# An Empirical Examination of the Current State of Publically Available Nanotechnology Guidance Materials

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## Background

Nanotechnology not only offers the promise of new enhancements to existing materials but also allows for the development of new materials and devices. The potential applications of nanotechnology range from medicine to agriculture to health and environmental science and beyond.[1] Nanotechnology is growing at such a rate that Lux Research in 2007 estimated that nanotechnology will be incorporated into 15% of global manufactured goods by 2014.[2] The U.S. National Nanotechnology Initiative defines nanotechnology as the following: "(1) Research and technology development involving structures with at least one dimension in the range of 1-100 nanometers (nm), frequently with atomic/molecular precision; (2) Creating and using structures, devices, and systems that have unique properties and functions because of their nanoscale dimensions; (3) The ability to control or manipulate on the atomic scale."[3] Nanomedicine and its subcategories of nanotherapeutics and *in vivo* nanodiagnostics incorporate nanoscale materials with unique properties that can enable new or improved treatments and diagnostics for many diseases and disorders. Nanomedicine has become an increasingly common area of research, with one study identifying nearly 250 nanomedicine products in human testing or having already completed human subjects research review.[4]

These same properties that make nanotechnology potentially lucrative may also present bioethical challenges when applied to nanomedicine. Currently, the United States has regulatory and oversight mechanisms in place to manage ethical and safety concerns for all new and existing technologies. Under Title 45 of the Code of Federal Regulations part 46 (commonly referred to as the "Common Rule"), human subjects research must minimize risks to research subjects, ensure that risks are reasonable relative to any potential benefits, and obtain informed consent

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from all research participants.[5] However, there is debate among scholars over whether the current system adequately addresses ethical and safety concerns associated with nanotechnology. Issues relevant to this debate include not only concerns about human subjects involved in nanotechnology research but also concerns about occupational and community exposure to nanomaterials as nanotechnology research might expose laboratory workers, clinicians, research staff, or others, and the environment to potential nano-associated risks.[6]

There are some particular concerns regarding how nanomaterials interact with the human body. Depending on their route of exposure, some nanomaterials can penetrate and accumulate in organs and tissues differently than their bulk material analogues, and these behaviors can vary significantly across classes of nanomaterials.[7] The research to investigate the acute effect of these properties on the human body is still under development, and studies to evaluate the effect of chronic exposure to nanomaterials have not yet been conducted.[8] Indeed, a recent National Academy of Sciences report highlighted gaps in technical knowledge about nanomaterials and the resultant uncertainties when nanomaterials are used in human subject research.[9] Complicating the development of a uniform set of standards, however, is a lack of consensus about potential environmental health and safety risks of many nanomaterials and even less agreement (or indeed discussion) about the risks to human research subjects posed by nanomaterials.[10] All this suggests that there may be substantial uncertainty regarding potential risks and benefits for participants or the environment/community in a given nanotechnology clinical trial and impedes existing risk management strategies.[11]

Since there is not always specific guidance for nanomedicine human subjects research, researchers conducting these trials may look for guidance from other organizations. Consequently, the purpose of this study was to locate and categorize publically available nanotechnology policy or guidance documents or consent forms that could be used to guide research with human subjects and, in particular, to inform the development of consent forms for nanomedicine clinical trials.

## Methods

This research is part of a larger project entitled "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight," which was funded through the National Institutes of Health and the National Human Genome Research Institute Award #: 1-RC1-HG005338-01. This project created the first comprehensive recommendations on human research subject protections in nanodiagnostics and nanotherapeutic research. The project group leveraged the expertise of many subject matter experts in the fields of law, engineering, and ethics to evaluate current approaches to nanotechnology research oversight.

