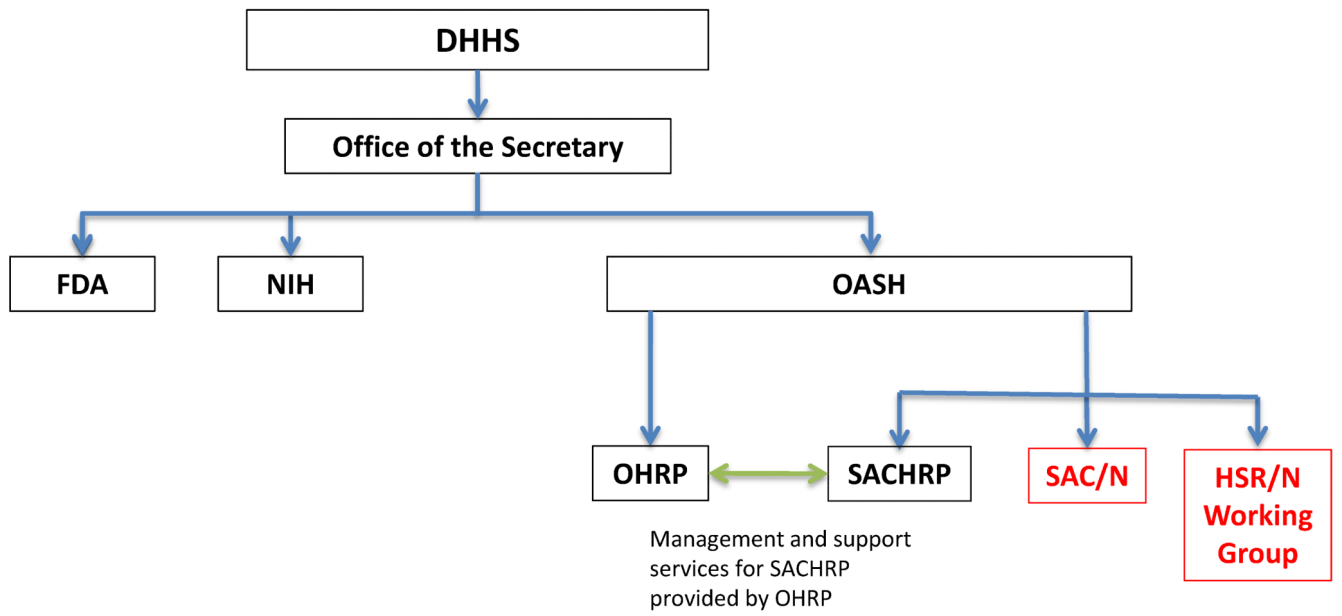


Figure 7. Organizational Chart for the HSR/N Working Group and SAC/N

Human Subjects Research in Nanomedicine (HSR/N) Working Group & Secretary's Advisory Committee on Nanomedicine (SAC/N)		
	Human Subjects Research in Nanomedicine Working Group	Secretary's Advisory Committee on Nanomedicine
Analytical Functions	<ul style="list-style-type: none"> Development of nanomedicine definition and/or characterization of key attributes for the purposes of data-gathering, issue-spotting, and oversight Identify and formulating plans for conducting analysis of nanomedicine research and coordinating among different agencies Identification and analysis of the characteristics and categories of existing and anticipated types of nanomedicine products for regulatory purposes Identification of potential areas of safety and ethical concerns for human subjects, as well as occupational, environmental, and bystander concerns in coordination with the NEHI Working Group Identification of other existing regulatory and oversight gaps in human subjects research in the nanomedicine arena 	<ul style="list-style-type: none"> Review the work of HSR/N, OHRP, and other offices pertaining to nanomedicine human subjects research oversight, including occupational, environmental, and bystander concerns that arise from research and products Provide forum where various stakeholders may offer input, including representatives from industry, community, and field research
Advisory Functions	<ul style="list-style-type: none"> Facilitating multi-agency collaboration on a Points-to-Consider document for oversight of nanomedicine human subjects research Providing advice to federal agencies as they develop their own regulations and oversight for nanomedicine human subjects research 	<ul style="list-style-type: none"> Consult with and provide advice and recommendations to Secretary, through the Assistant Secretary for Health, on matters pertaining to continuance and improvement of functions regarding nanomedicine human subjects research
Information Review Functions	<ul style="list-style-type: none"> Gathering and tracking of serious adverse events (SAEs) and safety monitoring data from FDA and NIH Providing a forum for and facilitate cross-agency sharing of knowledge and data of importance to nanomedicine human subjects research oversight 	<ul style="list-style-type: none"> Review ongoing work and planned activities of HSR/N, OHRP, and other offices/agencies responsible for nanomedicine human subjects research oversight Coordinate with NSET to track new finding that inform SAC/N's analytical and advisory functions
Protocol Reviewing Functions (if necessary)	<ul style="list-style-type: none"> Determine if protocol reviewing function is necessary Coordinating development of a nanomedicine protocol review process, if found necessary 	<ul style="list-style-type: none"> Provide forum for public discussion and input into the process of formation and how review occurs

