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Proposed Directions of Change to the Common Rule for Protecting Human Research Participants

RAND Responses

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Published 2011 by the RAND Corporation
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PREFACE

In July 2011, an Advance Notice of Proposed Rulemaking (ANPRM) was published in the Federal Register titled “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators.” Submitted by the Office of Human Research Protection (OHRP) of the Department of Health and Human Services (HHS), the notice proposes several directions of change in the Common Rule (45 CFR 46, Subpart A) that has regulated Institutional Review Board (IRB) protection of human research participants for over two decades with only minor revision (<http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18792.pdf>). Members of RAND’s Human Subjects Protection Committee, which serves as its IRB under a Federalwide Assurance (FWA 00003425), prepared comments to the ANPRM and sent them to the Federal Register on October 25, 2011. That response is currently in the public domain.

Because a large percentage of comments are likely to come from institutions heavily oriented toward clinical-biomedical research, RAND’s purpose in publishing its response is to help ensure that social-behavioral science implications of the proposed changes are taken into consideration.

Questions or comments about this publication should be sent to RAND’s IRB Chair, Tora Bikson (tora_bikson@rand.org) at the following address:

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**RAND Response to Federal Register Notice Volume 76, Number 143:
Human Subjects Research Protections: Enhancing Protections for Research
Subjects and Reducing Burden, Delay, and Ambiguity for Investigators**

Foreword

Please accept and post the comments submitted here by the RAND Corporation in response to the Advance Notice of Proposed Rulemaking that outlines contemplated revisions to the Common Rule. RAND's comments reflect the experience of an institution engaged in a substantial amount and diverse range of human subjects research that is chiefly social, behavioral, and educational (versus clinical or biomedical) in nature. However, we have had an institutional human subjects protection committee fulfilling an ethical research review role since 1969. Thus, our comments are informed by a lengthy history of reviewing human subjects research.

These remarks, both general ones and question-specific responses, are organized under the key issues OHRP identified to help respondents structure their deliberations. For convenience of reference, we have repeated the OHRP issue description as well the specific question before each set of comments.¹

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¹ While OHRP grouped the 74 questions under 19 issues, we have responded only to those that are relevant to social, behavioral, and educational research, omitting those that seem exclusively or predominantly to pertain to biomedical or clinical studies.

² As of November 1, 2011.

Issue 1: Data Security Protections, Privacy, and Confidentiality

Current rule	Changes being considered	Rationale for change
Issue 1: There are no specific data security protections for IRB-reviewed research: regulations require IRBs to determine, for each study, “when appropriate [that] there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.”	Specified data security protections would apply to such research, calibrated to the level of identifiability of the information being collected.	IRBs were not designed to evaluate risks to privacy and confidentiality and often have little expertise in these matters. Setting uniform specific standards will help to assure appropriate privacy and confidentiality protections to all subjects, without the administrative burden of needing a specific committee review of each study.

The proposed change addresses a situation that probably holds at many institutions: IRB members are not typically knowledgeable or interested in the detail of data security. The proposed solution attempts to provide a uniform regulatory standard for data privacy and security and to export responsibility for oversight out of the IRB and into some other entity within the research institution (or else out of institutions altogether).

The policy changes being considered assume that current IRB oversight for data privacy and security is indeed inconsistent and/or inadequate; that superior protection for data privacy might be obtained through a fundamentally different regulatory approach not aligned with the function of IRBs; and that the administrative savings associated with reducing IRB oversight in this way would outweigh any incremental institutional compliance costs associated with the new scheme.

All of these threshold assumptions are open to debate, and the solution of imposing broad new data safeguarding regulations on the research community is not the only possible response to current problems. A more straightforward and more limited solution, for example, might be to require the integration of data security experts into existing IRBs (the practice followed at RAND for many years now). The export of data safeguarding responsibility out of IRBs runs the risk of transferring oversight responsibility to other institutional entities, such as the risk management function, that

do not typically have human subject protection as a top priority. It is difficult to anticipate what the impact of such a transfer might be—with regard to either data safeguarding or administrative cost.

While unburdening IRBs, the move to adopt formal regulatory data protections necessarily adds some burden to research institutions and to individual researchers. Unless the new regulatory scheme contemplates no institutional compliance mechanism whatsoever, it seems likely that the risk assessments, mitigations, and documentation costs associated with the new approach could be substantial (cf. HIPAA). In practice, major new compliance costs associated with data privacy regulation may well be beyond the reach of small social science and academic research units. We could imagine a future in which the result of the proposed new data safeguarding approach might be to degrade the privacy protection currently afforded to research data, while simultaneously adding to administrative costs and impeding the conduct of legitimate research at small institutions. That would be a perverse result, if indeed it occurred.

In a different vein, by following the HIPAA model for data privacy regulation, the OHRP has tacitly accepted the technical context that HIPAA addresses. Specifically, HIPAA rules largely focus on the protection of already-acquired static data sets in healthcare settings, and typically assume the identifiability of the data in determining the degree of protection required. For research purposes, it should be noted that it is in the course of data collection that data records are most clearly identified. We would expect, then, that the highest levels of protection will be required during the data collection process. In many instances in research settings, this will pertain to devices and settings not fully anticipated by the HIPAA rules (e.g., mobile devices or laptops used in public settings, such as homeless shelters or outdoors), audio files (for instance, from taped focus groups), and paper forms.

Put another way, we would question whether current HIPAA data privacy and security standards are well tuned to the data privacy problems that frequently occur in data collection activities in social science research. We suspect that OHRP would need to formulate significant additional guidance and specifications in order to craft a data safeguarding scheme that would provide appropriate protection in (non-healthcare-related) research contexts. And we suspect that those additional rules and specifications

might significantly increase the compliance costs and burdens that institutions would face in meeting their obligations under the rules.

In considering the application of common data protection requirements for research studies, another way to assess requirements for data protection is to ensure that they appropriately match any promises made to subjects (of confidentiality, non-identifiability, data destruction at conclusion of research)—i.e., that processes are in place to ensure that those promises are kept.

A HIPAA-based regulatory scheme for data protection takes the opposite approach, and creates the likelihood of overprotection of data in some instances where risk is minimal and of underprotection in other instances where risks to human subjects is considerable. Again, the potential for perverse results seems to us to be very significant. Much depends on the contours of the new privacy rules that OHRP is now contemplating. While rules could probably be written to address some of the subtleties in risk associated with the conduct of research, it is not clear to us that it is possible to articulate a single, coherent regulatory data-protection standard; to have that standard closely aligned with current HIPAA rules; to reduce administrative oversight burdens and costs in connection with data protection; and to achieve satisfactory protection of human subjects, all at the same time.

With these general comments in mind, we respond to questions 54–66 below.

Part A. Consistently Characterizing Information With Respect to Potential for Identification

Question 54: Will use of the HIPAA Privacy Rule’s standards for identifiable and de-identified information, and limited data sets, facilitate the implementation of the data security and information protection provisions being considered? Are the HIPAA standards, which were designed for dealing with health information, appropriate for use in all types of research studies, including social and behavioral research? If the HIPAA standards are not appropriate for all studies, what standards would be more appropriate?

We believe the HIPAA standards are general enough to apply to human subject research broadly, but that additional standards and guidance may need to be developed to address specific research activities or vulnerable populations not fully contemplated by HIPAA. Again, we may encounter new challenges in determining “reasonable” data protections in settings not typically anticipated by the HIPAA standards. Specifically, data collection and the management of qualitative data in collaborative environments (e.g., SharePoint sharing of field notes), and data collection and management in connection with vulnerable persons (e.g., prisoners, children), seem likely to pose particularly significant problems. Notably, it is difficult to understand how the HIPAA standards apply to semistructured qualitative data not readily parsed into closed-ended variables.

Question 55: What mechanism should be used to regularly evaluate and to recommend updates to what is considered de-identified information? Beyond the mere passage of time, should certain types of triggering events such as evolutions in technology or the development of new security risks also be used to demonstrate that it is appropriate to reevaluate what constitutes de-identified information?

OHRP’s question appears to be compelled by theoretical demonstrations of re-identification. We don’t know that this concern corresponds to a real-world data safeguarding problem, however: i.e., how often does illicit re-identification of de-identified data really occur in practice, in any manner that puts human subjects at risk? However, if OHRP is going to assert a new set of data safeguarding standards, then periodic review of those standards (particularly in connection with de-identified data) seems like a reasonable thing to do. A regular five-year interval in formal review, with the ability to launch ad hoc reviews to address observed problems, seems like a reasonable approach.

Part B. Standards for Data Security and Information Protection

Question 58: Should the new data security and information protection standards apply not just prospectively to data and biospecimens that are collected after the implementation of new rules, but instead to all data and biospecimens? Would the

administrative burden of applying the rule to all data and biospecimens be substantially greater than applying it only prospectively to newly collected information and biospecimens? How should the new standards be enforced?

Clearly, there would be much greater protection if the proposed new standards apply retrospectively as well as prospectively. If OHRP chooses not to apply the new standards retrospectively, then it either implies that IRBs will need to continue doing some oversight of information risks in research for some new (but arguably retrospective) studies, over an indefinite period of time (undesirable)—or it implies that there won't be any oversight or protection for information risks in those studies (also undesirable).

The question about “administrative burden” evokes another question: “Administrative burden on whom?” Our intuition is that applying the new data security and information protection standards retrospectively will reduce the burden for IRBs. It might increase OHRP's enforcement burden (depending on what OHRP does to enforce the new standards); it might also increase the burden on some retrospective research projects that otherwise would not have to comply with the new standards. To us, the balance seems to be in favor of applying the new standards retrospectively. Assuming the new privacy standards are well framed and reasonable in the first place, we don't see why the research community shouldn't adhere to them, even for retrospective research.

How should the new standards be enforced? One obvious mechanism would be to set up some kind of OHRP enforcement and prosecution mechanism for going after violators—something that would place OHRP in an analogous role to what the Office for Civil Rights (OCR) plays in connection with HIPAA prosecutions today. We think that OHRP would need to have some role along these lines if researchers are going to take the new standards seriously. We also think that if OHRP does set up even a modest enforcement mechanism, tort liability under state law will pick up on the federal standards, such that violators will become subject to civil suit for breach of confidentiality or invasion of privacy when they breach the OHRP guidelines and an injury results.

The big enforcement question here is what role, if any, OHRP contemplates for institutional enforcement of the new privacy standards outside the IRB mechanism. If there is such a role, then the potential for major new compliance costs to institutions arises. If there is no such role, then concerns arise about whether protection for human subjects against privacy risks will be adequate. It's not clear that there is a single right answer here—but either way; OHRP would need to specify in detail what its intentions are with regard to requiring institutional oversight and enforcement in a new regulatory scheme for data safeguarding.

