

Streamlining Documentation Requirements for Expedited Studies

Question 1: Is the current definition of “minimal risk” in the regulations appropriate? If not, how should it be changed?

The University of Rochester believes that the current definition is largely adequate, but that it might be revised to expand and clarify the definition for use to assess risk.

The University of Rochester suggests a regulatory change to the current standard of “routine physical ... examinations” to allow more flexibility for investigators and IRBs. The common interpretation of “routine physical examinations” implies a set of medical procedures that are done as part of a “physical exam,” that is, measurements such as blood pressure, height, weight, visual acuity, and tests such as EKG, blood chemistry/cell-count, etc. It would give more latitude and be clearer to say “routine medical and dental examinations” because this encompasses the physical risks that the minimal risk standard defines, but are not limited to only the testing done in an “annual physical.” Other types of functional assessments and routine medical testing would be eligible, including medical procedures that do not require special written consent: for example, allergy skin testing, glucose tolerance testing, ocular tonometry with or without dilating drops, a single skin biopsy, and other common diagnostic testing techniques including ultrasound, infrared imaging, chest x-ray, MRI, and CT scans that deliver an effective dose of less than 3 Rem to adults and 0.3 Rem to children (ref: 21CFR361.1(b)(3)(i-ii)).

Although the current regulations stress the probability and magnitude of harm or discomfort as measures of risk, the University of Rochester believes that there is a third dimension in the determination: adequacy/effectiveness of risk mitigation mechanisms that are planned or in place to decrease risk. This third dimension is already somewhat captured in the approval criteria in section 111(a)(1)(i), but should be expanded upon in guidance with examples.

It would help to clarify what “daily life” means. We also believe that routine educational examinations and tests should be included in the definition, so a more complete regulatory definition would be (inserts underlined, deletions in ~~strikeout~~): “*Minimal risk* means that the probability and magnitude of harm or discomfort, ~~anticipated~~ introduced solely in by the research are not greater in and of themselves than those familiar and routine experiences ordinarily encountered in the daily life of the general population including or during the performance of routine ~~physical or~~ psychological, educational, medical, or dental examinations or tests.”

The University of Rochester does not believe a change to the minimal risk definition to include a standard for informational risk is necessary; however, we believe that what constitutes minimal informational risk in the course of collecting and storing data from research subjects should be discussed and should be elaborated upon in guidance.

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Federal guidance should be issued that incorporates the six SACHRP recommendations on risk determination (SACHRP Letter to HHS Secretary, January 31, 2008):

“The regulatory intent of minimal risk is to define a threshold of anticipated harm or discomfort associated with the research that is ‘acceptably-low’ or ‘low enough’ to justify expedited review or waiver of consent.

“The IRB’s evaluation of the harms and discomforts of the research should consider the nature of the study procedures, other study characteristics, subject characteristics, and steps taken to minimize risk.

“In its estimate of research-related risk, the IRB should carefully consider the characteristics of subjects to be enrolled in the research including an evaluation of subject susceptibility, vulnerability, resilience and experience in relation to the anticipated harms and discomforts of research involvement.

“To satisfy the definition of minimal risk, the estimate of the anticipated harms and discomforts of the research for the proposed study population may not be greater than an estimate of ‘the harms and discomforts ordinarily encountered in daily life or during the performance of routine medical and psychological examinations or tests.’

“While the harms and discomforts ordinarily encountered differ widely among individuals and individual populations, an ethically meaningful notion of ‘harms and discomforts ordinarily encountered’ should reflect ‘background risks’ that are familiar and part of the routine experience of life for ‘the average person’ in the ‘general population.’ It should not be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population.

“In summary, minimal risk should be applied in manner that recognizes that risks are procedure-specific and population-dependent, but that the notion of ‘acceptably-low’ risk is fixed. When the harms and discomforts of the proposed research as they are anticipated to impact the study participants are judged to fall below this acceptably-low risk threshold, the research is said to be ‘minimal risk’.”

