INTRODUCTION

The Challenge of Nanomedicine Human Subjects Research: Protecting Participants, Workers, Bystanders, and the Environment

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The growing capacity to build and manipulate materials at the nanoscale is both thrilling and challenging. Engineering at the level of atoms allows much needed problem-solving and innovation, but also raises questions about how to assess the effects and safety of the materials created. The promise and the challenge are especially acute in the domain of nanomedicine. Nanotherapeutics and *in vivo* nanodiagnostics (diagnostics used within the human body) have the potential to solve long-standing problems, including how to ferry drugs across the blood-brain barrier to treat brain tumors, how to find and destroy tiny micrometastases before cancer progresses, and how to transport corrective genes into human cells without the dangers of viral vectors. But none of these applications is possible without first testing the safety and efficacy of these interventions in human beings. And human subjects research in nanomedicine raises fundamental questions.

First, there are a host of questions about how to protect the human participants themselves. Many of these questions are the familiar ones that arise when testing interventions in any area of emerging technology. But answering those questions can be difficult when more work is needed to specify the attributes of concern that characterize various nanomaterials, familiar toxicological testing methods may not be adequate, and the long-term fate of nanoparticles in the human body is still under study. These uncertainties complicate decisions about when to authorize first-in-human trials of a new intervention, how to assess the risks of a proposed protocol, and how to obtain consent to participate in the face of significant unknowns. Making ethical judgments under the federal regulations governing human subjects research — the Common Rule[1] and the Food and Drug Administration's equivalent[2] — can be difficult.

The challenges, however, go beyond the question of how to protect human participants. A growing literature addresses the occupational risks of exposure to nanoparticles. This can raise questions about the safety of a nanomedicine protocol not only for the human participant, but also for laboratory workers and clinicians who may be exposed to the nanomaterials. Beyond the occupational concerns, there can be questions of bystander exposure, when protocols potentially involve exposure of family members and close contacts. Lastly, there are environmental questions. Excretion and shedding by the human participants and disposal of laboratory waste may involve release of nanomaterials into the environment.

The human subjects concerns are challenging enough. If nanomedicine trials were only a chance to think systematically about how best to protect human subjects while advancing the science, that itself would be worthwhile. After all, oversight of human subjects research in domains of emerging technology — gene transfer research, stem cell research, and the like — has become a crazy quilt of different approaches.[3] The federal regulations prescribe a baseline regime and rules, but the questions of when to add further, exceptional oversight (as in the case of gene transfer research in human beings) and what that added oversight should look like call for a more systematic and

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predictable approach to governing human subjects research than is evident so far. Developing organizing principles and criteria to systematize oversight of human subjects research for emerging technologies is a tall order by itself.

But nanomedicine human subjects research demands even more. It calls for coordination and integration of what are now largely separate domains of analysis. In any institution conducting human subjects research, there are likely to be distinct committees imposing separate rules to determine the acceptability of a single research protocol's approach to human subjects, workers, bystanders, and the environment. There is limited precedent for integrating these analyses. In the domain of recombinant DNA and synthetic DNA research, Institutional Biosafety Committees (IBCs) do consider issues going beyond the human subject to laboratory containment levels, personnel training, and whether protocols address issues such as potential transmission of viral infection to close contacts.[4] However, IBCs operate under the *NIH Guidelines*, which are particular to recombinant and synthetic DNA research, not nanomedicine.[5]

Because nanomedicine is a fast-emerging arena of tremendous potential therapeutic and diagnostic importance, figuring out how best to oversee human subjects research is vital. Research conducted as part of this project has shown that there are already scores of investigational products in the human subjects research pipeline, as well as a substantial number of nanomedicine interventions on the market.[6] So the pressing question is how to oversee and evaluate research protocols in a way that adequately considers human participants, workers, bystanders, and the environment. What can we learn from the last 35 years of oversight for human subjects research since promulgation of what is now the Common Rule? And conversely, what does thinking deeply about oversight for nanomedicine human subjects research suggest for oversight of human subjects research more generally in domains of emerging technology?

To answer these questions, we convened a multidisciplinary project group, with experts in nanomedicine, drugs and devices, toxicology and public health, occupational health, food and drug law and policy, research ethics, and bioethics more broadly. Funded by an American Recovery and Reinvestment Act (ARRA) Challenge Grant from the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH), we embarked on a three-year process. We conducted empirical research to identify current approaches to nanomedicine research ethics, as well as the state of the field of nanomedicine. We found that although there were a substantial number of nanomedicine trials under way, there was little guidance available on the specific issues raised by those trials.[7] We set out to analyze and address this gap.