Question 59: Would study subjects be sufficiently protected from informational risks if investigators are required to adhere to a strict set of data security and information protection standards modeled on the HIPAA Rules? Are such standards appropriate, not just for studies involving health information but for all types of studies, including social and behavioral research? Or might a better system employ different standards for different types of research? (We note that the HIPAA Rules would allow subjects to authorize researchers to disclose the subjects' identities, in circumstances where investigators wish to publicly recognize their subjects in published reports and the subjects appreciate that recognition.)

RAND thinks one simple observation deserves mention: the HIPAA standards are already complicated. Any OHRP effort that involves developing “different standards to apply to different types of research” will inevitably become even more complicated. Greater complexity in applicable privacy rules is not desirable and should be avoided as much as possible.

In general, we believe that HIPAA standards for safeguarding the privacy and security of information should be sufficient to protect human subjects. It is not obvious to us why different standards or safeguards ought to apply to non-healthcare-related research. This being said, we do think there are additional subtleties to consider in the research context, given that some identifiable records will be very sensitive and others not so sensitive. The rules probably should in some way accommodate this difference. If we nevertheless want to keep the rules as simple as possible, perhaps the best way to formulate this is to stipulate that any research data that have the potential to pose meaningful risk of harm to human subjects, and that are identifiable, ought to be protected under the rules. That seems simple enough to articulate, at least.

Would study participants be sufficiently protected from informational risks under HIPAA-style privacy protections? Much depends on the details. Potential advantages include clearer standards, clear application to researchers, civil (and/or criminal) administrative enforcement via OHRP, and likely civil liability for major violations under state tort law. The drawback to the proposal is that the current regime of IRB involvement means that there is a group of people in every institution who are actually reviewing and thinking about every new research study and the informational risks it poses and whether the study can go forward or needs to be revised on that basis. In some ways, that's a much more aggressive form of oversight and monitoring than would occur under the new proposal, even though the proposal involves greater potential sanctions for researchers who violate the rules. Although we are guardedly optimistic that the proposed new rules would be sufficient to protect human subjects, we think it is entirely unknown whether or to what extent the proposed regime would represent a real improvement over the status quo.

Question 60: Is there a need for additional standardized data security and information protection requirements that would apply to the phase of research that involves data gathering through an interaction or intervention with an individual (e.g., during the administration of a survey)?

In general, we favor more standardization and stronger protection in research data collection activities over data storage. In our view, the former is where we actually observe greater risk to human subjects: We see more problems in data collection (when data are necessarily identified in most instances) than we typically do with analytic data sets where the best practices and institutional controls for data protection seem to be well-established. Examples of problems we periodically observe come from the loss of laptops and human error in the process of data collection (e.g., sending the wrong field notes to an informant/source). All of this being said, we do not have specific suggestions for how OHRP ought to augment or modify HIPAA rules in order to focus stronger protection and oversight on data collection activities. This is clearly a point where OHRP would need to articulate specific guidance and clarification in any new data safeguarding rules that it seeks to promulgate.

Question 61: Are there additional data security and information protection standards that should be considered? Should such mandatory standards be modeled on those used by the Federal government (for instance, the National Institute of Standards and Technology recently issued a “Guide to Protecting the Confidentiality of Personally Identifiable Information.”)?

Our experience with other, non-HIPAA-based data safeguarding standards (including NIST) is that they can be highly burdensome to comply with. We do not see the alternatives as being preferable to HIPAA as a template for new regulation, given the trade-offs between effective data protection and cost that are embedded in them. Note that there may be data safeguarding standards that apply to accounting and financial systems that are more manageable to implement (e.g., SAS 70) but may be less applicable to the kinds of data and risk that apply in the research context. One possible advantage to adapting accounting standards to the research context would be the availability of consultants to prepare the documentation and consultation that might be required.

Question 62: If investigators are subject to data security and information protection requirements modeled on the HIPAA Rules, is it then acceptable for HIPAA-covered entities to disclose limited data sets to investigators for research purposes without obtaining data use agreements?

Our intuition is that the answer here is mixed—both yes and no. Yes, in the sense that the new regulatory framework would make investigators subject to similar data security requirements as are HIPAA covered entities, so that for purposes of federal regulation and enforcement, disclosures to investigators from covered entities would still be subject to a very similar level of privacy protection under federal law.

No, in the sense that a HIPAA covered entity could still be at liability risk for making a disclosure to an investigator who then turns around and somehow does something with the data that violates the obligations of the covered entity under HIPAA (regardless of the fact such misbehavior might also put the investigator at liability risk under OHRP’s new rules). Our guess is that covered entities are still going to want data-use agreements, even though we don’t think that there’s likely to be any need for them from a federal regulatory perspective.

Question 63: Given the concerns raised by some that even with the removal of the 18 HIPAA identifiers, reidentification of de-identified datasets is possible, should there be an absolute prohibition against re-identifying deidentified data?

In practice, we think that an absolute prohibition against re-identifying data is probably unnecessary (and unlikely to prevent deliberately criminal misconduct like fraud or identity theft in any event).

Is there ever a situation where there might be a legitimate research purpose for re-identifying de-identified data? Probably. Could that activity safely be undertaken as long as the investigator then protected the re-identified data pursuant to OHRP's new privacy standards for identified data? Probably. Is this likely to come up very often, if "de-identification" really does protect the privacy of individual records in the first place? No, it shouldn't.

In general, we think that this issue ought to be covered by the initial consent given by human subjects to the data collection activity in the first place. The agreement provided at the time data is originally collected should follow the data forever. If the investigator means to allow for re-identification of data, then consent must be provided as a predicate to the original research or data collection activity.

Question 64: For research involving de-identified data, is the proposed prohibition against a researcher reidentifying such data a sufficient protection, or should there in some instances be requirements preventing the researcher from disclosing the de-identified data to, for example, third parties who might not be subject to these rules?

We think that the purpose of de-identified data sets is precisely to be able to use and share data for research purposes without having to worry about posing informational risk to human subjects. The essential question, then, is whether de-identification is real and not readily subject to being reversed, in which case there shouldn't be restrictions on sharing a de-identified data set: or whether de-identification is a sham and is never sufficient to safeguard the privacy interests of research subjects, in which case a de-identified dataset should never be shared. OHRP needs to revisit the issue of whether de-identification is sufficiently robust to be maintained at all as a part of its new privacy law framework; whether the risks of re-identification are truly significant in

practice; and whether the key concerns with re-identification involve actual research activities as opposed to criminal expropriation of data for purposes of identity theft or fraud.

Question 65: Should registration with the institution be required for analysis of de-identified datasets, as was proposed in Section II(B)(3) for Excused research, so as to permit auditing for unauthorized re-identification?

The drawback to the proposed registration is that it creates more administrative burden and oversight in connection with an activity that was originally contemplated to be low risk (i.e., working with a de-identified dataset). Again, as noted above in answer to Question 64, if there is truly a significant risk associated with re-identifying a de-identified dataset, then maybe we should simply get rid of the HIPAA-style provisions that allow investigators to use de-identified datasets without having to worry about privacy or security issues.

This question boils down to weighing the benefits of added oversight against the burdens and costs of that oversight. If unauthorized re-identification is an uncommon or small problem, then registration is unlikely to be helpful. We are concerned that the burden proposed here, "...auditing for unauthorized re-identification," could be dramatically out of scale with the risk, such that registration is difficult to justify.

Question 66: What entity or entities at an institution conducting research should be given the oversight authority to conduct the audits and to make sure that the standards with regard to data security are being complied with? Should an institution have flexibility to determine which entity or entities will have this oversight responsibility for their institution?

In our view, this question presumes that institution-level audits will indeed be conducted around re-identification of de-identified data. As we stated in the answer to Question 65, we are not convinced that this kind of auditing is likely to be cost-effective or cost-justified. Such auditing is likely to get very technical very quickly and might require significant computer and statistical expertise, as well as familiarity with the Common Rule, OHRP's privacy standards, and competence in doing internal investigations and compliance work. We suppose this kind of auditing could be done by

the institution's general counsel or compliance officer, with support from appropriate technical staff (possibly affiliated with the IRB). But much depends on the specific contours of the proposed audits; how audit authority and responsibility would fit into the proposed new privacy scheme; and what role, if any, IRBs would have in carrying out such audits.

Issue 3: Scope of Applicability of Federal Protections

Current rule	Changes being considered	Rationale for change
Issue 3: Federal protections only apply to studies that are funded by certain federal agencies (Common Rule agencies), or to clinical investigations that involve products regulated by the FDA.	Regulations would apply to all studies, regardless of funding source, that are conducted by a U.S. institution that receives some federal funding for human subjects research from a Common Rule agency.	Many have called for legislation to extend the Common Rule protections to all research with human subjects conducted in the U.S., regardless of funding source. This change would help narrow the current gap in protections.

Question 71: Should the applicability of the Common Rule be extended to all research that is not Federally funded that is being conducted at a domestic institution that receives some Federal funding for research with human subjects from a Common Rule agency?

RAND strongly supports this proposed regulatory change.

As the ANPRM notes, many institutions already voluntarily extend the applicability of their FWAs to all research involving human subjects, regardless of the source of funding. Since 1980, RAND has extended the applicability of the Belmont guidance for ethical conduct of research, as now reflected in the Common Rule, to all of the human subjects research it conducts. On the basis of our experience, we support the proposed regulatory change for both principled and practical reasons.

On the one hand, extension of the Belmont principles contributes to a culture that consistently values the ethical quality of research as envisioned in that report. Currently, even research to which 45 CFR 46 applies but is determined to be exempt from review is nonetheless obligated to adhere to these principles. The clear basis is that all research involving human participants should be conducted ethically, even if it doesn't require further IRB review.

The proposed change will further promote the principle of fairness by leveling the playing field for competitively bid research. Under the current system, institutions that apply the human participant protections afforded by the Common Rule across all funding sources are systematically disadvantaged in comparison with competitors who do not need to take these ethical constraints into account; as a result, participants in some competitively awarded research may be put at risk of harms that might have been avoided if a different institution had won the project.

Additionally, the proposed change might help curtail IRB "shopping" while at the same time precluding institutions from gaming the system by deciding whether or not IRB review will be required for a non-federally-funded project for competitiveness reasons, even if the project involves more than minimal potential risk to human participants.

