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SPECIAL FOCUS: GOVERNANCE OF NANOBIOTECHNOLOGY

Designing oversight for nanomedicine research in human subjects: systematic analysis of exceptional oversight for emerging technologies

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Abstract The basic procedures and rules for oversight of U.S. human subjects research have been in place since 1981. Certain types of human subjects research, however, have provoked creation of additional mechanisms and rules beyond the Department of Health & Human Services (DHHS) Common Rule and Food and Drug Administration (FDA) equivalent. Now another emerging domain of human subjects research—nanomedicine—is prompting calls for extra oversight. However, in 30 years of overseeing research on human beings, we have yet to specify what makes a domain of scientific research warrant extra oversight. This failure to systematically evaluate the need for extra measures, the type of extra measures appropriate for different challenges, and the usefulness of those measures hampers efforts to respond appropriately to emerging science such as nanomedicine. This article evaluates the history of extra oversight, extracting lessons for oversight of nanomedicine research in human beings. We argue that a confluence of factors supports the need for extra oversight, including heightened uncertainty regarding risks, fast-evolving science yielding complex and increasingly active materials, likelihood of research on vulnerable participants including cancer patients, and potential risks to others beyond the research participant. We suggest the essential elements of the extra oversight needed.

Keywords Nanomedicine · Human subjects research · Research oversight · Exceptional oversight · IRBs · Governance

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For over 30 years, the basic procedures and rules for oversight of U.S. human subjects research have been set. In 1981, the Department of Health, Education and Welfare (HEW) promulgated regulations governing human subjects research (codified at 45 C.F.R. part 46). In 1991, these became the basis for the Common Rule, covering 18 federal agencies and the research they sponsor. Comparable, though not identical, regulations from the Food and Drug Administration (FDA) (21 C.F.R. parts 50, 56) date from 1981 as well. While both the Common Rule and the FDA equivalent have seen additions and amendments over the years, the oversight system they set in place has been remarkably stable. Both rules require researchers seeking to conduct research on human participants to obtain advance approval from a local Institutional Review Board (IRB), usually based at the researcher's home institution. The IRB applies the standards

articulated in the regulations and maintains ongoing supervision for the duration of the research.

Certain types of human subjects research, however, have prompted creation of added mechanisms and rules for extra review. These exceptional categories of research include the following.

- Human *gene therapy* protocols (more properly known as "human gene transfer research") are reviewed not only by local IRBs, but also by the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) at its discretion, as well as by the Center for Biologics Evaluation & Research (CBER) at the FDA. Under the *NIH Guidelines*, Institutional Biosafety Committees (IBCs) also review the safety of proposed protocols (NIH 2009).
- Certain forms of *pediatric research* receive extra review by federal committees ("407 panels," named for the relevant subsection of the human subjects research regulations), because the research is not otherwise approvable under federal regulations but "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." (45 C.F.R. § 46.407). The local IRB asks the federal Office for Human Research Protections (OHRP) to convene the 407 panel to make recommendations.
- For research involving *emergency interventions* to which human subjects cannot effectively consent in advance of use, IRBs must apply special rules, report to OHRP that certain requirements have been met, comply with FDA rules on emergency research (when applicable), and create an independent data safety monitoring board (DSMB) to oversee the research (21 C.F.R. § 50.24; OPRR 1996). Research involving *fetal tissue transplantation* requires signed statements from the woman terminating the pregnancy, the physician conducting that procedure, and the researcher, all under a Congressional statute enacted to cover this type of research (42 U.S.C.S. § 289g-1).
- Research involving *intentional dosing with pesticides* is subject to special rules promulgated by the Environmental Protection Agency (EPA), requires central review at EPA, and use of "an independent Human Studies Review Board (HSRB) to obtain expert peer review of both proposals for new research and completed third-party intentional dosing" (EPA 2010).
- There are further types of research, such as *xenotransplantation* in human beings, that have prompted calls for procedural innovation including a central, federal IRB (Levine and Caplan 1986), but without success.
- Additional domains of research not yet applied to human beings have also prompted creation of exceptional oversight regimes. For the emerging field of *synthetic biology*, both the RAC and the National Science Advisory Board on Biosecurity (NSABB) at NIH have proposed amendments to the *NIH Guidelines*, including lab biosafety requirements and "criteria for determining when introduction of a drug resistance trait into a microorganism must be reviewed and approved by the NIH Director" (DHHS, NIH and OBA 2010).
- For research (including synthetic biology) raising *dual-use* concerns, NSABB has called for federal creation of extra oversight mechanisms, including some kind of monitoring capacity, and extension of research oversight into the private sector (DHHS and NSABB 2010).

Now another emerging domain of human subjects research—nanomedicine—is prompting calls for extra oversight (Lenk and Biller-Andorno 2007; Resnik and Tinkle 2007; Bawa and Johnson 2008; DeVille 2008; Fadeel and Garcia-Bennett 2009; Harris 2009; Hoet et al. 2009; Hansen 2010). (See Table 1 for a list of recent proposals.) Nanomedicine is a burgeoning field of research that strives to exploit unique properties of material that emerge at the nanoscale, variously defined as 1–100 nm (NNI 2010) up to 1–1000 nm (FDA 2010). Researchers are working to develop nanodiagnostics and nanotherapeutics, including non-viral nanovectors for gene therapy, nano drug-delivery mechanisms, and nanomaterials that differentially bind to cancerous micrometastases and facilitate imaging for early detection (Wagner et al. 2006; Virdi 2008). However, characteristics of nanoparticles and nanomaterials, including size and surface reactivity, have contributed to emergent physico-chemical properties that allow the particles and materials to interact with the body in new ways (Chan 2006; Hoet et al. 2009). Some of these novel properties are therapeutically advantageous, such as the ability to cross the

Table 1 Inventory of major proposed approaches to oversight of nanomedicine human subjects research, 2007–2010

Year	Author/proponent	Proposed approach	Core recommendations
2010	R. Bawa	New FDA center	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	B. Fadeel & A.E. Garcia-Bennett	Individual assessment of new nano-materials	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	S. Harris	Risk and characteristic-based regulation	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	P. Hoet et al.	Individual assessment of new nano-products	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	R. Bawa & S. Johnson	Expanded federal ethics guidance and oversight	Recommends heightened requirements for in vivo and ex vivo research before clinical research is approved.
			Should emphasize unpredictable risks for newer materials in risk/benefit analysis.
			Should make sure that subjects receive all details of studies, including information on risks, benefits, and confidentiality.
2008	K.A. DeVille	Central repository of nano-studies	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	N. Staggers et al.	Expanded federal ethical guidance	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	J. Virdi	Multi-criterion decision analysis	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	C. Lenk & N. Biller-Andorno	Elevated testing standards for nanomaterials and expanded view of risks	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.

Table 1 continued

Year	Author/proponent	Proposed approach	Core recommendations
2007	D.B. Resnik & S.S. Tinkle	Additional safety requirements for nano-studies	Data safety monitoring boards 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.

The publications listed above offer recommendations for oversight of nanomedicine human subjects research. The list is organized in reverse chronological order (most recent to least recent). The full citations for all publications appear in references

blood–brain barrier. However, these novel properties can also lead to risk through bioaccumulation (accumulation of particles in organs of the body), translocation (as when crossing the blood–brain barrier is not intended), infiltration and interaction with the immune system, bioreactivity, DNA toxicity, persistence, and agglomeration (formation of larger nano-structures) (Chan 2006; Faunce and Shats 2007; Staggers et al. 2008; Fadeel and Garcia-Bennett 2009; Hoet et al. 2009).