The guidance should specifically develop the concept of risk minimization and mitigation, which would allow for the possibility that a study/procedure with slightly greater than minimal risk could become minimal risk, but would not allow all activities with greater than minimal risk to qualify as minimal risk, i.e., risk minimization/mitigation modifies probability and magnitude, but does not eliminate either. The guidance should underscore that an IRB cannot reject minimal risk status solely on the basis that risk minimization could be improved upon, e.g., investigators should not be required to destroy linkages in an otherwise minimal risk study even though it would arguably lessen the risk.

Question 2: Do 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?

While “assure” may be too strong a word, the University of Rochester believes that the suggestion in the ANPRM to eliminate routine continuing review for minimal risk studies is sound as long as changes to research are requested/approved and unanticipated problems are reported to the IRB if/when they occur. That said, continuing review does provide a reality check on the assumptions that lead the IRB to initially approve a study. Typically, the first continuing review after enrollment begins is the most valuable because the investigator and the IRB have information from actual experience on which to base further approval to conduct the study. Of course, the level of expected risk and the experience with the research methods used in minimal risk research rarely justify annual continuing review; the negative findings on continuing review tend to be best characterized as “documentation sloppiness.” We note that section 103(b) will need a conforming amendment and possibly 46.502(e)(2) as well because protocols will be active without a continuing review during the preceding twelve months (i.e., is the number collected from institutions to be reflective of research activity by investigators at the site or just IRB review activity, or both).

As part of continuing review, many sites require that the last signed consent form be submitted to the IRB. This procedure is useful in uncovering problems in the conduct of research. If annual continuing review is discontinued, it may be useful for federal guidance to be developed that would contain examples of auditing techniques that use methods less intensive than the current continuing review procedures to monitor research on an ongoing basis both on site and in simple, IRB office-based document review, such as requiring that the last signed consent form be submitted with a study completion report.

The criteria for IRBs to determine that an expedited initial review study should undergo continuing review should be based upon study-specific concerns that would affect the potential for increasing risk beyond minimal or that might lead to anticipated problems. For example, a new investigator or a student-investigator who may be unfamiliar with the techniques/methods to be used in a study may increase the chance of unrecognized (by the investigator) inadvertent risks and errors, e.g., recruiting inappropriate subjects or changing methods without approval. Research that involves vulnerable populations and/or some concern about study conduct that could not be addressed/assured in the initial review might be a reason to schedule a continuing review. If new data standards are developed and implemented, unfamiliarity with the data security mechanisms may lead to some difficulty and gaps when investigators try to apply the new regulations. This may be a reason to have a continuing review scheduled. Again, non-proscriptive guidance could be helpful for institutions in designing systems that are effective and efficient.

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?

The University of Rochester supports the suggestion in the ANPRM to eliminate the routine continuing review for studies with greater than minimal risk when the remaining study activities only include those that could have been approved under expedited review, as long as unanticipated problems are reported to the IRB if and when they occur or are discovered (presumably a rare occurrence). We note that section 103(b) will need a conforming amendment and possibly 46.502(e)(2) as well because protocols will be active without a continuing review during the preceding twelve months (i.e., is the number collected from institutions intended to be reflective of overall research activity by investigators at the site or just IRB review activity, or both). We believe that requiring continuing review in these conditions is unnecessary, and the justification for requiring such review currently given by OHRP in guidance (Guidance on IRB Continuing Review of Research; November 10, 2010) seems to unreasonably stretch a point. As stated in that guidance, “Continuing review and re-approval of a research project at least annually is required so long as the project continues to [...] obtain: data about the subjects of the research through intervention or interaction with them; or identifiable private information about the subjects of the research. With respect to obtaining identifiable private information, [...] OHRP considers obtaining identifiable private information to include: [...] using, studying, or analyzing identifiable private information (including identifiable biological specimens), even if the information was already in the possession of the investigator before the research begins.” We agree with the suggestion in the ANPRM and believe it will relieve the unnecessary burden this peculiar interpretation has caused.