On the other hand, there are practical benefits to such an extension of the Common Rule. Among them, two are salient. First, projects supported by a non-federal source often receive subsequent supplemental or follow-on funding from an agency bound by the Common Rule. That would then require IRB review that would, at minimum, entail a delay and further might necessitate procedural changes; both would be costly in terms of time and effort and may have negative impact on the scientific quality of the research. Second, many peer-reviewed research journals—not just those in clinical and biomedical fields but also in social and behavioral research domains—will not accept papers submitted for publication without evidence of IRB review and approval.

Issue 4: Reporting of Adverse Events

Current rule	Changes being considered	Rationale for change
Issue 4: Adverse events and unanticipated problems occurring in research are reported to multiple agencies and with various time-lines, with no central database as a repository for such data.	A single web site would be created for the electronic reporting of all such events: this would meet all federal reporting requirements and the collected data would be stored in a single database. Reporting requirements would be harmonized across agencies.	This reform would enhance the capacity to harness information quickly and efficiently to identify and respond to risks from experimental interventions, while also decreasing administrative burdens imposed by existing framework.

RAND opposes the proposal to create a centralized database and procedures to report unanticipated problems and adverse events, except in highly specified cases involving clinical or biomedical research. Such a database would be useful only if the definitions of these constructs (“unanticipated problems,” “adverse events”) and their relationships are clarified contextually and only if there is a well-articulated explanation of how these terms are to be interpreted in ways that enable and facilitate generalizable research. Clearly defined fields in event reports that would enable meaningful data comparisons across research projects in varied health domains could do a great deal to support evidence-based decisionmaking in practice as well as further clinical/biomedical research efforts. However, inclusion of the majority of social, behavioral, and educational research would likely increase IRB burden while not yielding data useful for analysis or for enhancing human participant protections. Further, we want to call attention to the effort and cost of maintaining an up-to-date, accurate, and usable centralized data repository; it is critical to determine the likely user population and to involve representative users in its development if it is to have any value at all. Finally, it would be important that reporting to such a centralized database *not* be seen as a substitute for interactions between projects and IRBs or among investigators pursuing multi-site projects employing common protocols.

Question 67: Is the scope of events that must be reported under current policies, including the reporting of certain “unanticipated problems” as required under the Common Rule, generally adequate?

The scope of reportable events is not adequately specified and needs improvement, particularly in the social-behavioral research domains and particularly where nonmedical effects (e.g., social and informational risks) are involved.

Current OHRP guidance defining “unanticipated problems involving risks” refers the construct of risk both to the research procedures themselves and to the characteristics of the subject population. The latter condition especially warrants clarification in relation to social-behavioral research for well-understood reasons—“risks” are to be conceptualized in relation to the life of an average healthy U.S. resident. Further, current OHRP guidance defines adverse events in terms of “untoward or unfavorable *medical*” occurrences. Although the guidance indicates that while resultant harms most often occur in the context of biomedical research, they can also occur in social-behavioral studies; the scope of the latter circumstances is most notably in need of specification.

Question 68: With regard to data reported to the Federal government:

- a. Should the number of research participants in Federally funded human subjects research be reported (either to funding agencies or to a central authority)? If so, how?**
- b. What additional data, not currently being collected, about participants in human subjects research should be systematically collected in order to provide an empirically based assessment of the risks of particular areas of research or of human subjects research more globally?**
- c. To what types of research should such a requirement apply (e.g., interventional studies only; all types of human subjects research, including behavioral and social science research)? In addition, are there other strategies and methods that should be implemented for gathering information on the effectiveness of the human subjects protection system?**

We begin our response to the envisioned centralized database by responding first to subquestion c. The envisioned data repository should be restricted to clinical/biomedical studies, whether interventional or observational, that have well-specified data fields

where findings could reasonably be subjected to aggregation and/or meta-analysis. This condition would rarely apply to behavioral, social, or educational research, even to intervention studies, apart from those studying psychological or behavioral health and relying on standardized diagnostic clinical measures. Research that does not rely on standardized data definitions would not be productive to include in a centralized event database. Qualitative data from semistructured interviews and surveys would not be worth attempting to include in any centralized reporting procedures.

For highly structured, well-defined datasets, it would be highly desirable to report numbers of participants in addition to numbers who suffered specifically defined unanticipated adverse events; this is critical to estimating the importance of the events when aggregating them (see subquestion a). With respect to subquestion b, the response should depend on the answer to c—certain types of standardized information are relevant only given the nature of the projects that will be subject to standardized reporting. At minimum, across all reports, dates of the most current report should be provided. Additionally, for clinical/biomedical projects, it would be well to report, in addition to adverse events, events that are regarded as “near misses” (that is, events that would have resulted in unanticipated adverse outcomes except for an emergency intervention triggered by systematic safety monitoring and/or chance observation).

Question 69: There are a variety of possible ways to support an empiric approach to optimizing human subjects protections. Toward that end, is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?

This question is one that itself is best answered empirically. In pursuit of an answer, it would be desirable to find out from the relevant federal agencies the types of adverse event information they now use and the form in which they would like to have such information, and then to run some prototype trials. It is a costly endeavor to build and maintain such a database and ensure that it is up-to-date and reliable, so assuring its integrity and value to the expected user base is a critical consideration. We also want to underscore the need to promote real-time sharing of information about adverse events among collaborating investigators in multi-site protocols.

Question 70: Clinical trials assessing the safety and efficacy of FDA-regulated medical products (i.e., phase II through IV studies) are generally required to register and, following study completion, report summary results, including adverse events, in the publicly accessible database ClinicalTrials.gov. Is the access to information on individual studies provided by this resource sufficiently comprehensive and timely for the purposes of informing the public about the overall safety of all research with human participants?

Because RAND does not engage in this type of research, we have no specific response to the question. However, we suggest that the response to question 69 above is relevant.

Issue 5: Nature and Elements of Informed Consent

Current rule	Changes being considered	Rationale for change
Issue 5: Current provisions of the Common Rule provide only basic information about the elements of informed consent and how consent documents should be written. Many consent forms are too long and hard to understand and fail to include some of the most important information.	The regulations would be revised to provide greater specificity about how consent forms should be written and what information they should contain. The goal would be consent forms that are shorter, more readily understood, less confusing; that contain all of the key information; and that can serve as an excellent aid to help someone make a good decision about whether to participate in a study.	The informed consent of the subject is critical to the conduct of ethical research. The proposed changes will substantially enhance the quality of consent in many studies.

RAND supports the aim of making consent forms clearer, shorter, and more effective. The question is whether more specific rules about what written consents should contain will accomplish that goal. With a few exceptions, adding additional specific instructions to the Common Rule specifying the content of consents and publishing approved consent templates would seem unwise. Doing so risks exacerbating the very ills sought to be remedied by overemphasizing the consent form at the expense of the consent process.

Question 35: What factors contribute to the excessive length and complexity of consent forms, and how might they be addressed?

In our experience, the excessive length and complexity of consent forms result from the tendency of some researchers and IRBs to rely on forms from past research projects, regardless of suitability to the project in question; the informal or formal adoption of conventions and favored usages by certain IRBs (a problem often acutely present in multi-site studies involving review by several IRBs); and the idiosyncratic requirements of government sponsors or regulators (e.g., a school district sponsor's blanket requirement that all consents include a particular statement or disclaimer, or a government agency's insistence that certain language and no other be used in a consent form to describe the protections afforded by a certificate of confidentiality). All of these factors share one thing in common: a failure to approach informed consent as a process.

Existing OHRP guidance rightly emphasizes the need for IRBs to treat consent as "a process, not just a form" (<http://www.hhs.gov/ohrp/policy/ictips.html>). This same notion is also recognized (albeit less explicitly than might be hoped) in the language of the Common Rule, which instructs IRBs to review the adequacy of the "consent procedure," as opposed to the consent form. See, e.g., 45 CFR 46.116(c), (d). This focus on ensuring the presence of elements of the consent procedure rather than specific language in a consent form allows IRBs the flexibility to consider the particular circumstances of the project under review and tailor the procedure to ensure that subjects are given sufficient information to make an informed and autonomous decision to participate.

One strategy to combat the factors leading to long, complex forms is to revise the relevant portion of the Common Rule (45 CFR 46.116) to make more explicit the nature of informed consent as a process tailored to the circumstances of the research project under review. Where consent forms are employed, researchers should avoid reliance on generic formulations, favored usages and conventions followed for no better reason than they were once used before. The Code of Ethics for the American Anthropological Association provides language that may be instructive: "Informed consent, for the purposes of this code, does not necessarily imply or require a particular written or signed form. It is the quality of the consent, not the format, that is relevant." (1998 AAA Code of Ethics, Principle III.A.4, <http://www.aaanet.org/committees/ethics/ethcode.htm>). Of course, requiring consents to be written in language as brief and simple as possible would also help.

Question 36: What additional information, if any, should be required by the regulations to assure that consent forms appropriately describe, in clear and concise language, alternatives to participating in the research study and why it may not be in their best interests to participate? What modifications or deletions to the required elements would be appropriate?

Modifying the Common Rule to include specific requirements as to the content of consent forms would be unwise. Doing so overemphasizes the consent form at the expense of the consent process. Moreover, the Common Rule already requires that the consent process provide, in “language understandable to the subject,” information giving that subject “sufficient opportunity to consider whether or not to participate ” 45 CFR 46.116(a). If these instructions are followed, subjects will necessarily be apprised of risks attendant to research and to the voluntary nature of participation.

Question 37: Would the contemplated modifications improve the quality of consent forms? If not, what changes would do so?

We think not. These modifications overemphasize the importance of the consent form at the expense of the consent process. We would suggest instead that the regulations be modified to specifically emphasize consent as a process rather than a form. Where consent forms are used, investigators should avoid generic forms and templates. Instead, they should use clear, concise language tailored to the circumstances of the specific project and aimed at informing the subject of *all facts material to the decision to participate*.

Question 38: Should the regulations require that, for certain types of studies, investigators assess how well potential research subjects comprehend the information provided to them before they are allowed to sign the consent form?

We think the existing regulations already sufficiently address this issue by requiring that investigators provide, in language understandable to the subject, information giving the subject sufficient opportunity to consider whether or not to participate. Additional safeguards (in Subparts C and D) apply to prisoners and children, groups who often have diminished capacity to consent. In appropriate cases, IRBs may rely on these

regulations to require that researchers confirm comprehension before research proceeds. To impose a more general requirement that researchers obtain confirmation would appear unnecessary and unduly burdensome, at least for most social and behavioral research involving minimal risk.

Question 39: If changes are made to the informed consent requirements of the Common Rule, would any confirming changes need to be made to the authorization requirements of the HIPAA Privacy Rule?