With nanomedicine clinical research already under way, the question of whether this research requires extra oversight is pressing (Resnik and Tinkle 2007). But a definitive answer is difficult to provide. Despite 30 years of overseeing research on human beings, there is no systematic understanding of what makes a domain of scientific research warrant oversight beyond what the Common Rule and FDA equivalent already demand. The failure to systematically evaluate the need for extra measures, the type of extra measures appropriate for different challenges, and the usefulness of those measures hampers efforts to respond appropriately to emerging domains of research such as nanomedicine. It is time to evaluate systematically three decades of experience, in order to derive guidance for appropriate oversight of new domains of scientific research in human beings such as nanomedicine.

This article proceeds comparatively, by considering prominent domains of human subjects research in which extra oversight has already been implemented, in order to suggest a systematic approach to extra oversight and then apply that to nanomedicine. We do not consider here those areas of non-human research with special rules—bench and animal research. Human subjects research oversight offers the realm most germane to the question of whether nanomedicine research on human participants warrants extra review. Elsewhere, we have considered oversight of nanobiotechnology broadly (see, e.g., Paradise et al. 2009; Ramachandran et al. 2010).

We also focus in this article on federal and local institutional oversight; we do not consider state, county, and municipal oversight. The Common Rule explicitly provides that its federal requirements do not preempt state and local ones (45 C.F.R. § 46.101). The FDA equivalent provides similar allowances for state and local innovation (21 C.F.R. § 50.25; 21 C.F.R. § 56.103). However, few states regulate human subjects research generally in biomedicine (New York, Virginia, and less comprehensively California, though some additional states have specific rules for certain types of human subjects research such as reproductive research) (see, e.g., http://www.onlineethics.org/cms/17226.aspx). Thus, we focus on the most widespread system of human subjects review, the system mandated by the Common Rule and FDA equivalent, combining federal and local institutional review.

What is "extra oversight" for human subjects research?

Analyzing the need for extra oversight and its appropriate contours requires first describing the history and shape of basic oversight. Only when basic oversight fails or is inadequate would the costs

and effort of extra oversight, including potential delay in scientific progress, be warranted.

Numerous histories recount the development of the HEW rules adopted in 1981 to govern human subjects research, their subsequent refinement (including by HEW's successor, DHHS), their adoption by 17 other agencies to create the Common Rule, and their interpretation by what is now OHRP, as well as other authorities. (See, e.g., Woodward 1999) The FDA rules governing human subjects research share a similar oversight design, though are governed by authorities at the FDA, not DHHS, primarily in the Centers overseeing drug, biologics, and device approval. The Common Rule covers research that is funded or conducted by the signatory agencies, as well as other research conducted at universities and other institutions that render a broader Federalwide Assurance (FWA) that they will follow the rules for federally supported research more generally (45 C.F.R. § 46.101; OHRP 2009). The FDA rules cover all research to develop products that are regulated by the FDA, including drugs, devices, and biologics (21 C.F.R. § 50.1). Between the two regimes, most but not all biomedical human subjects research conducted by U.S. entities is covered. Studies not captured by federal funding requirements usually fall under FDA jurisdiction for research involving new drugs, devices, or biologics in interstate commerce (Charrow 2007). Periodic proposals have surfaced to extend the basic human subjects research oversight regime to all research, public and private (see, e.g., Charrow 2007). Since these have not been enacted, some areas of research by U.S. entities remain uncovered (Charrow 2007). Yet the importance of NIH funding in biomedical research plus the need for FDA approval of drugs, devices, and biologics means that the Common Rule and FDA equivalent are the dominant federal oversight mechanisms for human subjects research. Together, these regimes create the framework for basic oversight of human subjects research.

The basic oversight approach created by these federal rules is a federally mandated and federally structured oversight process conducted by the institution whose researchers are leading the research. The core of this process is the requirement that researchers obtain local IRB approval before conducting research on human beings. Even after approval is given, research is subject to ongoing IRB oversight (21 C.F.R. § 56.109). The current IRB system was proposed in the mid 1970s in response to a number of controversial federally funded studies, such as the Tuskegee Syphilis Study (see, e.g., McWilliams et al. 2003). Receipt of federal grant funds to support the research is contingent upon IRB approval and oversight. Institutions must render a Federalwide Assurance (FWA) that they will subject all federally funded research that falls under the Common Rule to IRB review under the regulations. Institutions may voluntarily extend their FWA to all human subjects research they conduct, even if not federally supported (Edgar and Rothman 1995; Jastone 2006; DHHS and OHRP 2010), though there is evidence of a decrease in enthusiasm for optional FWA extensions (Cohen 2006), and as of January 2006 at least 174 universities had opted out of voluntarily extending their FWAs (Shweder 2006). IRB oversight and approval is a prerequisite for drug, device, and biologic approvals through the FDA (see, e.g., Edgar and Rothman 1995).

Basic oversight has garnered criticism as well as praise. Some commentators have criticized IRBs for inadequate expertise in certain areas of research, as well as in statistical or clinical practice (Morse et al. 2001). The independence of IRB members has also been questioned, as they review protocols proposed by colleagues in their own institution and share with the researchers an interest in institutional grant funding and advancement (Edgar and Rothman 1995). An empirical literature has documented inconsistent decision-making among local IRBs (see, e.g., McWilliams et al. 2003), and there are widespread concerns about inadequate resources (see, e.g., IOM 2002). IRBs have also been criticized for failing to fulfill their duty of continuing review after the study starts (Hoffman 2001). Concerns about the quality of human subjects research oversight led to landmark reports from the Institute of Medicine (IOM) in 2001–2002. (Other organizations such as the Association of American Medical Colleges (AAMC) have weighed in as well.) The IOM reports concluded that the IRB system was overtaxed and reforms were needed. The rise of complex multicenter trials means the challenges for IRBs are only increasing (IOM 2001, 2002; Morse et al. 2001). The reports laid the groundwork for a system of voluntary accreditation for human research participant programs and called for multiple improvements in the oversight system for human subjects research. More

recently, commentators have continued to urge reforms, including calling for IRBs to make their reviews available to other IRBs and urging better public communication of serious adverse events (SAEs) in trials, including on ClinicalTrials.gov. (See, e.g., Lo and Grady 2009) Innovations such as the use of IRBs external to the institution are increasingly being considered (see, e.g., National conference on alternative IRB models 2006).