The purpose of this study was to identify publicly available nanotechnology guidance materials from outside of the scholarly, peer-reviewed literature. We chose to survey the non-scholarly literature here because it is uncommon for consent forms to be published within peer-reviewed journals. Moreover, documents from government agencies would not be available through reviews of the scholarly literature. Instead, these important documents would be available through the respective agency's website and would theoretically be best identified through a systematic set of Internet searches. The materials identified through these Internet searches are therefore available to everyone with an Internet connection (whereas the scholarly literature may have restricted access). Web searches are common ways of identifying information, a trend reflected in the inclusion of

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Table 1

## List of Organizations in Search Arenas

### Government Agencies

Centers for Disease Control and Prevention
Defense Advanced Research Projects Agency
Department of Homeland Security
Department of Defense
Department of Energy
Environmental Protection Agency
Food and Drug Administration
National Institutes of Health (main website)
National Cancer Institute
National Institute of Allergy and Infectious Disease
National Institute of Biomedical Imaging and Bioengineering
National Institute of Environmental Health Sciences
National Heart, Lung, and Blood Institute
National Human Genome Research Institute
National Institute for Occupational Safety and Health
National Nanotechnology Initiative
National Science Foundation
Office of Biotechnology Activities
Office for Human Research Protections
Occupational Safety and Health Administration

### Professional Organizations

International Association of Nanotechnology
American Society of Nanomedicine
American Academy of Nanomedicine
Biomedical Engineering Society
American Society for Mechanical Engineering
Society of Clinical Research Associates
Association of Clinical Research Organizations

### Project and University Websites of the 8 NIH-Funded Nanomedicine Centers

Georgia Tech
Project website: http://www.nucleoproteinmachines.org/
University of Cincinnati
Project website: http://www.vet.purdue.edu/PeixuanGuo/NDC/
University of California, Los Angeles
Project website: website: http://centerforcellcontrol.org/
Univ. of California/Lawrence Berkeley National Laboratories
Project website: No website listed
Baylor University
Project website: http://proteinfoldingcenter.org
University of Illinois, Champaign/Urbana
Project website: http://www.nanoconductor.org/
University of California, San Francisco
Project website: http://www.qb3.org/cpl/
New York University
Project website: http://www.mechanicalbiology.org/

### NIH-Funded Nanomedicine Clinical Trial Sites

Albert Einstein College of Medicine of Yeshiva University
AMAG Pharmaceuticals, Inc.
Amgen
City of Hope- Beckman Research Institute
Bristol-Myers Squibb
Robert Wood Johnson Medical School- Cancer Institute of New Jersey
Case Western Reserve University
CCOP Michigan Cancer Research Consortium
Cleveland Clinic
Columbia University
Cornell University
Duke University
Emory University
Fox Chase Cancer Center
Franklin Square Hospital Center
Fred Hutchinson Cancer Research Center
Indiana University
Johns Hopkins University
Mayo Clinic
Memorial Sloan-Kettering Cancer Center
Mount Sinai Medical Center
New York University
NorthShore University Health System
Northwestern
Ohio State University
Oregon Health Sciences University
Sequus Pharmaceuticals
University of Alabama at Birmingham
University of Arizona
University of Buffalo
University of California, Davis
University of California, Los Angeles
University of California, San Francisco
University of Colorado, Denver
University of Miami
University of Minnesota
University of New Mexico
University of North Carolina
University of Pittsburgh
University of South Carolina
University of South Florida
University of Southern California
University of Texas

| |
|---|
| University of Washington |
| University of Texas Southwestern Medical Center |
| Vanderbilt-Ingram Cancer Center |
| Virginia Commonwealth University |
| Virginia Mason Medical Center |
| Wake Forest University |
| Washington University, St. Louis |
| Wayne State University |
| **Google Search** |
| Google |
| www.google.com |

Internet-search strategic training by some academic institutions.[12]

Comprehensive Internet-based searches were conducted from December 2009 to November 2010. Five search arenas were used to identify documents: (1) government agencies identified by the project group as associated with nanomaterials (20 agencies); (2) professional organizations identified as associated with nanomaterials (7 organizations); (3) college/universities identified by clinicaltrials.gov to have conducted nanomedicine clinical trials (51 organizations); (4) project/university websites of NIH-funded nanomedicine centers (8 centers); and (5) sites identified through a general Google search. A descriptive list of organizations in the five search arenas can be found in Table 1.

Search terms were selected through discussions with the project group members who are nanotechnology content experts. Seventeen nanotechnology related search terms were used in the following general categories for each search arena: general nano terminology (e.g., nanomaterials [10 terms]), nanostructures (e.g., dendrimers [6 terms]) and suspension chemistry terminology (e.g., colloid [1 term]). Additional search terms were added to narrow down the potential number of hits. A description of the terms used for each arena is found in Table 2.