Not necessarily. The HIPAA Privacy Rule and the Common Rule address different issues and serve different purposes. A HIPAA authorization establishes the conditions under which a covered entity may use or disclose protected health information, including for research. Such an authorization must be in writing, and it must contain certain “core elements” and “required statements.” These elements and statements have to do with factors pertaining to the disclosure itself, including who is authorized to get the health information, what information will be disclosed, and how the authorization may be revoked. See, e.g., 45 CFR 164.508(c)(1), (2). By contrast, consent under the Common Rule may be written or oral and pertains to the more general issue of securing agreement to participate in research, regardless of whether such research involves disclosure of health information.

Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required? For example, should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?

We believe there are a number of changes to existing regulations that could improve the informed consent process. It would be a mistake, however, to pursue an approach that simply adds to the existing list of items that must be disclosed (such as relationships between the investigators and the study sponsors). Doing so would complicate the regulations further, thus increasing administrative burden of compliance on regulated actors. Perhaps more importantly, it would focus attention on the checklist of “required” disclosures without regard to the degree to which such disclosures meaningfully improve the informed consent process. If revisions are to be made, the focus should

instead be on articulating general principles aimed at ensuring full and informed consent that can be applied across many different research contexts.

First, as noted above, we suggest revising 45 CFR 46.116 to make explicit the nature of informed consent as a process that must be tailored to the circumstances of the research project under review. In this process, consent forms may play a part, but forms are not a substitute for consent. And forms should be brief, clear, and tailored to the study at hand.

Second, we suggest adding, perhaps as a superseding and initial element or principle of informed consent, the requirement that *researchers disclose all information they reasonably suspect to be material to a subject's decision to participate*. This broad formulation avoids adding to the checklist of potentially irrelevant items and instead puts the focus where it most belongs. This approach is generally consistent with the common law of medical informed consent in most states, which requires physicians to disclose information potentially material to the patient. See Merz & Fischhoff, "Informed Consent Does Not Mean Rational Consent: Cognitive Limitations on Decision-Making," 11 *J. Legal Med.* 321 (1990). It is also consistent with catchall general principles contained in the professional codes of conduct of many professional societies and organizations. See, e.g., Ethical Principles of Psychologists and Code of Conduct, Standard 8.2 (requiring disclosure of "foreseeable factors that may be expected to influence [subjects'] willingness to participate").

Question 41: What changes to the regulations would clarify the current four criteria for waiver of informed consent and facilitate their consistent application?

The lack of clarity with respect to the availability of waiver stems largely from the wording of criterion (2) "the waiver or alteration will not adversely affect the rights and welfare of the subjects," and criterion (4) "whenever appropriate, the subjects will be provided with additional pertinent information after participation." See 45 CFR 46.116(d).

Criterion (2) is worded very broadly, so it is uncertain just what factors the IRB is to consider. At some level, any waiver of an element of informed consent will "adversely affect the rights and welfare of the subjects." This is because a waiver takes away rights

that would otherwise be secured by the elements of informed consent. Thus, the elements of consent are presumably not the sort of “rights” contemplated by this language. At the same time, it would appear that “adverse effect on rights and welfare of subjects” is intended to mean an adverse effect pertaining to something other than risk to subjects. This is because waiver is not possible unless criterion (1)—which requires risks to be minimal—is also satisfied. It would therefore appear that criterion (2) was intended to require IRBs to consider non-risk-related factors that more generally concern the rights and welfare of subjects. These factors could include whether there are other statutes or regulations that obligate researchers to obtain informed consent before using the data for research purposes, such as the HIPAA Privacy Rule (applicable to medical records), or the Family Educational Rights and Privacy Act (FERPA) (applicable to public school records). They could also include consideration of the sensitivity of the data and an assessment of the views and attitudes of the subject population with respect to their research use. In our view, these are all reasonable matters for the IRB to consider. However, the language of criterion (2) should be clarified or guidance issued to make this explicit.

Criterion (4) seems to apply, if at all, only to scenarios involving intervention or interaction with subjects. Accordingly, its presence raises potential confusion as to whether waiver is permitted in cases where research does not involve interaction or intervention but is limited to retrospective records review. Clarifying that waiver is potentially available in records-only research would be helpful.

Question 42: In circumstances where the regulations would permit oral consent, what information should investigators be required to provide to prospective subjects? Are all of the elements of informed consent included at 45 CFR 46.116 necessary to be conveyed, or are some elements unnecessary? If some elements should not be required for oral consent, which ones are unnecessary?

Consistent with the comments made above in connection with our response to Question 36, we believe the proper focus should be upon informed consent as a process. Whether consent is to be obtained in written or oral form, the goal is the same: ensuring that the subject has the opportunity to make an informed and uncoerced decision whether to participate. Accordingly, we see no basis for drawing any distinction between the elements of oral consent and written consent. The same elements should apply to both.

We note, however, that element (4), referencing description of alternative procedures or courses of treatment, seems to apply only to research involving interventions. Accordingly, we recommend that it be moved under category (b) as an additional element to be included “when appropriate.”

Question 43: Are there additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent?

In certain cases, a written consent form may be the only document identifying the subject as a participant in research. As recognized in 45 CFR 46.117(c)(1), in such cases, absent a compelling contrary justification for obtaining written consent, oral consent would appear to be appropriate. We continue to recommend oral consent as the preferred default option for most minimal-risk research.

Question 44: Are there types of research involving surveys, focus groups, or similar procedures in which oral consent without documentation should not be permitted? What principles or criteria distinguish these cases?

In most cases, the primary risks associated with survey and focus group research are informational, and arise from the threat of breach of confidentiality. While there are no bright-line rules, written consent may be more appropriate than oral consent where documentation is more likely to promote the integrity of the consent process. This may be the case for research that involves complex procedures. Such complexity may be better understood where the subject is required to review and sign a form. Written consent may also be more suitable where the information gathered is particularly sensitive, and thus the risks of disclosure must be fully explained to the subject. Again, the process of signing the form may be more likely to focus the subject’s attention on the nature and magnitude of the risk than an oral review of the same material. Of course, there may also be cases where written consent is required by other federal or state statutes or regulations. For example, research involving a survey followed by a medical records review may require a HIPAA Privacy Rule authorization form to allow release of records.

Question 45: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent? Are there other circumstances in which it should not be necessary to obtain additional consent for the research use of currently available data that were collected for a purpose other than the currently proposed research?

This question can and should be answered by applying criteria (1) through (3) in 45 CFR 46.116(d) for determining when waiver of informed consent is permissible. (Criterion (4), which pertains to follow-up with subjects “whenever appropriate,” would not appear to be applicable to research involving only records review but no interaction or intervention.)

Criterion (1) requires that risks be minimal. Since the risk of records-only research is informational, criterion (1) would require the IRB to determine that there is a data safeguarding plan in place that minimizes risk of inadvertent or unauthorized disclosure.

Criterion (2) requires that “the waiver or alteration will not adversely affect the rights and welfare of the subjects.” As noted above in response to Question 41, the wording of this criterion is ambiguous and should be clarified. However, it is reasonable to interpret it to refer to rights and welfare of subjects as recognized by other statutes and regulations, and also to societal norms and individual expectations about the data and their use in research. Under this interpretation, the IRB would first need to determine whether there are federal, state, or local laws that require informed consent. Obvious federal examples would include the HIPAA Privacy Rule (applicable to certain identifiable health information) and the Family Educational Rights and Privacy Act (FERPA), which protects the privacy of identifiable student records. The IRB should also consider whether there is reason to believe that the subjects would have consented to the research had they been asked. This may involve consideration of factors such as the sensitivity of the data in question, individual expectations about the privacy of those data, the identity of the researchers, and the purpose of the research.

Criterion (3) requires that the research “could not practicably be carried out without the waiver.” This requires an evaluation of circumstances of the subject population and the challenges to obtaining consent. In cases where the subject population is very large,

spread out over a wide geographic area, and/or contact information is not available or is unreliable, waiver is more likely to be appropriate. By contrast, it is difficult to see justification for waiver under criterion (3) if the subject population is small, contact information is reliable, and soliciting consent is relatively easy.

Question 46: Under what circumstances should future research use of data initially collected for a different research purpose be permitted without consent? Should consent requirements vary based on the likelihood of identifying a research subject?

In our view, waiver of informed consent for future research use of research data should be governed by the same principles as for future research use of data originally gathered for non-research purposes. That is, waiver should be allowed only where criteria (1) through (3) in 45 CFR 46.116(d) are satisfied. These waiver conditions should be invoked only when the original consent protocol did not specify that the data would be destroyed and/or would not be made available for other future research purposes

Issue 6: Review Requirements for Multi-site Studies

Current rule	Changes being considered	Rationale for change
<p>Issue 6: Each site in a study requires IRB review. Although the regulations allow one IRB to carry out the review for multiple sites, it is common for a single study conducted at multiple sites to have many IRBs separately reviewing the study.</p>	<p>For all of the U.S. sites in a multi-site study, the changes propose a single IRB of record.</p>	<p>There is very little evidence that having multiple IRBs review the same study results in enhanced protections for subjects. By diffusing responsibility for that review, it might actually contribute to weakened protections.</p>

Subject to the responses below, we support streamlining IRB review of multi-site projects by requiring designation of a central IRB as the reviewing institution of record.

Question 30: What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies?

Mandating use of a single IRB of record is preferable to simply encouraging use. The benefits of centralized IRBs are well documented by commentators, including those cited in the ANPRM. These benefits sharply outweigh any advantages conferred by local IRB review. It is also our experience that the chief reason local IRBs resist centralized review is perceived legal risk associated with deferral. Local IRBs have been concerned (perhaps understandably) with OHRP's stated approach of enforcing Common Rule compliance at the site level, even in circumstances where a central IRB is designated responsibility for ensuring compliance. Moreover, indemnification from central IRBs, while hypothetically available, has not, as a practical matter, been obtainable. By shifting responsibility for institutional compliance to the central IRB, OHRP will remove the chief obstacle to local deferral. We would nonetheless anticipate that in such a scenario some local IRBs would still be reluctant to give up responsibility for review, possibly due to lingering (though, in future, unfounded) concerns about legal risk. This would potentially result in the substantial burdens of multiple IRBs continuing for some studies. Mandating the use of a central IRB would ensure a swift transition to an era of greater efficiency for all.

Question 31: How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution's specific perspective or the needs of their population, or that a centralized IRB may not share an institution's views or interpretations on certain ethical issues?