In addition to IRBs operating under the Common Rule and FDA equivalent, some trials use DSMBs (variously called Data Safety Monitoring Boards, Data and Safety Monitoring Committees, and Data Monitoring Committees) (Glasser and Williams 2008). DSMBs have been used in a subset of trials, especially those using randomization and blinding, beginning in the 1960s. As Gordon et al. (1998, p. 2 (footnote omitted)) recount, "it has gradually become standard to use DSMBs in large-scale randomized clinical trials, multicenter clinical trials, and single center trials (especially in blinded studies)." DSMBs are so widely used now that they are appropriately considered part of basic rather than "extra" review. In the decade from 1990 to 2000, the reported use of DSMBs rose from 13 to 25% of trials (Sydes et al. 2004). DSMBs monitor studies and analyze the data produced as the trial progresses, as well as adverse events, to protect the safety of participants. This recognizes the difficulties in having the Investigator monitor a blinded study. The DSMB can scrutinize the risks and benefits falling on the control group, treatment group, and placebo controls. These boards perform risk–benefit analysis during a trial based on data collected to date, and may decide to take action to protect human subjects, including terminating the trial (Gordon et al. 1998; Morse et al. 2001; Goodman 2007). Both the Common Rule and FDA equivalent call for data monitoring, without explicitly requiring DSMBs (45 C.F.R. § 46.111; 21 C.F.R. § 50.24). Though in many studies, Investigators themselves may be able to perform the monitoring function, in randomized, blinded, and multi-center studies this poses challenges and a DSMB may be appropriate (Gordon et al. 1998). In addition, some Institutes within NIH call for DSMBs in certain studies (Gordon et al. 1998) and NIH requires DSMBs for all phase III trials, although they may be used in phase I and II trials that are blinded, multicenter, or high risk (McLemore 2006).

DSMBs, too, have garnered criticism. There is no uniform set of regulations or guidelines governing their operation (Gordon et al. 1998). Further, communication from DSMBs about safety concerns may run to the trial sponsor and through the sponsor, the Investigator; these concerns may reach the IRB only then and through the Investigator. Gordon et al. (1998, p. 4) complain that in this scenario, "the IRB is unable to examine the unfiltered findings of the DSMB." Uniform, direct methods of reporting to IRBs would assist IRBs in discharge of their duty of ongoing review and lighten the burden on IRBs to collect and analyze data (Morse et al. 2001). Drazen and Wood (2010, p. 478) have recently argued that "[t]he current way that DSMBs are constituted and report has resulted in a loss of faith." They point to cases in which the DSMB lacked independence from the trial sponsor. They urge that DSMBs "be chosen and convened under the aegis of an independent public body," such as a respected foundation (Drazen and Wood 2010, p. 478).

As noted above, IRBs and DSMBs are used broadly enough that they should be considered part of basic review, rather than exceptional review. Institutions have additional broad review mechanisms to address worker and laboratory safety. Worker safety is generally overseen at the federal level by the Occupational Safety and Health Administration (OSHA), NIH, and the Centers for Disease Control (CDC) (Ogren 2003). At the institutional level, universities have laboratory safety committees (LSCs) and other mechanisms to oversee laboratory operations and worker safety, including a safety officer (SO) (Hoeltge 2001; Grizzle et al. 2010; Occupational Safety and Health Administration (OSHA) 2010; 29 C.F.R. part 1910). LSCs and SOs coordinate safety training, track and report emergencies, and assess work hazards in an effort to comply with OSHA and OSHA-approved state plan requirements (Hoeltge 2001; Gile 2010; Occupational Safety & Health Administration (OSHA) 2010). For research involving radiation, radiation committees also play an important institutional role, where radiation SOs oversee compliance with government regulation regarding exposure, monitor operations, and ensure sufficient training (Klein et al. 2009). Lab safety, worker safety, and radiation safety oversight is not limited to human subjects research. However, these safety oversight mechanisms complement the

oversight structure dedicated to human subjects research.

Once we leave the realm of IRBs and DSMBs, as well as the broader safety committees and mechanisms just noted, we move beyond basic oversight to "extra" review. The IBC is a type of local review committee developed specifically for rDNA research. Since IBCs were developed specifically to provide additional review for rDNA research, they should be considered part of "extra," not basic, review. While IRBs apply the Common Rule and FDA equivalent and thus focus on the protection and safety of the human participant in research, some technologies, such as rDNA research, raise safety concerns outside of the human subjects population. IBCs focus on environmental and population hazards of rDNA research, as well as research conformity with the *NIH Guidelines* (NIH 2009). In the 1980s, at the same time when the RAC was formed, NIH began to formulate rules for IBCs (NIH 2009). As in the case of IRBs, IBCs must approve a protocol through a committee review process before a study can begin (Beach 1999). The *NIH Guidelines* require local institutions conducting rDNA research to create an IBC with at least five members, at least two being people who are not affiliated with the institution (Krimsky and Ozonoff 1979). IBCs thus incorporate community perspectives regarding health and the environment (Bereano 1984). The IBC review process concerns itself with matters including laboratory containment levels for biological and physical agents, institutional procedures and practices, and training and expertise of personnel for dealing with various agents (NIH 2009). While IBCs were created specifically to deal with DNA research, some institutions have expanded IBC responsibilities to other domains, such as potentially hazardous agents (OBA 2010). Expanding the jurisdiction of the IBC rests in the discretion of the institution (NIH 2009).

Like IRBs and DSMBs, IBCs have been criticized. In 2004, The Sunshine Project (2004) published a survey of 390 committees, arguing that many IBCs were failing to meet federal requirements of accountability to NIH and to the public (see also Race and Hammond 2008). Although IBCs are intended in part to provide more protection and transparency for local communities, IBCs may fall short of addressing all issues of values and consent (Kimmelman 2005). The Sunshine Project's report further argued that IBCs were not equipped to take on new responsibilities for overseeing biological weapons research. Among the problems with IBCs is the reality that IBCs are generally smaller and have less staff support than IRBs, even though IBCs are asked to consider a wide range of bystander and environmental effects (Bereano 1984).

IBCs show that additional entities may be created at the local institutional level to augment the basic review that IRBs and DSMBs provide. "Extra" review can take other forms, though, both at the institutional level and at the federal level. Additional entities can be created at the federal level, dedicated to review of a certain kind of research. These entities may be triggered by local IRB request (as in the case of "407 panels" for pediatric research), may be standing committees providing advice, or may more stringently be standing federal committees whose approval is required for the research to proceed.

In addition to creating or tasking new federal and local bodies for "extra" review, additional guidelines or rules can be created to be applied by an already-existing body when it reviews certain kinds of research. This kind of added, targeted guidance can be created at the local institutional level (as when a university's human subjects protection program issues special guidance for IRBs reviewing certain forms of research) or at the federal level (as when OHRP or the FDA, for example, issues targeted guidance for local or federal application).

"Extra" oversight thus can take a range of procedural and substantive forms. To begin to systematize the observed forms, we offer a taxonomy of five types of extra review: (1) *Locally Driven Innovation* that may take the form of added guidance or rules for local institutions, IRBs, and Investigators, and may be driven by local conditions or negotiated with the community from which research participants come (e.g., Community Based Participatory Research (CBPR) yielding agreed additional protections); (2) *Federal Guidance for Local Oversight* that involves creating additional federal guidance for local review bodies (e.g., supplemental rules for research on emergency interventions); (3) *Federal Referral Option* that allows local IRBs to refer research that cannot be approved locally to a federal committee (e.g., "407 panels" in pediatric research); (4) *Federal Guidance Body* that establishes a standing federal body to provide guidance to local IRBs (e.g., a

"central IRB," as was proposed to grapple with the complexity of xenotransplantation issues (Levine and Caplan 1986) and as is offered by NCI through its Centralized IRB Initiative (CIRB) for Cooperative Group trials); and (5) *Mandated Federal Review & Approval* that creates a standing federal body or system (involving more than one entity) whose approval is required in addition to local approval in order to conduct certain types of human subjects research (e.g., the requirement that human gene therapy protocols be considered by the RAC at NIH and by the FDA, and approved by the latter; or required EPA approval of protocols involving intentional dosing of human participants with pesticides, plus consideration by EPA's Human Studies Review Board).