Searches were limited to the first 100 hits unless at least 30 relevant documents were located in the first 100 hits, in which case the search was expanded to the next 100 hits. For searches with less than 30 of the top 100 results being relevant documents, the chances were very small that less highly-ranked search results would yield a meaningful number of relevant documents. However, in none of the searches was this threshold met. All searches were completed on the main webpage for each organization. Websites that did not provide a search function were read in their entirety and the search function (Ctrl + F) was used to search for "nano" search terms.

To be included in this study, the document must have discussed the implications of nanotechnology more broadly than bench research: it must have discussed the effects on humans in some way (either as research subjects, in laboratory work, or the environment as it relates to humans). Presentations (without additional materials), Powerpoint presentations, and news articles were not included because they did not provide enough information to allow coding. Scholarly literature such as articles in professional journals was excluded because it was summarized as a separate part of the larger project entitled, "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight." Documents identified through the searches that had been produced outside of the United States were included as long as the document was written in English. After documents were collected, they were categorized and coded.

The coding form included 16 items with issues including general nanotechnology risk/benefit questions, occupational health questions, and information about clinical trials. Coding of documents was conducted in NVivo and Microsoft Access. Microsoft Excel was used to create a summary of findings. Inter- and intra- rater reliability was tested to evaluate the

Table 2
**Search Terms Used in Each Search Arena**

| |
|---|
| **General Nano Terminology** |
| Nano |
| Nano* OR nano! |
| Nanoscale |
| Nanotechnology |
| Nanobiotechnology |
| Nanomedicine |
| Nanocoating |
| Nanocomposite |
| Nanomaterial |
| Nanoparticle |
| **Nanostructure Terminology** |
| dendrimer OR dendrimeric |
| liposome OR liposomal |
| micelle OR micellar |
| nanorod |
| nanotube |
| SPIO OR USPIO OR (iron oxide AND contrast) |
| **Suspension Chemistry Terminology** |
| colloid OR colloidal OR nanocolloid OR nanocolloidal OR nanosuspension |

Table 3
**Descriptive Information for Documents Coded (N=175)**

| Specificity of Document | Document Affirmatively Addresses Category N (% of total*) |
|---|---|
| General, meant to apply to research broader than nano (but also includes nano) | 13 (7%) |
| Specific to nano research | 161 (92%) |
| Very general- little applies to nano | 1 (1%) |
| **Subject of Document** | |
| Research Subjects | 5 (3%) |
| Close contacts of research subjects | 0 (0%) |
| Occupational Health/Safety/Workers | 79 (45%) |
| Environment (includes lab waste and people unknowingly exposed) | 95 (54%) |
| Bench research | 91 (52%) |
| Clinicians | 0 (0%) |
| **Type of Document** | |
| Information about specific products or clinical trials | 0 (0%) |
| Policy statement | 3 (2%) |
| Guidance document | 14 (8%) |
| Manual | 17 (10%) |
| Consent form/model consent form/template for consent form | 2 (1%) |
| White paper with recommendations | 1 (1%) |
| Agenda for R & D/Strategic plan/ Budget forecast/action plans | 29 (17%) |
| Notes/Reports/Proceedings from conferences | 22 (13%) |
| Toxicology Profile/toxicology information | 7 (4%) |
| Protocol discussion/review | 3 (2%) |
| Report | 37 (21%) |
| Other (includes other website material) | 40 (23%) |
| **Is a specific type of nano-product discussed in the document?** | 14 (8%) |
| **Who produced the document?** | |
| Defense Advanced Research Project Agency (DARPA) | 0 (0%) |
| Department of Homeland Security (DHS) | 0 (0%) |
| Department of Defense (DoD) | 1 (1%) |
| Department of Energy (DOE) | 5 (3%) |
| Environmental Protection Agency (EPA) | 11 (6%) |
| Food and Drug Administration (FDA) | 6 (3%) |
| National Cancer Institute (NCI) | 3 (2%) |
| National Human Genome Research Institute (NHGRI) | 0 (0%) |
| National Heart, Lung, and Blood Institute (NHLBI) | 0 (0%) |
| National Institute of Environmental Health Sciences (NIEHS) | 2 (1%) |
| National Institutes of Health (main webpage) (NIH) | 2 (1%) |
| National Institute for Occupational Safety and Health (NIOSH) | 14 (8%) |
| National Institute of Allergy and Infectious Diseases (NIAID) | 0 (0%) |
| National Institute of Biomedical Imaging and Bioengineering (NIBIB) | 0 (0%) |
| National Nanotechnology Institute (NNI) | 15 (9%) |
| National Science Foundation (NSF) | 8 (5%) |
| National Toxicology Program (NTP) | 9 (5%) |
| Office of Biotechnology Activities (OBA) | 3 (2%) |
| Office for Human Research Protections (OHRP) | 0 (0%) |
| Occupational Safety and Health Administration (OSHA) | 0 (0%) |
| Foreign Gov (includes European Commission) | 11 (6%) |
| Foreign College/University | 6 (3%) |
| US College/University | 33 (19%) |
| Business/Corporation/Industry | 6 (3%) |
| Thinktank/SRI/RAND/Woodrow Wilson, etc. | 8 (5%) |
| Research Organization | 2 (1%) |
| Non-Governmental Organization | 4 (2%) |
| Joint Publication | 5 (3%) |
| Other (list) | 21 (12%) |
| **Does the document contain guidance for local oversight committees?** | 0 (0%) |

