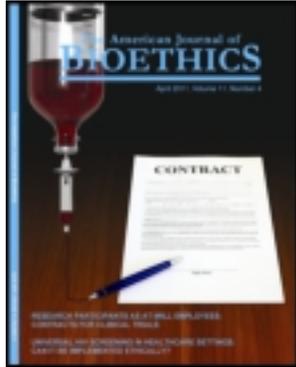


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Publisher: Routledge

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The American Journal of Bioethics

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/uajb20>

De Minimis Risk: A Proposal for a New Category of Research Risk

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Available online: 02 Nov 2011

To cite this article: Rosamond Rhodes, 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 (2011): De Minimis Risk: A Proposal for a New Category of Research Risk, *The American Journal of Bioethics*, 11:11, 1-7

To link to this article: <http://dx.doi.org/10.1080/15265161.2011.615588>

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Editorial

De Minimis Risk: A Proposal for a New Category of Research Risk

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This article derives from the “Human Microbiome and the Social Fabric” working group. Our views on the ethical, legal, and social implications of human microbiome research evolved over two years of discussion. They will be presented in a forthcoming volume to be published by Oxford University Press. Our work was funded by 1R01HG004856-01 as a component of the Human Microbiome Project, a National Institutes of Health (NIH) Common Fund initiative. We are grateful to Drs. Mark Babyatsky, Erwin Bottinger, and Marie Teil for their contribution to the group’s education during the early stages of this project.

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In response to the Department of Health and Human Services (DHHS) recently posted advance notice of proposed rulemaking, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators" (DHHS 2011) and the *New England Journal of Medicine* Sounding Board summary by Ezekiel Emanuel and Jerry Menikoff, "Reforming the Regulations Governing Research with Human Subjects" (Emanuel and Menikoff 2011), we write to offer a new approach to some of the problems that they identify. Critics have noted that current research regulations and institutional review board (IRB) policies impede research and limit or even discourage learning from clinical practice (Emanuel et al. 2004; Fost and Levine 2007; Resneck 2005; Schwab 2010). Regulations and policies related to informed consent and privacy protection are especially burdensome, time-consuming, and costly (Infectious Diseases Society of America 2009; Kulnych and Korn 2002; Vates et al. 2005). For some projects that pose only negligible risks to participants, meeting existing regulatory or institutional requirements is sufficiently onerous to discourage many legitimate research projects from being undertaken (Angrist 2010; O'Herrin, Fost, and Kudsk 2004). In response to these problems, rather than simply offering modifications to the existing framework, our remarks are intended to offer a solution that could make them more coherent. As we see it, the failure to distinguish negligible risk from greater risks and the failure to adequately appreciate research's social importance constitute critical oversights in research regulations. Our recommendations have direct bearing on the application of current regulations to several areas addressed by the proposed reforms: currently exempt activities, informed consent requirements, and minimizing information risks.

TWO MAJOR PROBLEMS THAT ARISE FROM CURRENT REGULATIONS

Exempt Activities

As the DHHS notice suggests, in some ways the current regulations are inconsistent in that they treat similar activities differently. When a project is deemed public health surveillance, or a quality assurance (QA) or quality improvement (QI) activity, it is exempt from the federal research regulations. Thus, informed consent and institutional review board (IRB) review are not required. When a similar project is counted as research, however, informed consent and IRB review requirements apply. There is no scientifically or ethically significant distinction between the exempt activities and those that are counted as research. Both activities employ scientific studies based on a theory-driven hypothesis; both involve systematic collection of data, analysis of the data, and drawing actionable conclusions that count as knowledge. Ethically, both activities rely upon contributions from human participants to achieve valuable societal