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

The University of Rochester believes that the current standard of “probability” and “magnitude” combined with the adequacy and effectiveness of risk mitigation mechanisms that are planned or in place to decrease risk adequately encompasses the prediction of whether an event might occur.

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?

The current regulations use both the probability and magnitude of harm or discomfort as measures of risk. Over the years since this standard was written, regulators and IRBs seem to have decided to err on the conservative side of this calculus. The standard has become if any severe risk is possible, no matter how small the probability, then it is greater than minimal risk. This distorts the ethical standards and does not acknowledge that there is a third dimension in risk determination, i.e., adequacy/effectiveness of risk mitigation mechanisms that are planned or in place to decrease risk. The concept of risk mitigation is somewhat captured in section 111(a)(1)(i). The University of Rochester believes that the determination of minimal risk should include risk mitigation.

Frankly, we live in a dangerous world, even those of us who are healthy and live in what could be considered a safe environment. What protects us from daily harm is risk mitigation—decreasing the chance that physical, psychological, and informational harm will befall us or lessening the damage that could be done if a risk becomes real. The system should not be driven by the most sensitive among us. Federal guidance and reason must allow investigators and IRBs to establish reasonable risk-reduction methods (e.g., exclusion criteria and specific warnings in the consent process) that would provide protection for the few highly susceptible individuals who might potentially be exposed to the research. No specific measures or tests to assess risk are needed.

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?

For a long time, there have been debates whether including a specific question about, for example, being abused as a child, in a survey form or during an interview could be an adverse psychological risk. Granted, it is conceivable, perhaps even inevitable, that some person somewhere could become upset or even have a psychological crisis from awakening old memories; however, the system should not be driven by the least common denominator. The University of Rochester believes that the regulations must allow investigators and IRBs to establish reasonable risk-reduction methods (e.g., exclusion criteria and specific warnings in the consent process) that would provide adequate protection (the regulatory standard) for the few highly susceptible individuals who might potentially be exposed to the research.

The University of Rochester supports the concept in the ANPRM that places legal risk, social risk, economic risk, and educational risk in a single category of “informational risk,” which derive from inappropriate use or disclosure of information and could be harmful to study subjects or groups. We agree that most research risks to the individual can be categorized into one of three major types—physical, psychological, and informational risks—with other harms, such as legal, social, and economic, viewed as variations on the core categories. We look forward to further expansion of this concept in federal guidance and how we might implement institutional systems for investigators and our IRB to consider risk in research development and review.

Any research that uses only surveys or surveys and interviews with adults who can give legally effective consent should be considered minimal risk, regardless of the actual questions in those surveys and interviews. IRBs should not be required to review minimal risk questionnaires, study measures, etc., but investigators should certify that the appropriate and adequate protections and risk mitigation strategies will be in place to maintain the risk level at or below minimal. Surveys and interviews with children as subjects may need to have an independent determination whether the research risk is commensurate with this category because of the additional privacy concerns for children and parents. For adults who have been adjudicated as legally incompetent or for those with temporary or permanent decisional incapacity, survey and interview research that will use permission of a legally authorized representative to enroll subjects should be required to have a determination whether the research is minimal risk. The regulations and/or guidance should not use the

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term “competent adults.” Instead, it should use the term “an adult who is able to give legally effective informed consent.” Guidance should explain the definition of “incapacitated.”