* *Percentages correspond to total number of documents (N=175)*

precision of coding. Inter-rater reliability was determined to be 92% and intra-rater reliability was 97%.

## Results

*Document Description*

Despite conducting 5,083 individual searches, only 175 documents were located. These documents represented a wide range of type of documents. The most common type of document was website material (23%); the least common type of document (1%) was white papers, a non-peer reviewed report produced by an agency or organization (generally labeled by the organization as a "white paper"). Table 3 provides basic descriptive information about the documents that were coded. The majority of the documents were specific to nano-research (N=161; 92%). The environment and/or people unknowingly exposed were the subjects most often addressed in the documents (N= 95; 54%) followed by bench researchers, occupational health/safety/workers, and research subjects (52%, 45%, 3%, respectively). No document discussed the effects of nanotechnology on close contacts of research subjects or clinicians.

A plurality of documents (N= 33, 19%) were produced by colleges and universities. The National Nanotechnology Initiative produced the most documents out of U.S. federal agencies that were searched (N=15, 9%). None of the documents provided local oversight guidance, e.g., for institutional review boards.

*Human Research Subjects*

While the primary objective of this comprehensive search was to locate guidance documents directed at human subjects research, only five documents (3%) discussed human research subjects. Of these, two documents (40% of research subject documents; 2% of total documents) were from the NIH's Recombinant DNA Advisory Committee (RAC). These documents provided the RAC's comments about nanotechnology protocols in human subjects research. However, with the exception of stating that the nanoparticles used have off-target toxicity, these documents do not explicitly discuss nanotechnology.

Of the remaining three documents, two were consent forms and one was an ethics guide. One consent form was a protocol using a nanoparticle imaging agent. The protocol did not state that the radioactive Technetium sulfur colloid used as an imaging agent was a nanoparticle. In addition, the only risks stated related to this particle are related to high dose radiation. The other consent form identified was for a homeopathic silver hydrosol nutritional supplement. This protocol mentions the solution contains nanoparticles, but the only risks of treatment are related to silver exposure, not nanoparticle exposure.

*Occupational Health/Safety*

Half of the 175 documents were related to occupational health issues for laboratory workers who might come into contact with nanomaterials. These documents addressed a range of issues from measuring exposure to nanomaterials to clean-up and disposal to recommendations for controlling exposures to nanomaterials. Although these issues were addressed in many documents, some of the documents stated that there was not enough information about nanomaterials to make recommendations. Table 4 shows the number and percentage of documents that affirmatively addressed, negatively addressed, or did not address each occupational health issue.

*Risks/Benefits*

To better understand how the documents address human subjects, both in terms of human subjects research and occupational health/safety, it was necessary to determine how the documents address the risks and benefits of nanotechnology. Table 5 shows the number and percentages of documents that discussed the various risks and benefits of nanotechnology.

## Benefits of Nanotechnology

Thirty-seven percent (N=65) of the documents described the benefits of nanotechnology. The majority of these documents gave a description of the benefits of nanotechnology in very general ways, often in a laundry list of potential benefits that nanotechnology might sometime bring. In general, most documents discussed anticipated benefits of nanotechnology rather than benefits that currently exist.