goals, while not exposing any individual to unreasonable burdens or risks.¹

Conducting public health surveillance, QA, and QI studies can provide important social benefits. Yet the criteria for drawing a line between what counts as research and what does not are vague. The U.S. regulatory distinction between treatment and research derives from the 1979 Belmont Report (National Commission for the Protection of Human Subjects 1979). The definition of "research" was then articulated in the 1991 "Federal Policy for the Protection of Human Research Subjects," informally known as the "Common Rule." According to this stipulation, "research" is "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" ("Protection of Human Subjects" 2009a). All scientific studies are, however, designed to produce knowledge, and all knowledge is generalizable, regardless of whether it comes from activities that are identified as research or as public health surveillance, QA, or QI. Data garnered from public health surveillance are analyzed, and the conclusions that follow from the analysis are the knowledge that supports interventions to contain infection, improve health and clinical outcomes, and prevent further spread of diseases. Similarly, QA data from the systematic documentation and analysis of hospital activities provide the knowledge that guides hospitals to assure the quality of their care. The knowledge generated from QA data allows institutions to detect and rectify practices that put people at risk, including deviations from standard operating procedures and unforeseen results of new cost containment measures. And data from QI activities lead to knowledge that is used to alter practice so as to achieve the highest quality care at the most reasonable cost. Analysis of QI data provides the knowledge base that allows institutions to compare the quality and efficiency of their performance to national databases, to implement programs that improve patient outcomes, and to avoid errors (Cohen et al. 2008). The knowledge gained is generalizable even when those at an institution initiating a QI intervention believe that it applies only to their own circumstances, because when it turns out that another institution confronts a similar circumstance, the QI data will be useful and relevant.

Using the current regulatory distinctions, 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 what to call their studies (Kofke and Rie 2003; Lynn et al. 2007). The controversy over whether Peter J. Pronovost's famous checklist study should have been counted as research or QI is a case in point (Baily 2008; Flanagan, Philpott, and Strosberg 2011; Gawande 2007; Kass et al. 2003; Miller and Emanuel 2008; Pritchard 2008; Pronovost et al. 2006). Dr. Pronovost and his institution determined that his standard of care interventions were QI, and therefore IRB review and

1. Variations on this argument are elaborated by Rhodes (2005a; 2005b; 2008a; 2008b; 2009).

obtaining informed consent from each intensive care unit (ICU) patient involved in the study were not required. If instead they had determined that the study was research, the IRB would have had to review it and the investigators would have had to obtain informed consent from each patient who was involved. As a QI activity, every patient could have been included in the study. As research, patients or surrogates could have withheld consent and refused to participate, excluding relevant data and skewing the study findings. The point is that experts disagree about whether the Pronovost study is research or QI. It is certainly important for research regulations to define what research is. Nevertheless, the current regulatory definitions that attempt to draw sharp lines between research, public health surveillance, QI, and QA (and between research and innovation) focus on distinctions that make no moral difference and have no scientific basis.

Even though most public health surveillance, QA, and QI activities are overseen by an agency or institutional committee, as exempt activities there is no regulatory framework that requires review and oversight. When activities meet the regulatory definition of research, in a sense, the current regulations create informed consent obstacles that are too great for investigators, particularly when the risks involved are negligible. At the same time, by exempting public health surveillance, QA, and QI from regulatory requirements the regulations do too little to assure participants and the public that these activities are well designed and involve only reasonable risks. As some agencies and institutes have recognized, some form of review and oversight should be required for all of these activities.²

In many circumstances, obtaining informed consent for studies that are exempt from the regulations is not possible whereas the public good that they serve is significant. For example, the Pronovost checklist study could not have obtained consent from many of the ICU patients as they were either unconscious or lacked capacity as a result of their condition (Kofke and Rie 2003). In other circumstances, obtaining informed consent is inefficient or counterproductive. In public health surveillance, for instance, the risks to participants are typically minuscule, and data may be needed from every individual for cancer registry tracking of the population or from every individual 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 thereby divert scarce public health resources from other socially important activities. Again, because obtaining informed consent entails allowing people to refuse participation or withdraw from a project, a source of bias may be introduced to these critical activities. Selection bias remains one of the most frequent deficiencies of clinical studies. Some degree of selection bias is an acceptable price to pay in clinical research in which the risks of harm can be significant, where only small numbers

of participants are needed, and where the participation decision turns on numerous personal factors. In population studies that involve no physical risk to participants and where it is important to include everyone in the population, selection bias may be a serious problem and justify exemption from informed consent. This issue can be particularly significant because refusals could follow socioeconomic demographics; thus, allowing people to opt out could mean losing vital information from populations that researchers have the greatest need to study. Regulations should aim at minimizing such problems instead of exacerbating them.