Over the course of four Working Group meetings, we mapped the issues raised by nanomedicine human subjects research, with the help of guest speakers on specific aspects of the problem, and began to develop a group analysis and recommendations paper. Our work was aided by dividing into smaller groups to zero in on targeted issues and bring back recommendations for the full group's consideration. Through these iterative techniques and robust debate, we developed a draft article that was shared with guest speakers in advance

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of our project's public conference in September 2011. At that conference on "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight,"[8] experts and audience members reacted to our draft and arguments presented, while members of our project and invited others presented individual papers that became the seeds of articles in this published symposium. The day after the conference, the Working Group reconvened to consider the input we had received at the conference and make further changes in the group recommendations paper. Final changes were negotiated by e-mail.

We are proud to present in this issue a 12-article symposium publishing the project's consensus recommendations article[9] as well as individual articles offering in-depth analyses of specific issues. Together, these articles comprise the most comprehensive and innovative collection of work to date on the challenges of nanomedicine human subjects research, offering recommendations moving forward.

However, the significance of the body of work collected in this symposium extends further. We pioneer a systematic approach to oversight of human subjects research in domains of emerging technology with associated uncertainty about hazards, risks, and potential benefits. We map the architecture of what we call "baseline oversight" that applies to all biomedical human subjects research falling under the federal regulations, and then ask when is more needed, what should that added regime look like, and why. Our work suggests an approach to other areas of emerging technology involving human subjects research.

Equally important, we face the reality that some nanomedicine human subjects research will raise questions that go beyond protection of the human participant to the disparate oversight regimes in place for occupational, bystander, and environmental concerns. We suggest how to coordinate and integrate these oversight bodies and their approaches.

In doing this work, we take a chance that readers will misunderstand our focus on nanomedicine as a suggestion that nanomedicine research is categorically riskier than other research. It is important to bear in mind the careful analysis to the contrary offered in our group consensus paper. There we discuss at length the fact that nanomedicine interventions are highly diverse, some are already in use, and both the hazards and the risks require nuanced scientific as well as ethical analysis. Moreover, any protective regulatory and oversight regime has costs, including the human cost of delaying therapies and diagnostics that could prove of great benefit.

The articles in this symposium are the result of a careful integration of scientific, ethical, legal, and societal considerations. Our group debate, especially in our face-to-face meetings, was a prolonged and evolving conversation, deeply schooled in the history of U.S. oversight of human subject research. The debate was equally grounded in appreciation for the challenges posed by a set of technologies at the nanoscale that offer tremendous promise, while raising questions of how to protect human subjects, bystanders, workers, and the environment in the face of significant uncertainties. In response, the group consensus paper proposes a flexible, evolutionary approach to oversight. This is in keeping with an important literature on adaptive regulation and new governance.[10]

The U.S. investment on nanotechnology is substantial. The federal government's 2013 budget allocates $1.8 billion to the National Nanotechnology Initiative (NNI) alone, supporting research and development across 15 federal agencies, including NIH.[11] Despite major investment in nanotechnology and specifically in nanomedicine,[12] the challenges of nanomedicine human subject research have received only scattered attention and analysis, until now. We hope the work of this project will make a lasting contribution, both to the appropriate oversight of nanomedicine human subjects research, and to the evolution of a more systematic, 21st-century approach to human subjects research in arenas of emerging technology.

Acknowledgements

Preparation of this article was supported by the National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) ARRA Challenge grant #1-RC1-HG005338-01 on "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight" (S. M. Wolf, PI; J. P. Kahn, R. Hall, J. McCullough, Co-Is). The contents of this article are solely the responsibility of the author and do not necessarily reflect the views of NIH or NHGRI. Special thanks to the full investigator and project team, all Working Group members, the speakers who generously shared their expertise at project meetings and our September 2011 conference, and especially Audrey Boyle for outstanding project management. Further information on this project is archived at <http://www.lifesci.consortium.umn.edu/grantsresearch/NanodiagnosticsandNanotherapeuticsBuildingResearchEthicsOversight/Nanomed.html> (last visited October 15, 2012).

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