A document located from the University of California, San Francisco provides an example of this code that is representative of the documents. The document states, "Nanoparticles have the potential to have huge impacts in medicine, energy and electronics and new materials science and development."[13]

In contrast, one document from the European Union implied that nanotechnology has created few benefits. This was the only document that stated there was little benefit of nanotechnology: "…the commercially available products to date in most cases have brought about very limited societal benefits, including products of dubious importance such as stain-free fabrics, lighter and stronger tennis rackets and self-cleaning windows." The document goes on to state that "the optimistic assessments of the benefits of nanotechnologies and materials are reminiscent of the promises made when nuclear energy and biotechnol-

Table 4
**Descriptive Analysis of Occupational Health and Safety Issues**

| Occupational Health or Safety Issue | Yes – Recommended<br>N<br>(% of total*) | No – Not Enough Information to Make a Recommendation<br>N<br>(% of total*) | Not Addressed<br>N<br>(% of total*) |
|---|---|---|---|
| Does the document recommend exposure to nanomaterials be measured? | 11<br>(6%) | 3<br>(2%) | 161 (92%) |
| Does the document state how to clean up and dispose of nanomaterials? | 20<br>(11%) | 2<br>(1%) | 153 (87%) |
| Does the document provide recommendations for transportation of nanomaterials? | 10<br>(6%) | 0<br>(0%) | 165 (94%) |
| Does the document recommend development of an environmental surveillance plan? | 2<br>(1%) | 0<br>(0%) | 173 (99%) |
| Does the document recommend employers adopt risk management strategies specific to nanotechnology? | 33<br>(19%) | 0<br>(0%) | 142 (81%) |
| Does the document recommend development of hazard surveillance for nanomaterials as an essential component of employee occupational health plans? | 10<br>(6%) | 1<br>(1%) | 164 (94%) |
| Does the document recommend development of medical surveillance for workers potentially exposed to nanomaterials? | 5<br>(3%) | 2<br>(1%) | 168 (96%) |
| If yes, what type of surveillance? (N=5) | | | |
| Medical Testing | 2<br>(40%) | 0<br>(0%) | 3<br>(60%) |
| Surveys | 0<br>(0%) | 0<br>(0%) | 5<br>(100%) |
| Does the document include recommendations on how to control exposure to nanomaterials? | 44<br>(25%) | 2<br>(1%) | 129 (74%) |
| If yes, what type of recommendation? (N=44) | | | |
| Elimination | 4<br>(9%) | 0<br>(0%) | 40<br>(91%) |
| Substitution | 9<br>(20%) | 0<br>(0%) | 35<br>(80%) |
| Engineering | 37<br>(84%) | 0<br>(0%) | 7<br>(16%) |
| Administration | 24<br>(55%) | 0<br>(0%) | 20<br>(45%) |
| Personal protective equipment (e.g., clothing, respirators) | 40<br>(91%) | 2<br>(5%) | 2<br>(5%) |

** Percentages correspond to total in each row (N=175, except where noted)*

ogy were first introduced…many chemicals and substances were welcomed for their benefits before their negative impacts on human health and the environment were identified and understood, including DDT, asbestos and PCBs."[14]

## Risk Comparison

Three documents (2%) compared risks to benefits. A comparison of risks to benefits was not addressed by the remaining 172 documents.

One of the documents (from the University of Minnesota) that presented a comparison of risks stated, "[S]ociety is both a supporter and watchdog of new technologies, and it strikes a balance between allowing technology to flourish and limiting it to acceptable use. Organizations play multiple roles, sometimes both promoting technology while ensuring its safety."[15] The second document that compared risks to benefits was proceedings from European Commission meeting. It contained the statement, "[A] survey carried out last year by researchers at the University of North Carolina established that the more people knew about nanotechnology, the more they thought the benefits would greatly outweigh the risks. The opposite was also true. This is a key point which indicates a well-informed public is likely to embrace nanotechnology and, whilst remaining wary of some of the risks, if they see it as bringing a major benefit to their lives."[16] The third doc-