The Common Rule aims to create a mechanism to ensure that ethical principles are followed, that some reasonable level of oversight is practiced, and that the rights of human subjects are being safeguarded. There is nothing in the Common Rule that suggests that more regulatory bureaucracy is better than less; or that local control and oversight is better than centralized control and oversight; or that redundant oversight by multiple IRBs offers stronger protection for human subjects; or that the cost-benefit tradeoff between protecting human subjects and exercising efficient oversight will

always favor more oversight and regulation rather than less, no matter how costly the extra oversight (as of multiple IRBs) actually is in practice.

In our view, “local knowledge” is a dubious rationale to support the continued involvement of local IRBs. Even for a centralized IRB review process in a multi-site trial (as proposed in the ANPRM), the reviewing IRB remains obliged to understand the details of the study, and the mechanics for carrying it out, in all relevant sites and locations. If there are pertinent local issues to be considered, the researchers are required to raise them, and the central IRB must evaluate them.

It is also unclear why “the public should be concerned that a centralized IRB might not share a [local] institution’s views or interpretations about certain ethical issues.” The question assumes that the public has knowledge of the views or interpretations of particular IRBs with regard to particular ethical issues, which seems highly unlikely. It is equally unclear that the public ought to have influence over whether local versus non-local standards apply. An IRB that meets OHRP requirements presumably is either doing satisfactory oversight work consistent with the ethical principles of the Common Rule or should be subject to sanction by OHRP. Ultimately, local standards provide no obvious compass to guide reviews, and there appears to be little legitimate public interest in reviews beyond ensuring that the Common Rule is being applied in a conscientious and consistent matter to safeguard the interests of human subjects.

Question 32: To what extent are concerns about regulatory and legal liability contributing to institutions’ decisions to rely on local IRB review for multi-site research? Would the changes we are considering adequately address these concerns?

We believe that IRBs resist centralized review chiefly because of perceived legal risk associated with deferral. Shifting Common Rule enforcement compliance away from the local IRB to the central IRB will help address this problem, as will mandating the use of central IRBs.

Question 33: How significant are the inefficiencies created by local IRB review of multi-site studies?

In our experience, multiple local IRB reviews of multi-site studies impose significant and sometimes crippling burdens on researchers and IRBs alike—burdens not offset by any increased protection for subjects. Changes in forms requested by one IRB can trigger a cascade of downstream reviews and approvals. On occasion, these changes themselves prompt further changes that feed back into this loop. The attendant delays and wasted effort drive up costs of research significantly, depleting scarce resources. In addition, confusion in such studies surrounding the proper chain of reporting for adverse events or unexpected problems may result in institutions being unaware of incidents. Alternatively, institutions may disagree as to the proper response to such incidents after they arise.

Question 34: If there were only one IRB of record for multi-site studies, how should the IRB of record be selected? How could inappropriate forms of “IRB shopping” — intentionally selecting an IRB that is likely to approve the study without proper scrutiny — be prevented?

Forum shopping could presumably be prevented relatively easily by setting forth a few jurisdictional principles for selection of the central IRB. As a default, the central IRB might be that of the lead investigator’s home institution or, alternatively, the IRB for the site with the greatest anticipated enrollment of human subjects.

Issue 7: Harmonizing Guidance Across Agencies

Current rule	Changes being considered	Rationale for change
Issue 7: Each Common Rule agency, and the FDA, is authorized to issue its own guidance with regard to interpreting and implementing the regulations protecting human subjects. That guidance may substantially differ from agency to agency.	The ANPRM does not propose a specific change but through questions, seeks to determine whether or not the differences in guidance from agency to agency are justified by differences in the applicable statutes or missions of those agencies, and if not, to determine how to make guidance more uniform.	If the differences in guidance are not justified, then it would be appropriate to eliminate those differences.

RAND supports efforts to harmonize guidance across federal agencies regarding the protection of human subjects. As the ANPRM recognizes, agency guidance necessarily encompasses both an interpretation of the regulations protecting human subjects and specific administrative criteria governing the implementation of those regulations. In RAND's experience, the basic principles of human subjects protection described in the Belmont Report and embodied the Common Rule are well understood among federal agencies. Specific implementation is another matter. Inconsistencies arise among agencies—and, indeed, between separate components of the same agency—with respect to the standards and level of administrative review applied to similarly situated projects, even after approval by the responsible IRB. Projects are often overburdened by unpredictable, duplicate, or unnecessary secondary review procedures that may be generated, in part, by the lack of uniform implementing guidance. In RAND's view, uniform guidance would substantially alleviate such burdens and lead to the consistent protection of human subjects.

Question 72: To what extent do the differences in guidance on research protections from different agencies either strengthen or weaken protections for human subjects?

In the ideal case, the existing regulatory scheme would afford the same basic research protections to all human subjects. The reality is, however, that differences in guidance necessarily lead to varying levels of agency scrutiny for similarly situated research projects. Projects are thus often overburdened by unpredictable, duplicate, or unnecessary secondary review procedures that do not result in greater protections for human subjects. Different approaches to research protections also create room for inconsistent determinations about what constitutes research subject to IRB review, potentially leaving certain human subjects unprotected. Uniform guidance would facilitate the consistent application of regulatory standards and ultimately strengthen research protections for human subjects.

Question 73: To what extent do the existing differences in guidance on research protections from different agencies either facilitate or inhibit the conduct of research domestically and internationally? What are the most important such differences influencing the conduct of research?

RAND believes that inconsistent agency approaches significantly inhibit human subjects research without providing additional protections for the subjects. As indicated above, similar projects may be overburdened by duplicate or unnecessary secondary review procedures that are extremely difficult to predict. It is also important to note that these inconsistencies arise not only among agencies but between separate components of the same agency as well. In certain instances, component procedures may not be clearly articulated, transparent, or well understood even across the same agency. The challenges faced by the Department of Defense (DoD) provide a good example. Although the overarching guidance provided to DoD components in DoD Directive 3216.02 incorporates basic references to the Common Rule and Belmont Report and directs each component to establish "Human Research Protection Programs" (HRPPs), the implementation of HRPPs throughout the agency and the review procedures instituted by DoD components have varied considerably. Ultimately, the lack of a uniform approach among and within agencies (such as the DoD and others) can increase the cost of research, frustrate researchers and local IRBs, and, at worst, lead some investigators, institutions, and sponsors to try to circumvent IRB oversight because varying agency

guidance ultimately makes the review process too costly, inconsistent, and unpredictable. While it is true that certain populations and unique agency missions may require unique protections and may benefit from specific guidance, the current inconsistencies and varying agency guidance, in the aggregate, substantially inhibit the research community's approach to human subjects research without enhancing protections for human subjects in return.

The unnecessary administrative burden described above is also frequently increased by differing interpretations of the interplay between the Common Rule and other federal regulations. The ANPRM rightly mentions HIPAA considerations, but RAND would also call attention to the Privacy Act (the "Act"). During the human subjects review process, Common Rule agencies regularly characterize research records created by private institutions as "systems of records," thus triggering additional administrative review by various privacy offices under the Act. Such review is often unnecessary and adds little, if anything, to the protections already required under the Common Rule.

Privacy Act review is inappropriate for research institutions like RAND for several reasons. First, independent research institutions do not qualify as "agencies" subject to the Act. (See *Krebs v. Rutgers*, 797 F.Supp. 1246, 1253 (D.N.J. 1992) (Rutgers University not federal agency); *Forsham v. Harris*, 445 U.S. 169, 179 (1980) (federal grants to medical researchers do not make the group an "agency").

Second, institutions like RAND usually do not fall within the extension of the Act to private contractors under subsection (m), which only extends the Act to such institutions if they operate a system of records "by or on behalf of the agency...to accomplish an agency function." (5 U.S.C. § 552a(m)(1).) As OMB notes in its Privacy Act guidance, this language should be construed narrowly and was "intended to limit the scope of coverage to those systems actually taking the place of a Federal system which, but for the contract, would have been performed by an agency and covered by the Privacy Act." (Privacy Act Implementation, Guidelines and Responsibilities, 40 FR 28948 at 28951, 28976, July 9, 1975 (July 8, 1975) ("OMB Guidelines") (available at http://www.whitehouse.gov/sites/default/files/omb/assets/omb/inforeg/implementation_guidelines.pdf.)

RAND believes that this limitation should normally preclude the application of the Act to federally contracted research. For example, in 1976—with this limitation in mind—the Department of Health, Education, and Welfare (HEW) concluded that “the requirements of the Privacy Act of 1974 are not applicable to HEW research and other contracts which call for the contractor merely to furnish to the HEW contracting agency statistical or other reports, even though it is necessary for the contractor to establish a system of records to perform the contract.” (May 14, 1976, ltr. from W. Taft to J. Ottina, attached as Appendix IV to Comptroller General Report 8418, “Privacy Act of 1974 Has Little Impact on Federal Contractors 40 (released Dec. 7, 1978) (“Comptroller Report”).) Federal courts have taken a similar approach. (See *Boggs. v. SE Tidewater Opportunity Project*, No. 2:96cv196, 1996 WL 274381 *2 (E.D. Va. May 22, 1996) (subsection (m) inapplicable to community action agency that was “not in the business of keeping records for federal agencies.”))

Accordingly, RAND believes that agencies often unnecessarily (and inconsistently) invoke the Privacy Act in circumstances analogous to the situation analyzed by HEW 30 years ago. RAND would therefore recommend that new uniform guidance take into account the interaction between the Common Rule and other federal regulations and specifically caution agencies against unnecessary invocation of the Privacy Act in the research context.

Question 74: If all Common Rule agencies issued one set of guidance, would research be facilitated both domestically and internationally? Would a single set of guidance be able to adequately address human subjects protections in diverse populations and contexts, and across the broad range of research contexts (including biomedical, national security, education and other types of social and behavioral research)?

Notwithstanding certain variations in research populations and contexts, RAND believes that common guidance issued by all Common Rule agencies would facilitate domestic and international research and enhance protections for human subjects. As indicated above, current inconsistencies undercut human subjects protections. As a practical matter, this means that similar projects may be overburdened by duplicate or unnecessary secondary review procedures that are extremely difficult to predict and provide no material benefit to the subjects they are intended to protect. These

inconsistencies arise not only between agencies, but within separate components of the same agency as well. In certain instances component procedures may not be clearly articulated, transparent, or well understood even across the same agency, thus leading to inconsistent reviews and standards of protection. The challenges faced by the DoD provide a good example. Although the overarching guidance provided to DoD components in DoD Directive 3216.02 incorporates basic references to the Common Rule and Belmont Report and directs each component to establish “Human Research Protection Programs,” the implementation of such programs throughout the agency and the review procedures instituted by DoD components have varied considerably. Ultimately, the lack of a uniform approach among and within agencies (such as the DoD and others) can increase the cost of research, frustrate researchers and local IRBs, and, at worst, lead some investigators, institutions, and sponsors to try to circumvent IRB oversight because varying agency guidance ultimately makes the review process too costly, inconsistent and unpredictable. While it is true that certain populations and unique agency missions may require unique protections and may benefit from specific guidance, the current inconsistencies and varying agency guidance, in the aggregate, substantially inhibit and undermine the research community’s efforts to protect human subjects.