Elaborating five models of extra oversight

All oversight of human subjects research in the United States that is subject to the Common Rule or FDA equivalent involves both local and federal activity; it is the federal Common Rule and FDA equivalent that require local IRBs and guide their actions. However, when considering models for extra oversight beyond the basic approach, the five models of extra oversight that we have identified constitute a spectrum. They run from most *local* control (Model 1) to most *federal* control (Model 5) (see Table 2). Here, we elaborate their characteristics as they array along that spectrum.

1. Locally driven innovation

The first model involves minimal federal oversight, allowing institutions and IRBs to develop their own protocols and rules based upon prior experiences and local expertise. For instance, federal regulation of genomics research has necessitated local innovation for a number of reasons including the range of research designs, a high percentage of epidemiological studies, issue complexity, and high rates of multicenter studies (McWilliams et al. 2003). In addition, large-scale genomic research increasingly involves archiving samples and data for future reanalyses, raising challenging consent and privacy problems. Issues confronting local IRBs reviewing genomics studies include concerns over privacy, informed consent, and intellectual property (Hook et al. 2004). Privacy concerns have been particularly daunting because of the potential for participants to be re-identified due to the uniqueness of their DNA. In addition, privacy may worry not only the individual participant, but also their biological kin, due to shared genetics (Hook et al. 2004). Thus, scrutiny of documents posted on university websites to guide human subjects research reveals not only general guidance documents, but also specific documents to guide genetic or genomic research (see Lawrenz and Sobotka 2008). This kind of local innovation provides added guidance to local investigators, IRBs, and other review bodies (if the institution elects to create alternative review bodies for research not subject to the Common Rule or FDA equivalent, as discussed above).

2. Federal guidance for local oversight

The next model maintains reliance on local oversight but provides supplemental federal guidance. An example is the extra oversight created for research on emergency interventions. This involves DHHS and FDA additions to the standard rules guiding IRBs, reliance on an independent DSMB, and community consultation (OPRR 1996). Since research on emergency interventions will often be conducted when the human participant is experiencing a life-threatening emergency such as a cardiorespiratory arrest, the participant will frequently not be able to consent. Surrogate decisionmakers may also be unavailable. Thus, the focus of the supplemental rules is to guide IRBs on when to allow waiver of the usual consent rules and when supplemental mechanisms, such as advance community consultation and DSMB oversight, are needed. Variation on the normal IRB approval process may be sought through OHRP, especially for multi-site studies (45 C.F.R. § 46.114). These provisions allow institutions to "enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort" (45 C.F.R. § 46.114).

3. Federal referral option

This model allows local IRBs to submit controversial research protocols to a government agency for special

Table 2 Overview of five models of extra oversight

Model	Core characteristics	Examples
(1) Locally Driven Innovation	No additional federal oversight or body created. At local level, human subjects research authority and institution may create additional rules and protocols.	Local human subject protection rules regarding informed consent in genomics research.
(2) Federal Guidance for Local Oversight	Federal body creates supplemental guidance for specific area of research. The rules created offer guidance to local institutions and may require use of special measures to protect human subjects.	Supplemental rules for research on emergency interventions.
(3) Federal Referral Option	Local IRB reviews study protocol and may refer study to federal agency or panel for review and approval. Federal panel is then convened following procedures that govern the review process. Upon federal approval of protocol, the study returns to local IRB for regular oversight. Another version allows use of a centralized IRB for review.	"407 panels" for pediatric research. NCI's Centralized IRB Initiative (CIRB) option.
(4) Standing Federal Guidance Body	Standing federal body or institution is created to provide guidance for a specific area of research or type of study.	Proposed federal IRB or national xenotransplantation advisory committee.
(5) Mandated Federal Review & Approval	Rules require all research in area to go to special federal committee or body for review. Some review may be advisory; other review may be to seek needed approval of study. Upon reviewing the protocol, the committee may choose to approve, modify, or disapprove the study. Body also provides central database to track studies and expertise in study area.	The RAC and FDA for human gene therapy protocols. EPA's Human Studies Review Board (HSRB) for pesticide research.

review and approval. An example is "407 panels," which are used to consider certain pediatric research protocols (45 C.F.R. § 46.407). When IRBs receive research proposals that involve children and appear to fall under § 46.407, they may request that OHRP convene a 407 panel. The IRB request for 407 panel review means that the IRB has found that the research is not otherwise approvable, but presents a "reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children" (45 C.F.R. § 46.407). OHRP then determines whether a 407 panel is appropriate and whether the particular research is subject to FDA regulations. If so, the FDA will convene its Pediatric Ethics Subcommittee to review the proposal with OHRP assistance (OHRP 2005). Federal 407 panels are useful for considering the challenging ethical question of whether to allow research that otherwise is not approvable under federal rules, and to allow it because of the knowledge to be gained about a significant pediatric health problem. Beyond 407 panels, the National Cancer Institute (NCI) at NIH now offers the option of using a central IRB through its Centralized IRB Initiative (CIRB) for adult and pediatric Cooperative Group clinical trials; local IRBs may decide to rely on this central review as a substitute for local review. (http://www.ncicirb.org/)

4. Standing federal guidance body

A more intensive form of federal involvement would be to create a standing federal body to advise on a category of research protocols. Xenotransplantation

research provoked a call for just such a body in the mid-1980s. In 1984, an infant born with hypoplastic left heart syndrome received a baboon heart transplant, then died 21 days later, sparking significant controversy. Critics argued that too much power was given to local review committees to review risky research proposals raising complex ethical questions and that a body to offer federal guidance was needed. One proposal suggested creating a federal IRB or a national xenotransplantation advisory committee, a body that would review proposed research involving xenotransplantation, given the higher potential public health risks, animal welfare concerns, and risks to human subject (Levine and Caplan 1986; FDA 2001). This model would be most effective when the research involves a complex topic that raises important safety or ethical issues that may outstrip the expertise and capacity of local IRBs or may lead to unacceptably divergent decisions from one local IRB to the next. A variation on this proposal in the field of genomics and cancer research would creates a national IRB to oversee multicenter studies, studies that cross institutions and states, thereby complicating local review (Christian et al. 2002; McWilliams et al. 2003). While the FDA and OHRP already recognize the value of designating a central IRB when multiple centers collaborate on a trial (FDA 2006; OHRP 2010), this proposal would go further to create a standing federal IRB available to perform this function. Central bodies offer the benefit of standardization of the evaluation process and may expedite the development of guidance for researchers.