The difference between scientific activities called "research" and those that are not is imprecise because often there is no significant difference. Rather, there is only a stipulation framed in uninformative terms. In contrast, the most ethically significant difference between studies is the level of risk to which human subjects are exposed and the importance and likelihood of the expected benefits. As such, we propose that the regulatory focus should emphasize the assessment of participants' exposure to risk in relation to the anticipated societal benefits, rather than the determination of whether or not a scientific study should be considered research.

Biobank Studies

The advent of genetic biobanks, sample banks, and human microbiome research has created further dilemmas. Genome research and microbiome research, far more than clinical trials, require broad participation. Furthermore, most of the sample collection and future use associated with microbiome and biobank genetic studies are likely to involve only minute physical risks, the kind of risks involved, say, in having a cheek swab. In most cases, the physical risks are so small compared with the risks of everyday life, that we consider them *de minimis*. Although some authors have cautioned about risks to privacy in biobank research, policies and security measures have been put in place to minimize the chance of a breach in confidentiality.

Biobanks and sample banks obtain consent from those who donate their samples. When samples are collected, however, neither researchers nor donors can know the full extent of the research projects that will be performed using their samples in the future. Although donors can give informed consent to having blood samples drawn and blanket consent for future research use of their samples, they cannot at that time provide meaningful informed consent to any specific future studies because they have no information about those future studies. When blanket consent is obtained, biobanks and sample banks are unable to conform with several of the General Requirements for informed consent enumerated in the Common Rule at 45§46.116a&b. Although the Common Rule already permits IRBs to waive requirements for informed consent when "the research involves no more than minimal risk to the subjects" and when "the research could not practicably be carried out without the waiver or alteration," researchers fear that IRBs will be reluctant to grant waivers, particularly for studies involving genetic material.

2. It goes beyond the scope of this article to define just how oversight should be implemented. Each institution, health department, IRB, biobank, or agency could create an adequate mechanism.

To avoid the informed consent problem, some centers resort to anonymizing samples. This makes it nearly impossible to re-identify the sample donors, thereby protecting donor privacy.³ Although anonymizing allows investigators to use the materials without obtaining informed consent, it also means that investigators are unable to match samples with the donors' medical record or contact donors again when doing so would enhance research aims. Such measures limit the sample's associated phenotype information, and thereby severely diminish its scientific value.

RECOMMENDATION FOR A NEW CATEGORY OF RESEARCH RISK

In light of these considerations, we suggest that a new category of research risk be created, *de minimis* risk. Existing U.S. federal regulations and some IRB guidance documents refer to three categories of research risk: (1) minimal risk, (2) a minor increase over minimal risk, and (3) more than a minor increase over minimal risk. According to 45 CFR 46.102(i), "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" ("Protection of Human Subjects" 2009a). For example, a study involving only a blood draw would count as minimal risk because the risks of the procedure are no greater than the risks associated with a routine physical examination. We use the term "*de minimis* risk" to indicate a subcategory of minimal risk that would apply to studies involving only negligible physical risk where nothing dangerous is done to the body and no likely or significant social or psychological harms are foreseen. Obtaining informed consent should *not* be an absolute requirement for studies that involve only this subcategory, vanishingly small level of *de minimis* risk.