Table 5
**Document Discussion of Risks and Benefits of Nanomedicine**

| Risk/Benefit Area | Yes – Addressed Affirmatively<br>N<br>(% of total*) | Yes- Addressed Negatively<br>N<br>(% of total*) | Not Addressed<br>N<br>(% of total*) |
|---|---|---|---|
| Does the document contain a statement(s) that describes the nano-specific potential benefits of participation/exposure? | 65<br>(37%) | 1<br>(1%) | 109<br>(62%) |
| Does the document compare nano-specific potential risks to potential benefits? (e.g., may state comparison or ratio) | 3<br>(2%) | 0<br>(0%) | 172<br>(98%) |
| Does the document state that nano-specific risks may be uncertain, unpredictable, or not well understood? | 95<br>(54%) | 0<br>(0%) | 80<br>(46%) |
| Does the document state that nanotechnology/the intervention has special risk? | 57<br>(33%) | 4<br>(2%) | 114<br>(65%) |
| Does the document state that the effects seen in animal models might not predict human effects? | 4<br>(2%) | 0<br>(0%) | 171<br>(98%) |
| Does the document contain a statement regarding the privacy of personal data obtained from sensors? | 0<br>(0%) | 0<br>(0%) | 175 (100%) |

** Percentages correspond to total in each row (N=175)*

ument is a report from the European Environmental Bureau stating, "The potential for nanotechnologies and nanomaterials to bring about societal benefits (including positive environmental implications) needs to be proven and balanced carefully with potentially unwanted and unforeseeable impacts. The precautionary principle must be applied because scientific research to-date suggests that exposure to at least some nanomaterials is likely to result in serious harm to human health and the environment."[17]

## Risk Uncertainty

Over half of the documents (N=95) state that the risks of nanotechnology are uncertain. These documents generally stated outright that the effects of nanoparticles are unknown. The remaining 80 documents do not address any uncertainty associated with nanotechnology.

## Special Risk

Overall, 35% percent of documents discussed the issue of nanotechnology's special risk. Of these, 33% percent (N=57) of documents stated that nanotechnology had risk that was unique from conventional technologies. Two percent (N=4) stated that nanotechnology did not pose special risks. The remaining 65% (N=114) of documents coded did not address the potential uniqueness of nanotechnology risk. Documents were coded as discussing special risk if the document made claims that nanotechnology caused greater health risks or had different health risks from other materials. An example of statement of special risk is, "[B]ecause of their tiny size, certain nanoparticles appear to penetrate deep into the lungs and may translocate to other organs following pathways not demonstrated in studies with larger particles."[18] Four (2%) documents stated that nanotechnology did not have special risks. Generally, these documents implied that while nanotechnology might have some risk, the risks of nanotechnology are not any greater than risks presented by other emerging technologies.

## Comparison of Risk and Benefits

To further elucidate the documents' contents, Table 6 provides cross tabulations of the risks and benefits of nanotechnology discussed in each document with specific occupational health strategies.

Of the documents that said nanotechnology has benefits, 69% (N=45) also stated that the risk of nanotechnology was uncertain. Forty-eight percent of the documents that said nanotechnology had benefits stated that there were special risks associated with nanotechnology. Three percent of these documents claimed there was no special risk of nanotechnology.

Of the documents that stated risk was uncertain, 47% stated there were benefits to nanotechnology (N=45). Fifty-five percent of these documents also stated that nanotechnology contained special risk (N=52), while three stated that there was no special risk.

Table 6
**Risks and Benefits of Nanotechnology versus Occupational Health Strategies**

| Coding Determination | States Nano Has Benefits | States Nano Has No Benefits | States Risks Are Uncertain | States Special Risk | States No Special Risk |
|---|---|---|---|---|---|
| States Nano Has Benefits | | | 45 (47%) | 31 (54%) | 2 (50%) |
| States Nano Has No Benefits | | | 1 (1%) | 1 (2%) | 0 (0%) |
| Compares Risks To Benefits | 2 (3%) | 1 (100%) | 2 (2%) | 3 (5%) | 0 (0%) |
| Risks Are Uncertain | 45 (69%) | 1 (100%) | | 52 (91%) | 3 (75%) |
| Special Risk | 31 (48%) | 1 (100%) | 52 (55%) | | |
| No Special Risk | 2 (3%) | 0 (0%) | 3 (3%) | | |
| Measure Exposure | 3 (5%) | 0 (0%) | 10 (11%) | 8 (14%) | 0 (0%) |
| No Measurement Guidelines | 3 (5%) | 0 (0%) | 3 (3%) | 2 (4%) | 0 (0%) |
| Risk Management | 14 (22%) | 0 (0%) | 28 (29%) | 21 (37%) | 1 (25%) |
| Control Exposure | 13 (20%) | 0 (0%) | 29 (31%) | 21 (37%) | 0 (0%) |
| No Control Exposure Guidelines | 2 (3%) | 0 (0%) | 2 (2%) | 1 (2%) | 0 (0%) |
| TOTAL | 65 | 1 | 95 | 57 | 4 |