5. Mandated federal review & approval

Certain areas of research have proven so controversial that federal review has become mandatory. Human gene therapy is one of these areas. The review structure for gene therapy grows out of the structure created to review recombinant DNA (rDNA) research. Review of gene therapy protocols straddles NIH, where the RAC at the Office of Biotechnology Activities (OBA) considers protocols, and the FDA, where review is centered at CBER. RAC review and its relationship to FDA review have evolved over time. Early in development of human gene therapy, researchers needed RAC and FDA approval, as well as local IRB and IBC approval. In the mid-1990s, the then-Director of NIH altered the role of the RAC so that it became an advisory body rather than a body whose approval was a mandatory precondition for research. RAC now acts as an important issue-spotting body, whose meeting minutes and conclusions are public. The FDA continues its required review of gene therapy protocols, but protects the privacy of proprietary information (an FDA/RAC difference that has caused problems for tracking adverse events) (King 2002). The federal review provided by the RAC and FDA have also led to creation of a federal database to track gene therapy protocols. Though RAC and FDA review of gene therapy protocols has prompted an extensive literature with critique as well as praise, this general model of federal review responds to complex science raising challenging ethical issues and public concerns (see, e.g., King 2002). Technologies that raise significant ethical questions, prompt substantial public concern, are sufficiently complex scientifically that standing federal expertise is warranted, and would benefit from creation of a central database to track research experience may be well-served by this model of federal oversight. Yet another example of such a review body is EPA's Human Studies Review Board (HSRB), for research involving intentional dosing of human subjects with pesticides (EPA 2010).

When is extra oversight warranted?

The domains of human subjects research that have garnered extra oversight have posed a range of challenges. Some of these areas of research have represented *new science and technology whose risks were deemed uncertain but substantial*, including human gene therapy and xenotransplantation. Other areas have been characterized not by new science and technology, but by fundamental *new challenges to the current oversight rules*; examples are research on emergency interventions for which conventional consent could not be obtained, and pediatric research posing greater than minimal risk and not otherwise approvable but promising new insights into the relevant disease or condition. A third area has been *highly controversial research*; this includes fetal tissue transplantation, intentional dosing with pesticides, and dual-use research. Some domains of human subjects research garnering extra review have

manifested more than one of these three signal characteristics.

Levine et al. (2004) have offered their own roster of criteria for determining when research protocols require "special scrutiny." Yet their project appears to be aimed at identifying what studies need intensive review (such as first-in-human studies), even if no additional review bodies or rules are created. We are focusing instead on the precise question of when extra review bodies and/or extra review rules are needed. Careful application of the basic rules by the basic review bodies is what the basic review process is already meant to accomplish. Some protocols may well merit "special" care in use of that basic review process. But we are asking a different question: what sorts of research warrants more, the innovation of creating or using additional review bodies and/or creating or using new rules. This is the "extra" review we address.

Where does human subjects research in nanomedicine fit in our 3-way classification of studies needing "extra" review? Nanomedicine research fits easily into the first category. The science and technology involved in producing many nanomaterials is fundamentally new and there is substantial uncertainty about the characteristics and risks of many of the materials. Certain nanomaterials, specifically carbon nanotubes, have proven toxic on inhalation by nonhuman animals (Lenk and Biller-Andorno 2007; Staggers et al. 2008). Uncertainty surrounds the characterization of various nanomaterials, their action over various timeframes, bioaccumulation, and toxicity (Chan 2006). We are on a steep learning curve, trying to understand risks posed by these novel materials. Indeed, some of these materials and nanofabrications (such as nano-gold used to locate, image, and differentially destroy micrometastases) are highly complex, with multiple functions and the capacity to react differently depending on context (Fadeel and Garcia-Bennett 2009). The evaluation of proposed research involving nanomaterials can require expertise that research oversight authorities such as local institutional IRBs may lack.

Much nanomedicine research in human beings also raises significant challenges to current oversight rules. While the Common Rule and FDA equivalent overwhelmingly focus on risks to human participants themselves, nanomedicine research protocols may raise concerns that go beyond the human participant to close contacts, lab workers, the community, and the environment. Indeed, OSHA, NIOSH, and the EPA are already closely scrutinizing many of these risks (DHHS 2009; EPA 2009). Yet, the current system and rules for human subjects research provide no organized way to address these broader concerns and integrate them into the ethical considerations focused on human participants themselves. This is a major challenge.

Even the third category of research that has garnered extra review arguably applies to nanomedicine research. The public is still learning about nanotechnology, and there are signs of support for the positive potential of this technology (see, e.g., Bainbridge 2002). However, even among stakeholders educated on nano, there are widely divergent opinions on the best way to approach regulation (Hansen 2010). Davies (2009) concludes (on p. 8, citing a range of sources) that "existing oversight systems in the United States have been found to be largely inadequate to deal with current nanotechnology." This level of concern and controversy warrants in-depth analysis in a way that is open to public input and review.

Thus, much nanomedicine research involving human participants seems ripe for extra oversight, especially on grounds of scientific complexity, uncertainty, risk potential extending beyond the human participant, and public concern. There will be some nanomedicine research that does not raise these issues, as the nanoscale materials or processes are actually well-established and well-understood, and do not raise issues of heightened uncertainty and risk. Yet, it is not uncommon for "extra" review mechanisms (such as the RAC for gene therapy) to have responsibility for sorting those protocols that raise no new issues from those that do.

The range of issues raised by nanomedicine research, including concerns about worker and bystander safety and environmental effects, actually shows just how narrow human subjects research oversight has been, in failing to provide any mechanism to integrate concerns over worker safety, close contacts, community risks, and environmental effects. Thus, the design of extra oversight for nanomedicine research may allow creation of a more comprehensive model of research oversight, with potential applicability to other domains of science and technology that also raise these broader concerns.

Existing proposals for oversight in nanomedicine

With the rise of nanotechnology in medical research, some ethicists and scientists have begun to consider whether human subjects research in nanomedicine should be subject to additional oversight. Table 1 provides a summary of recent proposals. (Note that a broader literature exists discussing general oversight of nanotechnology; our discussion and Table 1 are restricted to proposals that focus on human subjects protections in nanomedicine research.) While they propose a range of innovations, none of these proposals systematically considers what basic review already accomplishes and what kind of need exists for extra review. Nor do they systematically consider what the relationship should be between local institutional review and federal review. These are the gaps we seek to fill.

One set of proposals adds substantive guidance to the existing system. The types of guidance proposed include heightened preclinical testing requirements (Lenk and Biller-Andorno 2007; Bawa and Johnson 2008; Fadeel and Garcia-Bennett 2009), long-term study follow-up (Lenk and Biller-Andorno 2007; Resnik and Tinkle 2007), increased and ongoing informed consent communications (Resnik and Tinkle 2007; Bawa and Johnson 2008), heightened risk assessment (Lenk and Biller-Andorno 2007; Bawa and Johnson 2008), case-by-case hazard identification (Hoet et al. 2009), increased focus on adverse events and possible catastrophic events (Lenk and Biller-Andorno 2007; Resnik and Tinkle 2007; Fadeel and Garcia-Bennett 2009), and use of multi-criterion decision analysis to evaluate risks and alternatives to the intervention (Virdi 2008). To address the FDA's difficulty in sorting nanoproducts by PMA, one proposal creates a new regulatory FDA classification system so that nano-products are sorted based on risk and special nano-characteristics (Harris 2009). Staggers et al. (2008) suggest formatting new guidance as had been done for other emergent technologies such as genetics. This set of proposals does not necessarily change how nanomedicine protocols progress through the review system, but offers guidance to existing institutions and agencies who are considering these studies. One analysis favors using existing approaches "to the maximum, revisiting them, and, when appropriate only, amending them" (Hansen 2010).

