De Minimis Risk: A New Category of Research Risk

Rosamond Rhodes, PhD, Mount Sinai School of Medicine

Corresponding Author:
Rosamond Rhodes, PhD
Box #1076
Mount Sinai School of Medicine
One Gustave Levy Place
New York, NY 10029
Phone: 212-241-3757
e-mail: rosamond.rhodes@mssm.edu
fax: 212-241-5028
ABSTRACT

In response to problems identified by critics of current U.S. research regulations and the recent HHS advance notice of proposed regulation reform, we identify a critical oversight in the regulations and offer a solution to make them more coherent. We propose creating a new category of research risk, *de minimis* risk. We use the term “*de minimis* risk” to indicate an even lesser degree of risk than what is currently considered minimal, where nothing inherently dangerous is done to the body. Our recommendation would make permission to conduct a study without informed consent the default position when only *de minimis* risk is involved; oral or blanket agreement may still be obtained when obtaining it is feasible and the burdens involved are reasonable. This proposal for establishing *de minimis* risk as a new category of research risk has several advantages. It puts the focus of research ethics where it belongs, on an assessment of risks and benefits. It also reduces unreasonable obstacles that have inhibited research. Our recommendation bears directly on areas addressed by the proposed reforms: exempt activities, biobank and sample bank studies, research on populations, the use of discarded biological samples.
De Minimis Risk: A New Category of Research Risk*

Rosamond Rhodes

In response to the Department of Health and Human Services (HHS) advance notice of proposed rulemaking,¹ this Commentary offers a new approach to some problems HHS identifies. Critics have noted that current research regulations and Institutional Review Board (IRB) policies impede research and limit or discourage learning from clinical practice.² ³ ⁴ ⁵ Regulations and policies related to informed consent and privacy protection are especially burdensome, time-consuming, and costly.⁶ ⁷ ⁸ For some projects that pose only negligible risks to participants, it is impossible to meet regulatory or institutional requirements, consequently, legitimate research projects cannot be undertaken.⁹ ¹⁰ Furthermore, genome and microbiome research, far more than clinical trials, require broad participation, whereas use of stored samples involves no physical risks.

The failure to distinguish negligible risk from greater risks and to appropriately consider research’s social importance, constitute critical oversights in research regulations. To address these problems, this proposal calls for establishing de minimis risk as a new category of research risk. This would put the focus of research ethics where it belongs, on the assessment of risks and benefits. It would also strike a reasonable balance between advancing biomedical science and societal health, and the importance of respecting persons. Studies that fit this category would be exempt from informed consent requirements because the risks involved are truly de minimis.

Problems
As HHS suggests, current regulations are inconsistent in that they treat similar activities differently. A project classified as public health surveillance, quality assurance (QA), or quality improvement (QI) activity is not counted as research and federal research regulations do not apply. Thus, informed consent is not required. When a similar project is counted as “research,” informed consent requirements apply. The line between exempt activities and research activities is often hard to discern. It is not surprising that institutions and public health agencies find themselves in quandaries about the classification of their studies.\(^\text{11,12}\)

In many circumstances, obtaining informed consent for exempt studies is impossible, inefficient, or counterproductive, whereas the public good they serve is significant. In public health surveillance, for instance, the risks to participants are typically miniscule, and data may be needed from everyone with a particular condition who presents in an Emergency Department or doctor’s office. Obtaining informed consent from each individual would require tremendous effort and divert scarce public health resources from other socially important activities. Also, because obtaining informed consent entails allowing people to refuse, a source of bias may be introduced to these critical activities.

Whereas important social benefits can be provided by conducting public health surveillance, QI, and QA studies, criteria for drawing a line between what counts as research and what does not are imprecise because there is no significant difference, only a stipulation framed in uninformative terms.\(^\text{13}\) In contrast, the most ethically significant differences between studies are the level of risk to which human subjects are exposed and the importance and likelihood of expected benefits. The regulatory focus should, therefore, be on participants’ exposure to risk in
relation to the anticipated societal benefits, rather than on deciding whether or not a study counts as research.