To be sure, arriving at a consensus will be a challenging process, but one that RAND believes merits the effort. The ultimate goal must be to arrive at uniform guidance that can be applied broadly across a range of populations and research contexts. Indeed, special attention should be paid to ensuring that Common Rule agencies create uniform implementing guidance not only among themselves, but specific components within individual agencies as well. To the extent that agency stakeholders in specific fields believe that special circumstances merit different or additional protections, they should be allowed to make the case for exceptions or enhancements during the consensus-building process. Despite the evolution and diversification of human subjects research since the Common Rule was first enacted, RAND believes that it is both feasible and appropriate to revise the current framework in order to create uniform guidance that takes into account the lessons learned over the last 30 years.

Issue 8: Reviewing More-Than-Minimal-Risk Research

Current rule	Changes being considered	Rationale for change
Issue 8: Research involving more-than-minimal risk requires review by a convened IRB.	This requirement would remain unchanged.	Higher-risk studies should be subject to the highest level of scrutiny.

RAND endorses the proposition that more-than-minimal risk research should be reviewed by the convened IRB. We would appreciate a more cogent definition of “minimal risk,” especially as it applies in social-behavioral research contexts that may themselves pose risks (for instance, in criminal justice, homeland security, or international security research). The current definition is not readily operationalizable; in particular, it offers little help for deciding how to combine likelihood of harm with magnitude of harm to arrive at a judgment of minimal versus more-than-minimal risk in field-based social-behavioral research settings.

Issue 9: Continuing Review of More-Than-Minimal-Risk Research

Current rule	Changes being considered	Rationale for change
Issue 9: Research that requires review by a convened IRB requires continuing review at least annually.	Continuing review would generally not be required after all subjects in the study have completed all study interventions, and the only remaining procedures are standard-of-care procedures that are used to obtain follow-up clinical information (e.g., standard annual CT scans to detect any spread of the patient’s cancer), and the analysis of the research data.	Since the research risks to subjects after completion of study interventions are limited to privacy and confidentiality concerns, which would be dealt with by the new uniform protections, this change would enable IRBs to focus attention on higher-risk protocols.

RAND supports proposals to transition research initially judged as involving more-than-minimal risk from convened IRB review to less burdensome continuing annual reviews, but only in clearly specified stages.

Question 3: For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?

Research that involves more than minimal risk should be reviewed annually by the convened IRB until the study reaches the point where all procedures judged to involve more than minimal risk have been completed. At the next annual review point, when remaining procedures are judged to involve only minimal risk and no adverse events have been reported in the interim, continuing reviews should be done on an expedited basis (as now happens under expedited review category 8) until no further primary data are being collected. At that point, no further continuing reviews should be required, although we would recommend a routine annual check to ensure that data protection safeguards remain in place or else that all identifiers have been destroyed and the remaining datasets are not identifiable by inference.

Issue 10: Eligibility for Expedited Review

Current rule	Changes being considered	Rationale for change
Issue 10: Research that poses minimal risk and includes only research activities in a list approved by the HHS Secretary is eligible to be reviewed in an “expedited” manner (e.g., with one reviewer, instead of a convened IRB).	This list would be updated now, and at regular intervals, using appropriate data about risks to the extent possible.	If the differences in guidance are not justified, then it would be appropriate to eliminate those differences.

We agree that research that poses minimal risk and falls into established categories should be reviewed in an “expedited” manner (e.g., with a designated reviewer(s) instead of a convened IRB), and we support expansion of the list of research activities that can be reviewed as such. However, the determination of minimal risk continues to be important, and either the appointed reviewer or the IRB Chair should have the ability to request additional reviewer(s) to assist in the expedited review if additional kinds of expertise are required to assess risk. If the expedited reviewers are in doubt about whether the proposed research meets the standard for minimal risk or fits appropriately into the established categories (on the “list”) and cannot resolve this by adding reviewers to assist in the expedited review, then the expedited reviewers should still have the ability to refer the project to a convened IRB for review. Even though prisoner findings can be made as part of expedited review, we do not believe that a single reviewer should make the prisoner determinations (and the expedited reviewers need to include a prisoner representative).

Question 1: Is the current definition of “minimal risk” in the regulations (45 CFR 46.102(i)—research activities where “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”)—appropriate? If not, how should it be changed?

We think this definition is appropriate, with two caveats. First, we suggest that the reference population be specified, for example, “in the daily life of the average American.” It is our understanding that this is the appropriate reference population, and this is important in considering international research and research with special populations. Second, it would be desirable for the definition to explain and provide examples of how probability and magnitude of harm or discomfort can be weighed in a combined judgment, relative to risks of daily life.

Issue 11: Continuing Review of Research Eligible for Expedited Review

Current rule	Changes being considered	Rationale for change
Issue 11: Research that is eligible for expedited review requires continuing review at least annually.	Continuing review would not be required of studies that are eligible for expedited review unless the reviewer, at the time of initial review, determines that continuing review is required, and documents why.	Research eligible for expedited review can involve only research activities that are included in the approved list. These activities are well understood, and it would be very unlikely that research involving such activities would lead to the new or unexpected risks with which continuing review is intended to deal.

We agree that, absent a stipulation at the time of expedited review that continuing review is required, projects approved in expedited review should not require continuing review. This concurrence assumes there is an approved data safeguarding plan, either based on adherence to uniform protections or on one that is specifically approved for this study by the IRB, provided that the project is not required to produce a public use dataset. If a public use dataset is required and the reviewer identifies a need specifically to review this prior to release, then the project can submit an amendment for review at the point the project is ready to undertake this task. The annual review of a minimal-risk project that is unlikely to lead to new or unexpected risk has no purpose and consumes considerable IRB administrative and researcher effort for compliance.

Question 2: Would the proposals regarding continuing review for research that poses no more than minimal risk and qualifies for expedited review assure that subjects are adequately protected? What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?

In most studies that can be approved in expedited review, subjects would receive adequate protection without annual reviews. However, if procedures involve novel aspects or may be difficult to carry out, additional review might be warranted. In the end, this has to be a judgment call by designated reviewer(s) since it is the novel features of a study that may indicate the need for additional review and these are difficult to specify in advance.

Issue 12: Minimal Risk in Research Eligible for Expedited Review

Current rule	Changes being considered	Rationale for change
Issue 12: For a research study to be eligible for expedited review, an IRB member must determine that it is minimal risk.	The “default” assumption will be that a study otherwise eligible for expedited review will be considered minimal risk unless a reviewer documents the rationale for classifying the study as involving more than minimal risk.	Since research that is eligible for expedited review can involve only research activities that are included in the approved list, very few such studies will involve more than minimal risk. This change will better assure that the level of review is well targeted to the level of risk.

We agree that a study that clearly fits into the categories for expedited review should be considered minimal risk unless the reviewer documents the rationale for classifying the study as involving or possibly involving more than minimal risk. It is important that research not be needlessly delayed or required to incur additional costs in pursuit of very remote risks or at the whim of a single reviewer. However, we would still suggest that a standard for “documentation” be set to recognize that it is the job of the reviewer to protect the interests of human subjects and the job of the project to establish that the proposed project fits the criteria for minimal risk. A possible standard for reviewers to use might be a reasonable probability of a significant risk or a small probability of an extreme risk related to some novel feature of the research that deviates from the procedures as described on the “list,” with the final determination of whether adequate documentation is provided to be made by the IRB Chair. The determination of minimal risk continues to be important, and a single reviewer should have the ability to request

additional reviewers if their expertise is required to assess risk. If the expedited reviewers are in doubt about whether the proposed research meets the standard for minimal risk and provides documentation that meets a reasonable standard established by the Chair, then the project should be referred to a convened IRB for review, if required.

Question 4: Should the regulations be changed to indicate that IRBs should only consider “reasonably foreseeable risks or discomforts”?

We do not agree that this change should be made. Of course, the designated reviewer(s) need to address “reasonably foreseeable risks or discomforts” first, and it is important to maintain some perspective, but consideration of the full range of possible risks should not be foreclosed. We find that IRBs are self-regulating; while some members may be concerned about extremely unlikely risks, other members engage to balance the discussion.

Question 5: What criteria can or should be used to determine with specificity whether a study’s psychological risks or other nonphysical, non-information risks, are greater than or less than minimal?

We don’t believe that this can be determined in advance with specificity. The reference standard has to be considered in relation to the study features, and a reasonable judgment should be made.

Question 6: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk? How should the characteristics of the study population (e.g., mental health patients) be taken into consideration in the risk assessment?

Current regulations specify special vulnerable populations, such as children, the mentally ill, prisoners, and others, who may have difficulty with cognitive aspects of consent or be in a position where some elements of coercion apply (for example, patients being asked by their physician to participate in research or being asked to consent while being prepped for a procedure). We believe these are adequate. The regulations also

indicate a range of sensitive topics that might lead to distress or negative consequences. These also seem appropriate and adequate.

Question 7: What research activities, if any, should be added to the published list of activities that can be used in a study that qualifies for expedited review? Should any of the existing activities on that list be removed or revised? For instance, should the following be included as minimal risk research activities:

- Allergy skin testing.
- Skin punch biopsy (limited to two per protocol).
- Additional biopsy during a clinical test (e.g., performing an extra colonic biopsy in the course of performing a routine colonoscopy).
- Glucose tolerance testing among adults.

We believe the list of activities should be revised to distinguish more clearly the types of interaction procedures frequently employed in social-behavioral-educational research that may be reviewed in expedited procedures. Now they are all bundled indiscriminately into category 7.

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently?

We think every two years would be adequate. This allows time for experience to accrue for a new procedure that might be considered.

Question 11: What are the advantages of requiring that expedited review be conducted by an IRB member? Would it be appropriate to instead allow such review to be done by an appropriately trained individual, such as the manager of the IRB office, who need not be a member of the IRB? If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review? If so, what would qualify as being “appropriately trained”? Would the effort to make sure that such persons are appropriately trained outweigh the benefits from making this change?