Only one proposal on our table explicitly addresses the roster of local institutional bodies that should perform oversight. Resnik and Tinkle (2007) suggest requiring the use of DSMBs for certain riskier studies. The principal purpose of using DSMBs would be to facilitate continuous risk assessment, and to assure that IRBs are kept apprised of adverse events occurring during studies (Resnik and Tinkle 2007).

Another set of proposals would create new federal agencies and institutions. DeVille (2008) would create a central repository of nanomedicine research studies. The repository would gather information on particular particles and monitor for adverse effects and events (DeVille 2008). Such a repository could be a useful resource for local IRBs, FDA Centers, and other bodies reviewing nano-protocols. However, the repository itself is not depicted as offering official guidance to government agencies and local IRBs. Bawa (2010) argues for the creation of a new nano-center to handle all nanomedicine applications at the FDA.

A number of the current proposals thus offer additional substantive guidance, while others would change the roster of oversight bodies performing review. We argue that successful protection of human subjects must incorporate both components. Entities should evaluate nano-trials in a manner recognizing emergent properties posing new and uncertain risks that fundamentally challenge current oversight approaches and ethical analyses, in ways already proving controversial. This will require innovation in oversight procedure and in the substantive guidance that oversight bodies apply.

Overseeing human subjects research in nanomedicine—using models 4 & 5

The emergent properties of nanomaterials challenge researchers' ability to predict and assess the risks posed to human subjects. This poses major ethical problems. Informing study participants of risks and eliciting informed consent to trial participation is problematic without a solid prediction of risks. Even deciding when preclinical and animal data warrant first-in-human trials can be fraught with difficulty. On top of these issues, some nanomaterials and trials may raise issues of worker safety, bystander and

community effects, and environmental risks. Evaluating both human subjects considerations and these broader concerns is complex and an oversight process for which there is little guidance.

Leaving these deeply challenging issues to local IRBs and review committees raises profound concerns. Local committees are unlikely to have the expertise to handle these complex issues. Indeed, to foist these issues on institution after institution seems markedly inefficient. It also courts inconsistent determinations. Far better would be to create a standing federal body positioned to summon the necessary expertise, collect information, monitor and systematize trials experience in a database, and devise guidance over time. This is a Model 4 approach, a standing federal body offering advice on the full range of perplexing issues, ethical, scientific, and societal.

One of the challenging issues facing such a federal body will be formulating guidance on what kind of trials really need full federal reviews of those issues, and which types do not. Not all nanomedicine products have novel properties with uncertain harms. The universe of nanomedicine is broad, and includes drugs, devices, biologics, vaccines, gene therapy vectors, and combination products. Some nanomaterials used in these interventions do not raise novel issues that differ from those raised by the material's non-nano form. Other products show emergent properties that may pose new risks. This suggests that some studies will not need additional oversight and subjecting them to such would prove a taxing and costly process. To provide additional oversight without unduly burdening research, an oversight body must sort studies that do and do not need extra review.

This makes Model 4 most appropriate for nanomedicine human subjects research oversight at this juncture. Both models 4 and 5 create a federal body to review protocols and provide guidance to researchers and their institutions. The difference between the two models is that oversight using Model 4 provides a standing central source of advice, whereas Model 5 oversight mandates federal review and approval. We suggest an incremental approach that would begin by creating a standing federal source of analysis and oversight (Model 4). This responds to the reality that researchers and regulators have yet to specify what categories of nanomedicine research warrant extra review at the federal level. A Model 4 federal body could establish a database collecting information on nanomedicine trials and make progress toward identifying those categories of nanomedicine research that require full federal review and approval in a Model 5 fashion. The Model 4 federal oversight entity could also make progress toward formulating extra substantive guidance needed to evaluate those nanomedicine trials warranting full federal review for human subjects concerns.

Some might argue that FDA review of nanomedicine trials already provides thorough review of the human subjects research concerns. However, the FDA's analysis has long focused on evaluation of safety and efficacy. The FDA certainly builds local IRB review into its oversight system (via the FDA regulations on human subjects research), but that does not assure the kind of searching ethics analysis we are urging of the cutting-edge issues posed by nanomedicine research trials. Indeed, commentators analyzing oversight of gene therapy trials have lauded the combination of RAC ethics analysis at NIH with FDA's analysis centered on safety and efficacy, as the FDA does not specialize in the kind of in-depth ethics analysis of novel issues and public illumination of the issues that the RAC offers (see, e.g., King 2002). Further, the ethics issues posed by nanomedicine research go beyond issues centered on the human subject to those affecting lab workers, close contacts, community members, and the environment. The FDA is not set up to analyze this full scope of issues, much less tackle the daunting task of integrating that ethics analysis with the analysis focusing on the human participant. As former-FDA Commissioner David Kessler and colleagues have noted in discussing the complementary functions of the RAC and the FDA, the RAC "ensures broad public discussion…particularly with regard to social and ethical concerns," while "[t]he FDA focuses on the development of safe and effective biologic products, from their first use in humans through their commercial distribution." (Kessler et al. 1993, pp. 1171–1172)

All of this supports the need for extra review at the federal level. Some might immediately urge mandatory review of protocols by a Model 5 body. We take a more cautious approach in urging a Model 4 approach at this early point, given lack of clarity about exactly what types of protocols and

interventions merit mandatory Model 5 review. Model 4 federal guidance body might well conclude that even while overarching guidance is being formulated, an entity is needed to perform required Model 5 review of the human subjects research concerns raised by a subset of nanomedicine trials. It is Model 5 in particular that has been used in the case of human gene therapy, another complex science and technology initially characterized by high uncertainty and risk. Indeed, the RAC and the FDA, using this extra oversight model, have already begun considering gene therapy protocols using non-viral nanovectors.

Meanwhile, a Model 4 body that sorts nanomedicine studies and suggests which types need the mandatory review of Model 5 is clearly needed. Discerning the patterns in nano-protocols and what types need extra review is a challenge. Characterizing nanomaterials and creating well-justified categories that can be used for oversight purposes is a work in process, far from accomplished. And that is just part of the analytic task that would face the Model 4 body. This body would need to go beyond seeking patterns in the materials and interventions being studied, to discern relevant patterns in the ethical issues posed in the context of human subjects research.

Where novel materials with emergent properties posing heightened risks and ethical challenges are identified, the Model 4 body could recommend a number of heightened requirements. Stringent examination of first-in-human trials, with careful examination of preclinical and animal data and their predictive power for human responses will likely be warranted. Active ongoing review of such trials may be warranted as well. Detailed consideration of risk assessment and characterization, and comparison to benefits if any, will likely be highly demanding. Appropriate selection of the participant population will require application of the prediction of risks and benefits in comparison populations, as well as consideration of what can be learned of significance in different subject populations. Consent issues will loom large, as research participant understanding of nanomaterials, their action, and risks may prove challenging, especially for complex and active materials that may behave in different ways depending on physiochemical environment.