** Percentages correspond to total in column. Percentages may sum to greater than 100% as documents can address multiple coding questions.*

Not surprisingly, the documents that stated nanotechnology had special risk were also the most likely to recommend risk management guidelines or provide recommendations to control exposure (both at 37%), compared to 29% and 31%, respectively of documents that stated risks were uncertain. Documents that stated there was no special risk did not contain guidelines for controlling exposure or risk management.

## Other Coding Categories

Only four documents (2%) stated that animal exposure assessments might have limited value in understanding human exposure. No documents discussed privacy issues related to nanotechnology.

## U.S./Non-U.S. Document Comparison

To investigate whether there was differential discussion of nanotechnology according to the document source, a comparison between documents produced in the U.S. and those produced by organizations abroad was made. Given the different cultures involved, we agreed that this comparison was the one most likely to show any differences that might exist. Because of the small sample size and the even smaller cell counts, cross tabulation and significance testing were not appropriate. Table 7 shows the number and percent of documents that affirmatively addressed, negatively addressed, or did not address each nanotechnology risk or benefit according to whether the document was produced by a U.S. or a non-U.S. source. Overall, the patterns in the U.S. and non-U.S. documents are quite similar.

Documents produced outside of the United States were more likely than documents produced within the United States to state that nanotechnology "has benefits" (45% [N=14 versus 35% [N=51]). However, the only document that explicitly stated that nanotechnology did not have benefits was produced outside the United States. There were no U.S. documents that stated that there were no benefits to nanotechnology.

Expressions of certainty regarding nanotechnology's risks appear to be similar regardless of where the document was produced. Both foreign documents and U.S. documents claimed that the risks of nanotechnol-

Table 7

**Nanotechnology Risk and Benefit Discussion by Document Source (U.S. versus Non-U.S.)**

| Nanotechnology Risk or Benefit | Non-U.S. Documents (N=31) | | | U.S. Documents (N=144) | | |
|---|---|---|---|---|---|---|
| | Yes – Addressed Affirmatively N (% of non-U.S. documents) | Yes – Addressed Negatively N (% of non-U.S. documents) | Not Addressed N (% of non-U.S. documents) | Yes – Addressed Affirmatively N (% of U.S. documents) | Yes – Addressed Negatively N (% of U.S. documents) | Not Addressed N (% of U.S. documents) |
| Does the document contain a statement(s) that describes the nano-specific potential benefits of participation/exposure? | 14 (45%) | 1 (3%) | 16 (52%) | 51 (35%) | 0 (0%) | 93 (65%) |
| Does the document state that nano-specific risks may be uncertain, unpredictable, or not well understood? | 17 (55%) | 0 (0%) | 14 (45%) | 78 (54%) | 0 (0%) | 66 (46%) |
| Does the document state that nanotechnology/the intervention has special risk? | 12 (39%) | 0 (0%) | 19 (61%) | 45 (31%) | 4 (3%) | 95 (66%) |
| Does the document compare nano-specific potential risks to potential benefits? (e.g., may state comparison or ratio) | 2 (6%) | 0 (0%) | 29 (94%) | 1 (1%) | 0 (0%) | 143 (99%) |
| Does the document state that the effects seen in animal models might not predict human effects? | 1 (3%) | 0 (0%) | 30 (97%) | 3 (2%) | 0 (0%) | 141 (98%) |
| Does the document recommend exposure to nanomaterials be measured? | 2 (6%) | 2 (6%) | 27 (87%) | 9 (6%) | 1 (1%) | 134 (93%) |
| Does the document state how to clean up and dispose of nanomaterials? | 3 (10%) | 0 (0%) | 28 (90%) | 17 (12%) | 2 (1%) | 126 (87%) |
| Does the document provide recommendations for transportation of nanomaterials? | 0 (0%) | 0 (0%) | 31 (100%) | 10 (7%) | 1 (1%) | 133 (92%) |
| Does the document recommend development of an environmental surveillance plan? | 0 (0%) | 0 (0%) | 31 (100%) | 2 (1%) | 0 (0%) | 142 (99%) |
| Does the document recommend employers adopt risk management strategies specific to nanotechnology? | 9 (29%) | 0 (0%) | 22 (71%) | 24 (17%) | 0 (0%) | 120 (83%) |
| Does the document recommend development of medical surveillance for workers potentially exposed to nanomaterials? | 0 (0%) | 1 (3%) | 30 (97%) | 5 (3%) | 1 (1%) | 138 (96%) |
| Does the document include recommendations on how to control exposure to nanomaterials? | 8 (26%) | 0 (0%) | 23 (74%) | 36 (25%) | 2 (1%) | 106 (74%) |