Our recommendation would make permission to conduct a study without informed consent the default position for studies that involve only *de minimis* risk. Thus, once a study was determined to involve only *de minimis* risk, it would be exempt from informed consent requirements and no IRB waiver would be required. It may still be appropriate to obtain oral agreement or blanket consent from study participants when investigators and/or reviewers determine that obtaining it is feasible and the burdens involved would be reasonable.⁴ For example, obtaining a cheek swab or using a leftover blood sample involve only *de minimis*

risk. In most circumstances, explaining that the sample is to be used for research and allowing the person to opt out of providing the sample is entirely feasible because the person is present and there are no significant burdens entailed by eliciting agreement. When it is feasible, because the effort involved in explaining and allowing for opting out is reasonable, obtaining agreement for cheek swab studies is justified and should be performed. In a time-sensitive study that involves unconscious trauma patients, the default position of not requiring informed consent or even agreement would apply because the risks involved are *de minimis*.

Our recommendations also incorporate a requirement for balancing risks and benefits. The three most important historical documents that articulate standards of research ethics explicitly endorse a view that research risks should be balanced against the societal benefits that the project promises. For example, Principle 6 of the 1947 Nuremberg Code states that "The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment" (*Trials of War Criminals* 1949). Similarly, in the original 1964 version of the Declaration of Helsinki, Basic Principle 4 states that "the importance of the objective is in proportion to the inherent risk to the subject," and Basic Principle 5 states that "Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others" (World Medical Association 1964). Also, The Belmont Report discusses the importance of the "Assessment of Risks and Benefits" in Part C, Application 2, and the Common Rule, 45CFR46.111a2, Criteria for IRB approval of research, provides that "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" ("Protection of Human Subjects" 2009b).

Nevertheless, bioethicists and IRB members often seem to give insufficient weight to the importance of social benefit. Instead they focus narrowly on protecting research participants from any harm, regardless of how unlikely, fleeting, or trivial. When the physical harms involved are negligible (e.g., small, momentary discomfort), and the psychological and social harms are unlikely and not significant, and when the study promises to provide a societal benefit, a reasonable assessment should conclude that the balance tips towards promoting scientific advance. Policies that consider just the risks and minimize the importance of the possible social benefits that research could provide express a distorted view of what ethics entails and thus produce regulations that are ethically flawed.

The category of *de minimis* risk would apply to a number of kinds of research and play a role in policy governing the conduct of such studies. Some examples of how the new category would be relevant are discussed below:

Exempted Research

The Common Rule, 45CFR46.101b, already implicitly employs such a standard when it exempts several kinds of

3. Methods of anonymization, to separate research samples from information about the donor, were devised to protect donor privacy. Recently, some critics and bioinformatics experts have argued that these measures do not provide absolute privacy protection of research samples (Dreiseitl, Vinterbo, and Ohn-Machado 2002; Malin et al. 2011; Rothstein 2010; Wjst 2010).

4. According to our use of the terms, "informed consent" is different from "oral agreement" and "blanket consent." As we explained earlier, it is not possible to provide informed consent when the future use of a sample is not known. Without that information, a sample donor may still agree to allow the sample to be used or even provide written blanket consent to unknown future uses.

studies from the regulations (“Protection of Human Subjects” 2009c). This section of the Common Rule exempts educational research, food evaluation, research involving existing data or specimens when they are publicly available, and research involving existing data when they cannot be identified or linked to the subjects. All of these activities should be identified as research, and it should be noted that all of these scientific studies involve only *de minimis* risk. Our proposal would include these presently exempt studies, as well as most studies that employ survey and focus group methodologies, under the new *de minimis* risk research category, thereby making explicit the reason for their informed consent and IRB review exemption.