In addition, a Model 4 federal oversight body can integrate human subjects concerns with issues of worker safety, exposure of close contacts, community effects, and environmental effects. This is an enormously challenging task with inadequate precedent (though the RAC at OBA has considered both human subjects concerns and broader issues raised by rDNA research, including potential effects on others, and EPA consideration of human subjects research may range beyond consideration of effects on the participant him- or herself). While NIOSH has begun to address nanomaterials in the workplace, little specific guidance exists pertaining to worker exposures in a human subjects laboratory setting. It is also unclear whether existing means of controlling biohazardous materials are sufficient for nanoparticles, which can penetrate where larger particles cannot. Analysis of environmental effects is also germane, as laboratory practices and waste as well as human subject excretion of nanomaterials can raise environmental concerns.

Oversight should evolve with greater knowledge of nanomaterials and nanomedicine interventions. Model 4 oversight should lead to triage, segregating those types of interventions and protocols suitable for continuing Model 4 guidance from those requiring mandatory Model 5 approval at the federal level. Over time, Model 4 review may also yield an understanding of what interventions and protocols need no extra review and are adequately handled through basic review. Oversight of human subjects research in nanomedicine should respond to greater understanding of nanomaterial properties and risks, with heightened review when needed and basic review when appropriate.

Conclusion: systematizing analysis of extra oversight

Nanomedicine research forces consideration of what extra oversight for human subjects research is needed. This article looks back over the three decades of modern human subjects research oversight to glean patterns in the design and application of extra oversight. We suggest three triggers for extra oversight—new science and technology posing uncertain but significant risks, human subjects research challenging the current oversight system by raising problems not well addressed by the prevailing rules, and highly controversial research raising issues of

trust and confidence. We argue that nanomedicine research qualifies for extra oversight under the first two categories and arguably the third as well.

We further argue that the design of extra oversight for nanomedicine research can benefit from comparison to the design of extra oversight in the past. We identify five models that have been used, ranging from those that preserve high levels of local control to those that introduce more federal control. By comparison to technologies raising similar issues, we argue for use of a model at the federal control end of the spectrum, at least at this early point in characterizing nanomaterials, analyzing their risks, and integrating into the ethics analysis of proposed protocols concerns that go beyond the human participant to workers, close contacts, community, and the environment.

Finally, we argue that extra oversight for nanomedicine is a moving target. Design of extra oversight should respond to changes in understanding of the science and risks, as well as evolution of public understanding. Over time, oversight authorities can focus their extra efforts on areas of human subjects research that remain particularly problematic as well as research proposals raising novel issues.

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References

Bainbridge WS (2002) Public attitudes toward nanotechnology. J Nanopart Res 4:561–570

Bawa R (2010) Regulating nanomedicine—Can the FDA handle it? Raj Bawa Biotechnology Consulting LLC. www.medical.wesrch.com/User_images/Pdf/XXF_12786 27200.pdf. Accessed 2 Oct 2010

Bawa R, Johnson S (2008) Emerging issues in nanomedicine and ethics. In: Allhoff F, Lin P (eds) Nanotechnology & society: current and emerging ethical issues. Springer, Dordrecht, pp 207–223

Beach JE (1999) Restructuring of the RAC. Food Drug Law J 54:49–53

Bereano PL (1984) Institutional biosafety committees and the inadequacies of risk regulation. Sci Tech Hum Values 9:16–34

Chan VS (2006) Nanomedicine: an unresolved regulatory issue. Regul Toxicol Pharm 46:218–224

Charrow R (2007) Symposium: censorship and institutional review board: protection of human subjects: is expansive regulation counter-productive? Northwest Univ Law Rev 101:707–721

Christian MC, Goldberg J, Killen J, Abrams J, McCabe M, Mauer J, Wittes R (2002) A central institutional review board for multi-institutional trials. N Engl J Med 346: 1405–1408

Code of Federal Regulations (1974) 29 C.F.R. part 1910

Code of Federal Regulations (1981) 21 C.F.R. parts 50, 56

Code of Federal Regulations (1991) 45 C.F.R. part 46

Cohen J (2006) Checking the box. HRPP Blog. hrpp.blogspot.com/2006/02/checking-box.html. Accessed 27 Dec 2010

Davies JC (2009) Oversight of next generation nanotechnology. www.nanotechproject.org/process/assets/files/7316/pen-18.pdf. Accessed 9 Dec 2010

Department of Health and Human Services (DHHS) (2009) Approaches to safe nanotechnology: managing the health and safety concerns associated with engineered nanomaterials. DHHS (NIOSH) Pub. No. 2009-125. www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf. Accessed 3 Apr 2010

Department of Health and Human Services (DHHS), National Institutes of Health (NIH), Office of Biotechnology Activities (OBA) (2010) Recombinant DNA research: proposed actions under the NIH guidelines for research involving recombinant DNA molecules (NIH Guidelines). Federal Register 75:21,008-21,010

Department of Health and Human Services (DHHS), National Science Advisory Board for Biosecurity (NSABB) (2010) Addressing biosecurity concerns related to synthetic biology, draft report. oba.od.nih.gov/biosecurity/pdf/NSABB%20SynBio%20DRAFT%20Report-FINAL%20(2)_5-21-10.pdf. Accessed 30 Aug 2010

Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP) (2010) What research does the Federalwide Assurance (FWA) cover? www.answers.hhs.gov/ohrp/questions/7143. Accessed 4 Jan 2011

DeVille KA (2008) Regulation and medical use of nanotechnology. In: Jotterand F (ed) Emerging conceptual ethical and policy issues in bionanotechnology. Springer, Dordrecht, pp 181–200

Drazen JM, Wood AJ (2010) Don't mess with the DSMB. N Engl J Med 363:477–478

Edgar H, Rothman DJ (1995) The Institutional Review Board and beyond: future challenges to the ethics of human experimentation. Milbank Q 73:489–506

Environmental Protection Agency (EPA) (2009) Nanomaterial research strategy. Office of Research and Development.