ogy were uncertain at a rate of a little over 50% (N=17 and N=78, respectively). While both U.S. and non-U.S. documents stated that there are risks associated with nanotechnology, two of the three documents that compared nano-specific risks to benefits were from non-U.S. sources (6% of non-U.S. documents versus 1% of U.S. documents)).

Interestingly, non-U.S. documents were more likely to provide recommendations to avoid nanotechnology exposure and exercise risk management strategies in the workplace. Twenty-nine percent (N=9) of foreign documents stated risk management practices were recommended compared to 17% (N=24) U.S. documents.

comparing the benefits of nanotechnology to its risks. There were few differences between U.S. and non-U.S. documents with respect to statements of risks and benefits. They were also more likely to recommend strategies to reduce exposure to nanomaterials in the workplace.

The findings also suggest that there is no consensus that nanotechnology is exclusively risky or exclusively beneficial and that both risks (even if unknown) and benefits are inherent to the technology. Given the lack of consensus on the (potential) risks posed by nanotechnology, it is perhaps not surprising that no consensus exists on what is needed to protect against occupational and environmental safety concerns.

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## Discussion

This study searched for publicly available guidance, such as documents, that advised researchers on how to address humans subjects research, especially in nanomedicine clinical trials, or discussed how researchers are addressing human subjects issues in their consent forms. Despite the large number of online searches that were conducted, few documents were found that discussed nanotechnology human subjects research issues. This finding could indicate that researchers and organizations are not making their documents publicly available through Internet search websites. It seems to indicate that more guidance regarding nanotechnology and human subjects research issues is warranted.

Due to the small sample sizes, low cell counts made it difficult to discern any trends between documents produced within the U.S. (i.e., government documents versus those produced by colleges/universities or other agencies). However, we were able to compare the content from documents produced in the United States to documents produced outside of the U.S. Many documents stated that there appeared to be benefits as well as risks of nanotechnology. More commonly, documents stated that risk was uncertain rather than stating that nanotechnology presents special risk. Only three of the documents found in this search suggested

Although this study used a comprehensive search and coding process, a number of limitations are acknowledged. The use of the Google search engine limits replication of the search process employed as the tool utilizes the user's geographical location to prioritize results. Additionally, Google selects links to place higher in the hits based on the webpage viewing patterns of the person searching. These problems become even more complicated if an agency changes its website design between searches. Furthermore, non-U.S. results are limited because the search focused primarily on searching U.S. government agencies and the Google search would limit foreign results to those only published in English on the U.S. Google search function (as opposed to the Google search for that document's country). An additional limitation is that it is likely that not all organizations discussing the risks to human subjects' nanomedicine research will post their documents online, so our search probably is an incomplete census of nanomedicine research documents. How this biases the results of the study is unknown given that we do not know what variables might affect online posting. The modest number of documents that resulted from the searches precluded tests for statistical significance between categories. Additionally, these data reflect only the documents

available at the time of the searches and additional documents may have become available since then.

In spite of these limitations, our extensive Internet searches suggest that a shortage of publicly-available guidance materials exists with respect to the benefits and risks of nanomedicine technologies. This may mean that researchers, practitioners, and policymakers have a smaller range of existing work to draw upon as they develop guidance materials for their own work, potentially inhibiting efforts to develop and promulgate standardized risk-benefit discussions for human research subjects or future testing.

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