Biobank and Sample Bank Studies

Even when the process of sample collection itself involves more than *de minimis* risk, subsequent use of samples in biobank and sample bank studies involves only *de minimis* risk of physical harm. The only foreseeable harms that we have identified related to the use of already collected samples concern confidentiality violations. These include the possible social and associated psychological harms from allowing legal proceedings, insurers, family members, employers, or others to violate confidentiality constraints and gain access to biobank materials. NIH Certificates of Confidentiality have been developed to address that need. Yet, some have argued that the Certificates are inadequate protection (Beskow, Dame, and Costello 2008; Currie 2005; Hermos and Spiro 2009; Melton 1990). Thus, the need to devise an effective mechanism for protecting samples from legal proceedings and other illegitimate access remains. When biobanks and sample banks are safeguarded from use in criminal investigations, immigration proceedings, insurance markets, and the like, and from confidentiality violations that could involve sharing personal information with family members or employers, studies using these samples will involve only *de minimis* risk. Directly responding to concerns about safeguarding the confidentiality of biobanks with stronger protections is a coherent and effective way of dealing with the problem. It is also a far better alternative than either having investigators sacrifice the value of samples by anonymizing them, or invoking the regulation’s definition of “human subject” to re-describe biobank and sample bank studies as something other than human subject research (e.g., human non-subject research) (Brothers and Clayton 2010).

Furthermore, to directly address the problems associated with obtaining informed consent, regulatory requirements should be adjusted to incorporate an exemption from informed consent for biobank studies. This can most easily be accomplished by classifying further research uses of samples as *de minimis* risk research. This should be the rule even for studies using de-identified samples linked to medical records (as opposed to anonymized samples). Because the physical risks involved in using these samples are only *de minimis*, and because recontacting sample donors to obtain study-specific informed consent is costly, burdensome,

sometimes unwelcome, and may not be feasible, informed consent for subsequent studies should not be required.

Research on Populations

Public health studies, as well as QI and QA studies that do not involve direct interference with participants’ bodies (e.g., sampling effluent from a community), should be considered *de minimis* risk. Because of the vanishingly small likelihood of physical risk, informed consent should not be required for these activities whenever general participation is needed and when obtaining agreement from individuals is not feasible (e.g., tracking infectious disease, adopting new methods of decontamination in a hospital).⁵

That said, investigators in this age of genetic and human microbiome research will increasingly need to rely on community trust and education to advance their work. Investigators and their institutions should establish transparent processes to consult with legitimate representatives of the communities involved to review the risks and benefits of research conducted within the community. Such processes are not currently required by regulations governing human subject research, but community consultation is an effective vehicle for establishing trust. It can also play a role in educating communities about the value of the research and encourage the broad participation that is critical to valid and reliable studies.

Discarded Biological Samples

In the course of clinical care, biological samples are routinely collected for analysis. The material that remains after its clinical purpose has been accomplished is often discarded. Some of these otherwise discarded samples will be valuable in various lines of research. The physical risks involved in using these samples are only *de minimis*, because nothing additional is done to the body of the sample donor. Although obtaining robust informed consent is not possible at the point when samples are collected, because it is often feasible to allow patients to opt out of the future research use of their samples, and because providing the opportunity to opt out would make the process transparent and more acceptable to patients, institutions should adopt an opt-out policy for the research use of remaining biological samples. Such a practice would allow remaining de-identified samples linked to medical records from patients who did not refuse to participate to be used in research without explicit informed consent.

5. Some individuals may worry about the possible psychological or social harms associated with such population research. An objective assessment of the social importance of developing accurate data and an objective analysis of the significance and likelihood of possible psychological or social harms could determine whether or not proceeding with a study without informed consent was well justified.

Patients without Decisional Capacity

In some states and in some institutions, surrogate consent for research with patients who lack decisional capacity is restricted or not accepted (Gong et al. 2010). Yet the value of collecting samples from people who cannot consent could be significant in some studies. Because of the negligible risks of harm, and the importance of advancing the social good, the involvement of patients without decisional capacity should be allowed for studies that involve only *de minimis* risk.

CONCLUSION

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 avoids the confusion engendered by relying on the stipulative and vague definition of research that leaves public health agencies and institutions with irresolvable dilemmas. A *de minimis* risk category also reduces the possibility of bias in population studies and reduces unreasonable obstacles that have inhibited research.