www.epa.gov/nanoscience/files/nanotechresearch_strategy_final.pdf. Accessed 20 Jan 2010
Environmental Protection Agency (EPA) (2010) Expanded protections for subjects in human studies research. www.epa.gov/oppfead1/guidance/human-test.htm. Accessed 28 Aug 2010
Fadeel B, Garcia-Bennett AE (2009) Better safe than sorry: understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical application. Adv Drug Deliv Rev 62:362–374
Faunce T, Shats K (2007) Researching safety and cost-effectiveness in the life cycle of nanomedicine. J Law Med 15:128–135
Food and Drug Administration (FDA) (2001) PHS guideline on infectious disease issues in xenotranplantation. OMB Control No. 0910-0456. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/UCM092858.pdf. Accessed 8 Sep 2010
Food and Drug Administration (FDA) (2006) Using a centralized IRB review process in multicenter clinical trials. www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm. Accessed 1 Dec 2010
Food and Drug Administration (FDA) (2010) Reporting format for nanotechnology-related information in CMC review. Center for Drug Evaluation and Research: Mapp 5015.9. www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf. Accessed 29 Aug 2010
Gile TJ (2010) Complete guide to laboratory safety, 3rd edn. HCPro, Marblehead
Glasser SP, Williams OD (2008) Data Safety and Monitoring Boards (DSMBs). In: Glasser SP (ed) Essentials of clinical research. Springer, Berlin, pp 151–158
Goodman SN (2007) Stopping at nothing? Some dilemmas of data monitoring in clinical trials. Ann Intern Med 146(12):882–887
Gordon VM, Sugarman J, Kass N (1998) Toward a more comprehensive approach to protecting human subjects: the interface of Data Safety Monitoring Boards and Institutional Review Boards in randomized clinical trials. IRB 20(1):1–5
Grizzle WE, Bell WC, Fredenburgh J (2010) General considerations concerning safety in biomedical research laboratories. In: Patrinos G, Ansorge W (eds) Molecular diagnostics, 2nd edn. Elsevier, London, pp 563–572
Hansen SF (2010) Multicriteria mapping of stakeholder preference in regulating nanotechnology. J Nanopart Res 12:1959–1970
Harris S (2009) The regulation of nanomedicine: will the existing regulatory scheme of the FDA suffice? Richmond J Law Technol 17(2):1–25
Hoeltge GA (2001) Laboratory safety. In: McClatchey KD (ed) Clinical laboratory medicine, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, pp 78–96
Hoet P, Legiest B, Geys J, Nemery B (2009) Do nanomedicines require novel safety assessments to ensure their safety for long-term human use? Drug Saf 32(8):625–636
Hoffman S (2001) Continued concern: human subject protection, the Institutional Review Board, and continuing review. Tenn Law Rev 68:725–770
Hook CC, DiMagno EP, Tefferi A (2004) Primer on medical genomics Part XIII: ethical and regulatory issues. Mayo Clin Proc 79:645–650
Institute of Medicine (IOM) (2001) Preserving public trust: accreditation and human research participant protection programs. www.nap.edu/catalog.php?record_id=10085. Accessed 7 Dec 2010
Institute of Medicine (IOM) (2002) Responsible research: a systems approach to protecting research participants. www.nap.edu/catalog.php?record_id=10508. Accessed 7 Dec 2010
Jastone LO (2006) Federal protection for human subjects research. Novinka, New York
Kessler D, Siegel J, Noguchi P, Zoon K, Feiden K, Woodcock J (1993) Regulation of somatic-cell therapy and gene therapy by the Food and Drug Administration. New Eng J Med 329:1169–1173
Kimmelman J (2005) Medical research, risk, and bystanders. IRB 27(4):1–6
King NMP (2002) RAC oversight of gene transfer research: a model worth extending? J Law Med Ethics 30:381–389
Klein LW, Miller DL, Balter S, Laskey W, Haines D, Norbash A, Mauro MA, Goldstein J (2009) Occupational health hazards in intervention laboratory: time for a safer environment. J Vasc Interv Radiol 20(7S):S278–S283
Krimsky S, Ozonoff D (1979) Recombinant DNA research: the scope and limits of regulation. Am J Pub Health 69(12):1252–1259
Lawrenz F, Sobotka S (2008) Empirical analysis of current approaches to incidental findings. J Law Med Ethics 36(2):249–255
Lenk C, Biller-Andorno N (2007) Nanomedicine: emerging or re-emerging ethical issues? A discussion of four ethical themes. Med Health Care Philos 10:173–184
Levine C, Caplan AL (1986) Beyond localism: a proposal for a national research review board. IRB 8(2):7–9
Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, Sugarman J (2004) "Special scrutiny": a targeted form of research protocol review. Ann Int Med 140:220–223
Lo B, Grady D (2009) Strengthening Institutional Review Board review of highly innovative interventions in clinical trials. JAMA 302(24):2697–2698
McLemore MR (2006) The role of the data safety monitoring board: why was the Avastin Phase III clinical trial stopped? Clin J Oncol Nurs 10(2):153–154
McWilliams R, Hoover-Fong J, Hamosh A, Beck S, Beaty T, Cutting G (2003) Problematic variation in local institutional review of multicenter genetic epidemiology study. JAMA 290(3):360–366
Morse MA, Califf RM, Sugarman J (2001) Monitoring and ensuring safety during clinical research. JAMA 285(9):1201–1205
National conference on alternative IRB models: optimizing human subject protection (2006). www.aamc.org/download/75240/data/irbconf06rpt.pdf. Accessed 4 Jan 2011
National Institutes of Health (NIH) (2009) NIH guidelines for research involving recombinant DNA molecules (NIH Guidelines). oba.od.nih.gov/oba/rac/guidelines_02/NIH_Gdlnes_lnk_2002z.pdf. Accessed 29 Aug 2010

National Nanotechnology Initiative (NNI) (2010) FAQs: nanotechnology. www.nano.gov/html/facts/faqs.html. Accessed 28 Aug 2010

Occupational Safety & Health Administration (OSHA) (2010) Laboratories. www.osha.gov/SLTC/laboratories/index.html. Accessed 4 Jan 2011

Office for Human Research Protections (OHRP) (2005) Special protections for children as research subjects. www.hhs.gov/ohrp/children/guidance_407process.html. Accessed 7 Sep 2010

Office for Human Research Protections (OHRP) (2009) Assurances. www.hhs.gov/ohrp/assurances/assurances_index.html. Accessed 10 Oct 2010

Office for Human Research Protections (OHRP) (2010) Use of a centralized Institutional Review Board (IRB) (2010). www.hhs.gov/ohrp/policy/correspond/CIRB20100430.html. Accessed 1 Dec 2010

Office of Biotechnology Activities (OBA) (2010) Institutional Biosafety Committees. www.oba.od.nih.gov/rdna_ibc/ibc.html. Accessed 8 Dec 2010

Office of Protection from Research Risks (OPRR) (1996) OPRR reports. www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm. Accessed 30 Nov 2010

Ogren MP (2003) An accident waiting to happen? Scientist 17(2):30

Paradise J, Wolf SM, Kuzma J, Ramachandran G, Kokkoli E (2009) Symposium introduction: the challenge of developing oversight approaches to nanobiotechnology. J Law Med Ethics 37(4):543–545

Race MS, Hammond E (2008) An evaluation of the role and effectiveness of Institutional Biosafety Committees in providing oversight and security at biocontainment laboratories. Biosec Bioterror Biodef Strat Pract Sci 6(1):19–35

Ramachandran G et al (2010) Recommendations for oversight of nanobiotechnology: dynamic oversight for complex and convergent technology. J Nanopart Res. doi:10.1007/s11051-011-0233-2

Resnik DB, Tinkle SS (2007) Ethics in nanomedicine. Nanomedicine 2(3):345–350

Shweder RA (2006) Protecting human subjects and preserving academic freedom: prospects at the University of Chicago. Am Ethnol 33(4):507–518

Staggers N, McCasky T, Brazelton N, Kennedy R (2008) Nanotechnology: the coming revolution and its implication for consumers, clinicians, and informants. Nurs Outlook 56(5):268–274

Sydes MR, Spiegelhalter D, Altman D, Babiker A, Parmar M (2004) Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. Clin Trials 1:60–79

The Sunshine Project (2004) Mandate for failure: the state of Institutional Biosafety Committees in an age of biological weapons research. www.sunshine-project.org/biodefense/tspibc.pdf. Accessed 8 Dec 2010

U.S. Code Service (1993) 42 U.S.C.S. §289g-1

Virdi J (2008) Bridging the knowledge gap: examining potential limits in nanomedicine. Spontaneous Gener 2(1):25–44

Wagner V, Dullaart A, Boek AK, Zweck A (2006) The emerging nanomedicine landscape. Nat Biotechnol 24:1211–1217

Woodward B (1999) Challenges to human subjects protections in US medical research. JAMA 282:1947–1952