Figure 8.
Functions of the HSR/N Working Group and SAC/N

Points-to-Consider Content	Recommendations
Procedural Guidance on Protocol Submission, Review & Reporting	
Review by FDA	<ul style="list-style-type: none"> FDA should review nanomedicine research protocols in accordance with its appropriate review pathway. FDA Centers (e.g., CDER, CBER) should identify safety

	issues (e.g., permanence, delayed effects) that may require additional consideration by IRBs, DSMBs (or similar), and bodies responsible for occupational and environmental review (including appropriately tasked IBCs).
Review by NIH	<ul style="list-style-type: none"> SRGs should identify any safety issues that require additional consideration by institutional review bodies.
Submission of data, monitoring, and adverse event reporting	<ul style="list-style-type: none"> FDA and NIH should flag potential need for IRBs to request additional preclinical data or more data safety monitoring, if uncertain risks exist or potential for long-term or delayed effects in humans. SAE reports and new findings of risk should include type and use of the nano-intervention and the nanomaterial characteristics that give rise to the risk.
Safety monitoring	<ul style="list-style-type: none"> Investigators, DSMBs, and other institutional data-monitoring bodies should conduct ongoing safety monitoring when a nanomedicine protocol is identified by FDA, NIH, or an IRB as presenting potential long-term risks to human subjects or significant uncertainty as to risk.
Substantive Guidance	
Describing the use of nano in the research protocol	<ul style="list-style-type: none"> Protocols should include an explanation of the purpose of using nanomaterials.
Appropriate considerations for research design and for anticipating risks and benefits	<ul style="list-style-type: none"> Protocols should describe how the research design minimizes risks to human subjects, and mechanisms for detecting harms and adverse events during the research.
Adequate preclinical and risk-assessment studies, including animal studies	<ul style="list-style-type: none"> Protocols should describe the preclinical research evidence, showing acceptability of research in humans and justification for the adequacy of preclinical studies. Protocols should identify the animal models used, the sample size of animals tested, the duration of animal studies, whether the studies were blinded or randomized, and whether the studies used different formulations, dosing, and administration routes than the protocol for human research.
Considerations for appropriate laboratory procedures in research	<ul style="list-style-type: none"> Protocols should describe laboratory procedures and demonstrate their adequacy for providing worker safety. OSHA and EPA should issue guidance for institutional bodies responsible for occupational and environmental review on appropriate nanomaterial contaminant and exposure levels that should be demonstrated by a protocol's containment and waste disposal practices, and guidance on the requirements for demonstrating adequate facilities and investigator and worker safety training.
Public health considerations	<ul style="list-style-type: none"> Protocols should describe and address mitigation of occupational, bystander, or environmental risks.
Selection of human subjects	<ul style="list-style-type: none"> Select subjects in accordance with regular practice and IRB requirements.
Occupational, bystander, and environmental considerations	<ul style="list-style-type: none"> Protocols should include information and data demonstrating minimized and reasonable risks to workers, bystanders, and

	<p>the environment.</p> <ul style="list-style-type: none"> • Protocols should include descriptions of clinical and laboratory practices for nanomaterial handling, containment, and disposal, including of biowaste. • Protocols identified by oversight bodies (i.e., FDA, SRGs, or IRBs) as presenting risks should be reviewed by appropriate institutional authorities tasked with addressing occupational, bystander, or environmental concerns, including consideration of adequacy of data supporting occupational, bystander, and environmental safety and adequacy of clinical and laboratory practices related to the handling, containment, and disposal of nanomaterials and biowaste containing nanomaterials. • Such review should take place concurrently with or before IRB review so as to contribute to IRB determination of whether to approve the research protocol. Review findings should be provided to DSMBs and other institutional monitoring bodies to inform safety and monitoring decisions. Where risks to bystanders exist, IRBs should ensure that protocols provide adequate procedures for informing those at risk and providing them with necessary information and training to minimize such risks.
Provisions for early termination of research	IRBs and DSMBs should ensure that nanomedicine protocols that present uncertain or serious risks to subjects provide clear triggers and procedures for halting research in the event of unanticipated adverse effects.
Informed Consent—Added elements, as necessary	
Risk of or opportunity for early termination	<ul style="list-style-type: none"> • Informed consent processes and documents should tell subjects under what circumstances their participation in the research may be terminated without consent, including a statement that the subject will be informed of any significant new findings in the course of the research that may affect his or her decision to continue participating.
Reproductive considerations	<ul style="list-style-type: none"> • Informed consent processes and documents should disclose potential reproductive risks (if any).
Long-term follow-up	<ul style="list-style-type: none"> • Informed consent processes and documents should inform research participants if they may be required to submit to follow-up and monitoring beyond the duration of the trial.
Notification of Previous Subjects Tested	<ul style="list-style-type: none"> • Informed consent processes and documents should inform participants how many individuals have been part of previous clinical trials with the same drug or intervention.

Figure 9. Outline of Proposed Points-to-Consider in the Design and Submission of Protocols for Research on Nanotherapeutics and *In Vivo* Nanodiagnostics in Human Participants