Allowing studies to proceed under the category of *de minimis* risk would 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*. Establishing this new category of risk, however, would not be granting automatic exemption from obtaining participants' agreement or blanket consent. The importance of each study, the feasibility of obtaining agreement, and the risks to the participants would still need to be assessed and balanced. When agreement or blanket consent can be obtained with a reasonable effort, investigators should obtain it even when the studies involve only *de minimis* risk. ■

REFERENCES

- Angrist, M. 2010. Urge overkill: Protecting deidentified human subjects at what price? *American Journal of Bioethics* 10(9): 17–18.
- Baily, M. A. 2008. Harming through protection. *New England Journal of Medicine* 358(8): 768–769.
- Beskow, L. M., L. Dame, and E. J. Costello. 2008. Certificates of confidentiality and the compelled disclosure of research data. *Science* 322(5904): 1054–1055.
- Brothers, K. B., and E. W. Clayton. 2010. "Human non-subjects research": Privacy and compliance. *American Journal of Bioethics* 10(9): 15–17.
- Clayton, E. W. 2005. Informed consent and biobanks. *Journal of Law, Medicine, and Ethics* 33(1): 15–21.
- Cohen, A. B., J. D. Restuccia, M. Shwartz, et al. 2008. A survey of hospital quality improvement activities. *Medical Care Research and Review* 105: 1–2.
- Currie, P. M. 2005. Balancing privacy protections with efficient research: Institutional review boards and the use of certificates of confidentiality. *IRB: Ethics and Human Research* 27(5): 7–12.
- Department of Health and Human Services. 2011. *Human subjects research protections: Enhancing protections for research subjects and reducing burden, delay, and ambiguity for investigators*. July 22. Available at: <http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18792.pdf>
- Dreiseitl, S., S. Vinterbo, and L. Ohno-Machado. 2002. Disambiguation data: Extracting information from anonymized sources. *Journal of the American Medical Informatics Association* Nov–Dec 9(6 Suppl 1): S110–S114.
- Emanuel, E. J., and J. Menikoff. 2011. Reforming the regulations governing research with human subjects. *New England Journal of Medicine* 365: 1145–1150.
- Emanuel, E. J., A. Wood, A. Fleischman, et al. 2004. Oversight of human participants research: identifying problems to evaluate reform proposals. *Annals of Internal Medicine* 141: 282–291.
- Flanagan, B. M., S. Philpott, and M. A. Strosberg. 2011. Protecting participants of clinical trials conducted in the ICU. *Intensive Care Medicine* 26(4): 237–249.
- Fost, N., and R. J. Levine. 2007. The dysregulation of human subjects research. *Journal of the American Medical Association* 298(18): 2196–2198.
- Gawande A. 2007. A lifesaving checklist. *New York Times*, December 30, Available at: <http://www.nytimes.com/2007/12/30/opinion/30gawande.html?pagewanted=print>
- Gong, M. N., G. Winkel, R. Rhodes, L. D. Richardson, and J. H. Silverstein. 2010. Surrogate consent for research involving adults with impaired decision making: Survey of institutional review board practices. *Critical Care Medicine* 38(11): 2146–2154.
- Hermos, J. A., and A. Spiro. 2009. Certificates should be retired. *Science* 323(5919): 1288–1299.
- Infectious Diseases Society of America. 2009. Grinding to a halt: The effects of the increasing regulatory burden on research and quality improvement efforts. *Clinical Infectious Diseases* 49(3): 328–335.
- Kass, N., P. J. Pronovost, J. Sugarman, C. A. Goeschel, L. H. Lubomski, and R. Faden. 2003. Controversy and quality improvement: Lingering questions about ethics, oversight, and patient safety research. *Joint Commission Journal on Quality and Patient Safety* 34(6): 349–353.
- Kofke, W. A., and M. A. Rie. 2003. Research ethics and law of health-care system quality improvement: The conflict of cost containment and quality. *Critical Care Medicine* 31(3): S143–S152.
- Kulynych, J., and D. Korn. 2002. The effect of the new federal medical-privacy rule on research. *New England Journal of Medicine* 346: 201–204.
- Lynn, J., M. A. Baily, M. Bottrell, et al. 2007. The ethics of using quality improvement methods in health care. *Annals of Internal Medicine* 146(9): 666–673.
- Malin, B., G. Loukides, K. Benitez, and E. W. Clayton. 2011. Identifiability in biobanks: models, measures, and mitigation strategies. *Human Genetics* 130(3):383–92. Epub July 8, 2011.
- Melton, G. B. 1990. Certificates of confidentiality under the Public Health Service Act: Strong protection but not enough. *Violence and Victims* 5(1): 67–71.