Genetic biobanks, sample banks and human microbiome research raise further dilemmas. Although donors can give blanket consent for future research use of their samples, neither researchers nor donors can know specifics about research projects that will eventually use samples. When blanket consent is obtained, biobanks are unable to conform with several of the General Requirements for informed consent enumerated in the regulations. Although Common Rule 45§46.116a&b permits IRBs to waive informed consent when “The research involves no more than minimal risk to the subjects” and “The research could not practicably be carried out without the waiver or alteration”, IRBs are reluctant to grant waivers, particularly for studies involving genetic material.14

To avoid informed consent problems, some centers anonymize samples.15 16 This makes it nearly impossible to re-identify sample donors. Anonymizing allows investigators to use samples without obtaining informed consent. It also leaves investigators unable to match samples with donors’ medical records or re-contact donors to enhance research aims. Such measures obliterate associated phenotype information, severely diminishing samples’ scientific value.

Recommendation

In light of these considerations, a new category of research risk should be created, de minimis risk. Existing U.S. federal regulations classify research risk in relation to minimal risk.14 “De minimis risk” would indicate a lesser degree of risk. This category would apply to studies
involving only negligible physical or psychological risk where nothing inherently dangerous is
done to the body. Obtaining informed consent should not be an absolute requirement for studies
that involve only de minimis risk, and permission to conduct studies without informed consent
should be the default position; oral or blanket agreement may be obtained when obtaining it is
feasible and the burdens involved are reasonable.

This recommendation also requires balancing risks and benefits. Although all of the most
important historical documents articulating standards of research ethics explicitly endorse the
idea that research risks should be balanced against societal benefits, current practice
often seems to ignore the importance of balance. Instead officials focus narrowly on protecting
research participants from any risks, regardless of how unlikely, fleeting, or trivial the
anticipated harm. When risks are negligible and unlikely, and the study promises societal
benefit, a reasonable assessment should conclude that the balance tips towards promoting
scientific advance. Policies that consider just risks, and deliberately ignore possible social
benefits, express a distorted view of what ethics entails and, therefore, produce ethically flawed
regulations.

The category of de minimis risk would apply to several kinds of research and play a role
in governing policy:

Exempted Research - The Common Rule, 45CFR46.101b, implicitly employs such a
standard when it exempts several kinds of studies. These studies all involve only de minimis
risk. Including them under the new de minimis risk research category, would make the reason
for exemption explicit.
Biobank and Sample Bank Studies – Even when sample collection involves more than *de minimis* risk, subsequent use of samples in studies involves only *de minimis* risk of physical harm. When biobanks are safeguarded from use in criminal investigations, immigration proceedings, insurance markets, and the like, and from confidentiality violations that could share personal information with family members or employers, studies using these samples will involve only *de minimis* risk.\(^{21, 22, 23, 24}\) Directly responding to concerns about safeguarding biobank confidentiality is a coherent and effective way of dealing with the problem, better than sacrificing the value of samples by anonymizing them or re-describing biobank studies as something other than human subject research (e.g., human non-subject research).\(^{25}\)

Discarded Biological Samples - Biological samples leftover from clinical care can be valuable in research. The risks involved in using these samples are only *de minimis* because nothing additional is done to patients’ bodies. Because allowing patients to opt-out of future research use of their samples when samples are collected is feasible, and because providing an opt-out opportunity would make the process more transparent and acceptable, institutions should adopt opt-out policies.

Research on Populations - Public health studies, as well as QI and QA studies that do not involve direct interference with participants’ bodies should be considered *de minimis* risk. Because of the vanishingly small likelihood of risk, informed consent should not be required for these activities whenever general participation is needed.
Acknowledgements

* This Commentary derives from work by the “Human Microbiome and the Social Fabric” working group. Our views evolved over two years of discussion aimed at developing policy recommendations related to issues raised by human microbiome research. Working group participants who endorse this recommendation and participated in conceptualizing and drafting it are: Jody Azzouni, Stefan Bernard Baumrin, Keith Benkov, Martin J. Blaser, Barbara Brenner, Joseph W. Dauben, William J. Earle, Lily Frank, Nada Gligorov, Joseph Goldfarb, Kurt Hirschhorn, Rochelle Hirschhorn, Ian Holzman, Debbie Indyk, Ethylin Wang Jabs, Douglas P. Lackey, Daniel A. Moros, Sean Philpott, Matthew E. Rhodes, Lynne D. Richardson, Henry S. Sacks, Abraham Schwab, Rhoda Sperling, Brett Trusko, Arnulf Zweig.

This work was funded by 1R01HG004856-01 as a component of the Human Microbiome Project, a National Institutes of Health (NIH) Common Fund initiative.

I have no conflicts of interest.

References


Hermos JA and Spiro A. Certificates should be retired. Science 2009; 323(5919): p1288-1299.