We believe that expedited review should be conducted by a designated IRB member(s) because reviewers need to be familiar with the regulations and standards used by the convened IRB to apply them. However, we do believe that some tasks that are currently carried out by committee members might be performed by IRB staff, such as reviewing compliance with contingencies specified by reviewers as a condition for approval. If the staff member has questions, the IRB members can be consulted.

Question 12: Are there other specific changes that could be made to reduce the burden imposed on researchers and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects? Are there specific elements that can be appropriately eliminated from protocols or consent forms? Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated? Conversely, are there specific additions to protocols or consent forms beyond those identified in this notice that would meaningfully add to the protection of subjects? What entity or organization should develop and disseminate such standardized document formats?

We believe the existing documents are needed. In other places in RAND's response, we have cautioned about the development of standardized consent and other documents, because of differences that exist among studies and the need to view consent as a process rather than to focus on the consent form. We would similarly caution about standardized reduction in the types of material investigators provide to subcommittees for consideration under expedited review because of differences in experience with human subjects research that exist among investigators. In our experience, investigators with significant experience in carrying out human subjects research readily and efficiently provide all needed information for review and have considered issues such as subject risk minimization and data safeguarding in their submissions. In contrast, less-experienced investigators do not do so; and, though they often express the greatest concern about the level of burden involved in preparing or iterating on the documents required for even expedited review, it is during the iteration between the IRB review subcommittee and those investigators that risks are considered and the researcher educated about how to minimize them. While significantly loosening documentation requirements across the board might indeed save experienced researchers time and increase efficiency, it would also potentially eliminate the interaction between the IRB and less-experienced researchers—whose education function can be important to the

protection of human subjects in ways that the substance of a review and ruling on a study cannot.

However, we believe that not every change to an approved document or procedure needs approval by the IRB again in expedited or convened full committee review. Better specification of the elements of a research project that do require review after alteration would be useful. For example, adding or deleting non-sensitive questions in a survey might not need re-review, but adding a new sensitive topic would. Minor changes in subject recruitment procedures might not need re-review. As projects evolve through testing and pilot experience, they often do change, but not in ways that affect risks to human subjects. The document submission and review, with associated delays in ongoing projects, is burdensome and might be curtailed.

Question 13: Given the problems with the current system regarding wide variations in the substance of IRB reviews, would it be appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the defaults described in Sections B(1), B(2)(a)(ii), and B(2)(b) above? Should IRBs have to report instances in which they require continuing review or convened IRB review of a study which involves only activities identified as being on the list of those eligible for expedited review? If an IRB that chose to override these defaults was required to submit a report to OHRP, would this provide useful information about any lack of appropriate consistency among IRBs so that clarifying guidance could be provided as needed, or provide useful information to OHRP about the possible need to revise the expedited review list or the continuing review requirements?

RAND disagrees with this suggestion. We believe the proposed process in itself would be burdensome to IRBs and to OHRP with no associated benefit. The relatively rare project where the principal investigator (PI) feels that the project is being put at risk through excessively burdensome review seems to be the issue here, so perhaps a clearly specified local IRB “grievance” process could be outlined for PIs of projects who feel they are subject to excessive review. It might be more appropriate to report grievances and the results to OHRP.

Issue 16: Determining Studies to be Exempt from Review

Current rule	Changes being considered	Rationale for change
<p>Issue 16: Although the regulations do not require administrative review before a study is determined to be exempt, most institutions follow current federal recommendations and carry out such an administrative review.</p>	<p>The recommendation that all such studies undergo administrative review would be eliminated. Researchers would file a brief “registration” form with their institution or IRB, and would be permitted to commence their research studies immediately after filing the form. Audits of a small percentage of studies would take place to ensure appropriate application of and compliance with the revised regulation.</p>	<p>The major risk in most studies that might qualify as exempt is a breach of confidentiality. Given that there will be clearer criteria to determine when a study meets the standards for exemption, and that all studies will be covered under appropriate data security protections, there should be little need for or benefit from reviewing each study before it commences to determine that it meets the criteria for being exempt.</p>

RAND disagrees with this change. This would seem difficult to implement effectively unless the changes suggested under Issue 17 are also adopted (allowing studies collecting identifiable data that might also pose a risk to legal, financial, or social standing to be categorized as exempt). The judgment of what creates identifiability and risk to standing may not always be clear to less-experienced researchers or those using methods they have not previously employed. It has been our experience that the level of education and understanding of the regulatory requirements among researchers can vary considerably from discipline to discipline and among individuals with different career histories before they come to research (or to research involving human subjects). This proposed change therefore creates a potential hole in protection caused by researchers who are insufficiently aware of the regulatory details who judge their projects exempt based on wrong information. If this process is supported only by low-level auditing, breakdowns resulting from such ignorance could persist for significant periods of time. While revising and clarifying the guidelines may fix this, there are often subtleties involved that the revisions would need to capture. They might also need to be revisited regularly to address methods involving emerging technology (such as GPS, in

vivo recording devices, or online tracking). Researchers may be unaware of how the information yielded by these devices affects participants' identifiability and risk. They may also be unaware of secondary subject issues that may arise or how to deal with consent in such cases.

Although the chief risks to participants could be reduced by data safeguarding, participants would still need to be made aware of these risks, and their autonomy in deciding to participate would need to be respected. This requires appropriate consent that may be difficult for researchers to implement on their own if they do not have a full understanding of the issues, as noted above. Procedures would need to be in place that assist with consent issues for exempt studies.

Question 19: Regarding the Excused category, should there be a brief waiting period (e.g., one week) before a researcher may commence research after submitting the one-page registration form, to allow institutions to look at the forms and determine if some studies should not be Excused?

RAND feels that a waiting period for "excused" studies is inconsistent with the proposed revision to procedures for handling exempt ("excused") projects. If there needs to be time to examine the content of the registration form, presumably someone is engaged in an activity akin to a screening review. The reviewer may require additional information to make the "excused" determination, and the process begins to look very much like how exemptions are now handled. RAND believes this registration plus a waiting process will generate confusion without making any material improvement in how exempt/excused projects are, in fact, handled.

Question 21: Is it appropriate to require institutions holding a Federalwide Assurance to conduct retrospective audits of a percentage of the Excused studies to make sure they qualify for inclusion in this category? Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements? Should some other method besides a random selection be used to determine which Excused studies would be audited?

RAND believes that auditing “excused” studies would be essential to ensuring that research activities and level of IRB oversight are appropriate and that the regulations should specify a minimum percentage of studies to audit to satisfy the regulatory requirements. However, it is unclear how auditing only a small percentage of studies would ensure appropriate application of the revised regulation in the majority of cases. Auditing a small percentage of specific types of studies or a proportion of the studies by a given researcher might do so, if any errors that the audit revealed trigger a full audit of a class of research or a researcher. In the event of full audits, a policy regarding the scope of such audits (e.g., retrospective, prospective) would need to be considered. It would also be critical, if only a small number of studies were audited, that this be done in a timely manner across a range of study types and researchers to minimize potential unidentified risks and harms to research participants. Furthermore, this suggests that the selection of studies to audit should not be entirely random but should consist of a stratified random sample representing a range of study types.

Question 22: Are retrospective audit mechanisms sufficient to provide adequate protections to subjects, as compared to having research undergo some type of review prior to a researcher receiving permission to begin a study? Might this new audit mechanism end up producing a greater burden than the current system? Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category? By allowing researchers to make their own determinations, without prospective independent review, will protections for some subjects be inappropriately weakened? If allowing researchers to make such determinations without independent review would generally be acceptable, are there nonetheless specific categories of studies included in the proposed expansion for which this change would inappropriately weaken protections for subjects? And will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?

RAND believes a retrospective audit is inadequate to protect research participants. Audits may identify problems with a small percentage of studies (those selected for audit) fairly quickly, depending on the timing of audits relative to study start, but would still allow some avoidable harm in those cases. Moreover, if audits were used to trigger wider investigations of certain researchers or practices, the resulting findings of error would almost certainly apply largely to studies that are already in progress or complete.

Thus, the results of audit would largely yield administrative information rather than provide protection to human subjects and, in contrast to prospective review, could result in greater burden for reviewers; autonomy, for instance, cannot readily be retrospectively restored. An audit system would also place undue burden on researchers by requiring them to become experts in human subjects issues and the sometimes nuanced decisionmaking involved in designating a study as exempt or “excused.”

Issue 17: Broadening Exemption Criteria for Research Using Educational Tests, Survey Procedures, or Observation of Public Behavior

Current rule	Changes being considered	Rationale for change
Issue 17: One of the six exempt categories applies to research using educational tests, survey procedures, or observation of public behavior, but not if both (i) information is recorded in a way that allows subjects to be identified, and (ii) disclosure of the subjects’ responses outside of the research could reasonably place subjects at risk of criminal or civil liability or cause damage to financial standing, reputation, or employability.	This exempt category would be broadened by eliminating criteria (i) and (ii) for studies that involve competent adults, i.e., such research would be exempt even if the information was recorded in an identifiable way and the disclosure could pose such risks to the subject.	The new data security protections obviate the need for (i) and (ii).

RAND does not agree with this change. The primary risk involved in such a change would seem to be a failure of researchers to implement appropriate and ethical procedures still required of them without the benefit of IRB advice or oversight. Researchers may not realize the conditions under which they need to obtain consent or may fail to do so. They may also fail to fully understand and therefore articulate risks of participation for participants without IRB guidance. Likewise, researchers may not be aware of the need to implement standard data security procedures proposed in Issue 1.

Question 14: Are these expansions in the types of studies that would qualify for this Excused category appropriate? Would these changes be likely to discourage individuals from participating in research? Might these changes result in inappropriately reduced protections for research subjects, or diminished attention to the principles of respect for persons, beneficence, and justice?

Eliminating oversight of studies that collect identifiable sensitive information (when adults are involved) is not appropriate. It places a heavy burden on researchers to understand and follow regulations without providing institutional resources and guidance. Would they have sufficient knowledge and experience to appropriately administer consent? Apply for a certificate of confidentiality to legally protect the identifiable data? While appropriate data safeguarding could at least reduce disclosure risks, there would be nothing in place to ensure that participation is equitably distributed or that participants are fully informed. Other risks to participants, such as the risk of psychological harm from participation (e.g., stress caused by answering questions), or stigmatization as a result of participation (as when an individual can be publicly observed to be participating in a survey that is publicly known to include only persons with a history of mental illness, persons with HIV, etc.), or physical harm from participation (for example, gang members who are publicly seen to participate in a survey might become targets of assault by fellow gang members who believe they are police informants). And dignitary harms are left completely out of account. For these reasons, the proposed change would almost certainly diminish attention to principles of respect, beneficence, and justice.