- Miller, F. G., and E. J. Emanuel. 2008. Quality-improvement research and informed consent. *New England Journal of Medicine* 358: 765–767.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. Washington, DC: DHEW Publication No. (OS) 78-0012.
- O'Herrin, J. K., N. Fost, and K. A. Kudsk. 2004. Health insurance portability accountability act (HIPAA) regulations effect on medical record research. *Annals of Surgery* 239(6): 666–673.
- Pritchard, I. A. 2008. OHRP correspondence: Letter to Dr. Peter Pronovost regarding indwelling catheter procedures, pp. 1–4. Washington, DC: U.S. Department of Health and Human Services, Office for Human Research Protection.
- Pronovost, P., D. Needham, S. Berenholtz, et al. 2006. An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine* 355: 2725–2732.
- Protection of Human Subjects. 2009a. 45 C.F.R. pt.46. 102(d).
- Protection of Human Subjects. 2009b. 45 C.F.R. pt.46. 111(a).
- Protection of Human Subjects. 2009c. 45 C.F.R. pt.46. 101(b).
- Resnick, D. B. 2005. Eliminating the daily life risks standard from the definition of minimal risk. *Journal of Medical Ethics* 31: 35–38.
- Rhodes, R. 2005a. Rethinking research ethics. *American Journal of Bioethics* 5(1): 7–28. Reprinted as the “Most controversial article” in AJOB’s 10 year history, *American Journal of Bioethics* (2010) 10(10): 19–36.
- Rhodes, R. 2005b. Reply to comments on “Rethinking research ethics.” *American Journal of Bioethics* 5(1): W15–W18.
- Rhodes, R. 2008a. Response to de Melo-Martin: “On a putative duty to participate in biomedical research.” *American Philosophical Association Newsletter on Philosophy and Medicine* 7(2): 12–13.
- Rhodes, R. 2008b. In defense of the duty to participate in biomedical research. *American Journal of Bioethics* 8(10): 37–38.
- Rhodes, R. 2009. Research Ethics: A decent proposal. In *Cutting through the surface: Philosophical approaches to bioethics*, ed. P. Herissone-Kelly, S. Holm, and T. Takala, 143–160. Value Inquiry Book Series. New York, NY: Rodopi.
- Rhodes, R., and D. A. Moros. 2010. Privacy overkill. *American Journal of Bioethics* 10(9):12–14.
- Rothstein, M. A. 2010. Is deidentification sufficient to protect health privacy in research? *American Journal of Bioethics* 10(9): 3–11.
- Schwab, A. 2010. The recipe for overreaching regulation. *American Journal of Bioethics* 10(8):55–56.
- Trials of war criminals before the Nuremberg Military Tribunals under control council law*. 1949. No. 10, Vol. 2, pp. 181–182. Washington, DC: U.S. Government Printing Office.
- Vates, J. R., J. L. R. Hetric, K. L. Lavin, G. K. Sharma, R. L. Wagner, and J. T. Johnson. 2005. Protecting medical record information: Start your research registries today. *Laryngoscope* 115: 441–444.
- Wjst, M. 2010. Caught you: Threats to confidentiality due to the public release of large-scale genetic data sets. *BMC Medical Ethics* 11: 21.
- World Medical Association. 1964. *Declaration of Helsinki*. Finland. Available at: <http://www.cirp.org/library/ethics/helsinki> (accessed July 20, 2011).