Question 15: Beyond the expansions under consideration, are there other types of research studies that should qualify for the Excused category? Are there specific types of studies that are being considered for inclusion in these expansions that should not be included because they should undergo prospective review for ethical or other reasons before a researcher is allowed to commence the research?

RAND does not agree with the proposed expansion, but if it is adopted, there are categories that should not be included. Research with persons who may be considered able to consent by regulatory standards but who may require special social, psychological, or legal protection (such as persons with HIV or mental disorder, those undergoing stressful life events, or those who may be involved in crimes) should not be

considered for inclusion in the expansion. Likewise, surveys and focus groups on topics that might expose persons to psychological social or physical harm during the survey (as a result of stressful questioning) should not be excused.

Question 16: Should research involving surveys and related methodologies qualify for the Excused category only if they do not involve topics that are emotionally charged, such as sexual or physical abuse? If so, what entity should be responsible for determining whether a topic is or is not emotionally charged?

Research that involves emotionally charged topics should not be excused given the potential for psychological harm during participation and the possibility that IRB review could reduce or eliminate such harm. An institutional IRB that includes one or more psychologists, psychiatrists, or other mental health professionals would ideally be responsible for determining whether such survey topics necessitate IRB review.

Question 17: What specific social and behavioral research methodologies should fall within the Excused category? Under what circumstances, if any, should a study qualify for the Excused category if the study involves a form of deception (and if so, how should "deception" be defined)?

The current exemption categories are appropriate. Most research that involves deception should be subject to review, although some kinds of deception (such as interventions that involve randomizing question ordering in a survey), or psychological surveys that do not disclose their full purpose solely in order to reduce response bias but are otherwise not sensitive, may be appropriately exempt or excused.

Moreover, the proposed term "excused" may exacerbate this problem because less-experienced researchers may interpret this term to mean that informed consent or data security procedures are not required. A different term or phrase that better conveys the meaning of the category, such as "PI responsible for compliance," should be considered. Many researchers will also need to be more fully educated regarding the regulations and their application for them to successfully undertake these responsibilities.

Question 18: Currently some IRBs make determinations regarding whether clinical results should be returned to study participants. How should such determinations be made if the study now fits in the Excused category? Can standard algorithms be developed for when test results should be provided to participants and when they should not (e.g., if they can be clinically interpreted, they must be given to the participants)?

RAND does not believe standard algorithms can be developed that could fit all studies and tests. Results that can be clinically interpreted have, for various reasons in the past, occasionally been withheld from research participants unless they opted to receive them. For example, HIV status was not always disclosed when the disease was not very treatable. Similarly, prior to changes in insurance eligibility laws, it was not necessarily desirable to learn of one's genetic vulnerabilities for various conditions, and it may currently not be desirable for psychological reasons in some cases. Since it may be the case that new tests with unanticipated implications become available, it is unwise to attempt to generate rules for researchers to implement on their own.

Question 20: The term "Excused" may not be the ideal term to describe the studies that will come within the proposed revision of the current category of exempt studies, given that these studies will be subject to some protections that are actually greater than those that currently exist. Might a term such as "Registered" better emphasize that these studies will in fact be subject to a variety of requirements designed to protect participants? We welcome other suggestions for alternative labels that might be more appropriate.

RAND agrees that a change in terminology is needed, but we disagree with the proposed change because it replaces one vague and commonly misunderstood term with another. Adopting a new term will also require administrative changes for IRBs without any benefit in terms of administrative efficiency or protection of human subjects. In implementing the changes discussed in Questions 14–19, it would seem essential that researchers understand that "exemption" shifts the onus for ensuring compliance with the regulations from the IRB to the researcher and does not mean that the procedures do not require careful review (by someone) for such compliance. The proposed term "excused" may exacerbate this problem because less-experienced researchers may interpret this term to mean that informed consent or data security

procedures are not required. A term or phrase that better conveys the meaning of the category, such as “PI responsible for compliance,” should be considered. Many researchers will also need to be more fully educated regarding the regulations and their application for them to successfully undertake these responsibilities.

Issue 18: Broadening Exemption for Other Types of Studies in Social and Behavioral Sciences

Current rule	Changes being considered	Rationale for change
Issue 18: Currently, research studies in the social and behavioral sciences that do not qualify for exemption category 2, but that involve certain types of well-understood interactions with subjects (e.g., asking someone to watch a video and then conducting word association tests), require IRB review.	The ANPRM does not propose a specific change, but seeks public comment on whether a broad subset of studies using common social and behavioral science methodologies can be identified that should be eligible for exemption 2.	To identify areas of research that do not warrant the current degree of regulatory oversight so that review requirements are better calibrated to the level of risk.

Although studies in the social and behavioral sciences often use established paradigms, such as eliciting responses to stimuli presented by video, the content of such interventions can pose risks to research participants, e.g., by causing psychological distress. Implementing this change would require articulating a comprehensive set of standards to define minimal risk social and behavioral interventions.

Issue 19: Broadening Exemption for Use of Secondary Data

Current rule	Changes being considered	Rationale for change
<p>Issue 19: One of the six exempt categories applies to research involving the use of existing data, documents, records, and pathological or diagnostic specimens, but only if the sources are publicly available or if the information is recorded by researchers in such a manner that subjects cannot be identified, directly or through identifiers linked to them.</p>	<p>The requirements in this category that (1) all the data or specimens must exist as of the time that the study commences, and (2) the researcher cannot record and retain information that identifies the subjects, would be eliminated. If a researcher chooses to obtain and record identifiable information, the subject’s consent would generally be needed (as required by the current rules), but that could be obtained at the time the materials are collected by using a general, open-ended consent to future research. With regard to studies using existing biospecimens, see Issue 2 above.</p>	<p>The new data security protections obviate the need for limitations in this exempt category.</p>

Issue 19 concerns the one exemption category which concerns only secondary data—that is, no direct interaction with human subjects—and the existing requirement that the use of such data can be exempt only if the sources are publicly available or if the information is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to them.

Two changes to this exemption are being considered. The first would allow investigators to use de-identified data that are still being collected in the field (that is, not “already on the shelf”). RAND supports this change. In fact, the word “existing” in this exemption has long been a problem, especially when the results of longitudinal data

collections carried out by others are being used and complete data collection may not be finished for years.

However, while supporting this change, we would highlight one issue. To the extent that there are changes in the content or process of the ongoing data collection whose use for research is exempted, such changes could alter the identifiability of the data and, depending on the content of the data collected, the risk to subjects. Even if direct identifiers are removed in a process of de-identification, the potential for identifiability by inference may still be a concern. Although this issue can be addressed at the point in time when exemption is considered, if the data collection process or content is changed, a previously de-identified dataset could become more readily identifiable (e.g., use of some technologies in data collection could inadvertently add metadata that could increase identifiability or more-detailed demographic or other questions could aid identifiability by inference).

This potential provides a counterweight to some of the other proposals considered in this ANPRM—since a purely administrative review for such exemption (or “excusing”) decisions would mean that this issue would only be considered in detail by the investigator involved. Similarly, exempting such uses of data collected in still ongoing efforts indicates they would not be “seen again” for review—meaning that changes that increase identifiability might not be recognized and steps might not be taken to address the risk (e.g., by stripping metadata that increased identifiability).

In addition, if use of such data is exempted from review, it is important to underscore that the separation between the investigators using the data for research and the ongoing or future data collection activities should be maintained—i.e., the researchers should have no influence (at least no direct influence) over what data are collected during future phases of the collection, since such influence would break down the distinction between this class of “existing” secondary data and situations where investigators may not themselves be collecting research data but control their collection by others. This is of particular importance given the range of datasets to which this exemption might apply. For example, while its application to data collected in a regular government survey process would likely be straightforward, recent discussion of the collection of data by military or security organizations that are subsequently used for research purposes—and the provision of advice or consultation by researchers to such

organizations during ongoing operations—could be more problematic. Ensuring this separation could require oversight of the research, depending on the situation and the level of experience of the researchers involved in human subjects research—meaning that purely administrative review is insufficient.

Considering the broad exemption of use of “existing datasets” with solely administrative review also potentially creates situations in which datasets whose ethical status is viewed as compromised (e.g., historical cases of medical data collected from prisoners who were directly and intentionally harmed during its collection) or potentially in question might be used in research without review by anyone other than the researcher(s) involved. Though this situation is less likely to arise for datasets where there is broad consensus regarding their ethical standing, more-complicated cases have arisen in our experience where full IRB review was necessary to consider the standing of even existing datasets and whether the use of some types of data in research was ethically acceptable.

In considering the second proposed change, RAND does not support the proposal that researchers be allowed to record and retain information that identifies the subject if an open-ended consent for future research is administered at the time the data are collected. We believe that this proposal is problematic for both practical and ethical reasons.

First, the issue of developing clear, appropriate, and comprehensive consent forms—or processes—is addressed elsewhere in this ANPRM. Given the range of datasets to which this exemption might apply, we believe there are fundamental practical problems with crafting a general consent that could appropriately inform subjects about the potential risks of future research at the time when data are originally collected. For example, in the social sciences, investigators often get information about individuals through abstraction of records— such as health or criminal records. Depending on the purpose of the research and the specific content of those records, the risks associated with that abstraction and analysis could vary from none to significant. How a general consent form or process could be framed that would appropriately inform an individual’s decision to approve future use irrespective of the research design and content domain is not clear to us. Whether general data security standards could be assumed to fully address those risks to the same extent as that afforded by restricting use only to data in

de-identified form is unclear, even if such standards are always rigorously and faithfully implemented.

Second, we believe that administration of such a generalized consent at the time of data collection for many of these types of datasets also may break down the distinction between the use of datasets collected primarily not for research purposes (a central focus of the exemption category) and other research data collections that require review. Data collected in circumstances such as the course of medical treatment, non-voluntary interactions between citizens and the government (e.g., collection of data in the law enforcement or court systems), or during military or security activities are obtained in circumstances where individuals may not be in a position to fully assess the risks of consenting to future research use of those data (e.g., during the stressful period of an acute medical treatment) or to believe that they can freely refuse to provide a general consent for future data use. The requirement that such datasets be used only in de-identified form limits potential risk to those individuals, given questions about whether fully informed and voluntary consent could be given in those circumstances. The proposal that a general consent administered in such circumstances be used to broadly allow future research seems to undermine the core requirement for fully informed autonomous consent by research subjects.

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