The evaluation of the risks of the research should consider steps taken to minimize risk, the nature of the study procedures, and subject characteristics. SACHRP suggested an evaluation of subject vulnerability (which the regulations define as susceptible to undue influence), susceptibility (to risk), resilience, and prior experience in relation to the risks and that the consideration should reflect “background risks” that are familiar and part of the routine experience of life for “the average [healthy] person” in the “general population.” Following this advice, the risk assessment should not be based on risks encountered in the daily lives of the proposed subjects if those risks are greater than those encountered by the general population, i.e., it would be appropriate to use subject population characteristics if they decrease susceptibility to the risks involved in the research (e.g., exercise testing in trained athletes), but not if the exposure to risk is higher than the general population risk (e.g., risk of death in stroke patients).

For mental health patients, there may be an increased susceptibility to risk (e.g., proclivity for relapse) if they are to be involved in some types of research. As with patients who have well-controlled chronic disease or unstable critical disease, increased susceptibility to risk should be considered in studies that employ untreated placebo controls or active treatment washout periods—particularly those involving rapid withdrawal or unsupervised withdrawal. Thus, the characteristics of this population should be considered in the justification for studies and the inclusion and exclusion criteria. In research with populations susceptible to risks, the person obtaining consent (or permission) has an increased obligation to ensure that the subjects (or their authorized representatives) are fully aware of the nature of the research design and its possible risks.

However, there are areas of social and behavioral research that may put an individual at greater risk, even with appropriate mitigation strategies. For example, research on illegal behavior would raise a greater informational risk and likely would be a good candidate for greater scrutiny. There are some established mechanisms for mitigation strategies, such as certificates of confidentiality. The purpose of the certificate is to protect identifiable research information from forced disclosure allowing those with access to research records to refuse to disclose identifying information on subjects to any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. But the certificate of confidentiality will not protect against breaches in confidentiality, so these studies may be greater than minimal risk.

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?

The University of Rochester believes that most minimal risk research should qualify for review under expedited procedures. A less burdensome mechanism than that suggested in the ANPRM would be to amend section 110 to allow any non-exempt study that the IRB determines to meet the minimal risk definition to receive expedited review (i.e., delete the requirement that the study must be both found to be minimal risk and on the published list). An example of added burden under the current regulations is that the IRB (staff, chair, or

reviewer) has to determine the study is minimal risk and then has to find it on the list. If all of the study activities are not there, then, even though it is minimal risk, it must be sent to a convened board, where the full membership has to determine it is minimal risk—again. Taking minimal risk studies to the full board adds additional burden because each study reviewed under convened procedures requires documentation though minutes and usually additional checklists and is wasteful of board members' time.

The University of Rochester believes that the level of procedural detail in the current list-based regulation is neither appropriate nor efficient. The current list should be moved to federal guidance and the categories should be expanded upon to develop a list of “safe-harbor” activities for determinations. These listed activities should be instructive examples of studies that are deemed to be minimal risk, not a comprehensive list of all possibilities. IRBs should have the discretion to review, under expedited procedures, studies not on the list but determined to be minimal risk.

Another reason to allow an IRB to make the minimal risk determination rather than finding activities on the expedited list relates to the management of ever-changing protocols. With each amendment, activities in different expedited categories can be added or removed, thus requiring administrative oversight and review to ensure the categories assigned are correct and recorded in IRB documentation. This is busywork and adds no benefit.

We believe that there are some activities on the list that should be revised. Category 1 (studies of non-IND drugs and non-IDE medical devices) should be revised to clarify what studies are permissible and to give examples. Also, standard intravenous lines (IVs) and peripherally inserted central catheters (PICC lines) should be added to the list of acceptable blood drawing methods in Category 2. Category 5 should be changed to permit research involving materials that have been collected or will be collected for purposes other than for the research undergoing expedited review. If there is no relief from the current task of requiring IRBs to assign expedited categories, then no categories can be removed to account for multiple activities within the same protocol (e.g., a study that uses a blood draw (Category 2), reviews medical records (Category 5), and administers a survey (Category 7)).

Question 8: Should some threshold for radiological exams performed for research purposes, that is calibrated to [the] background level of exposure, be identified as involving no more than minimal risk?

Yes, some exposure to radiation should be identified as involving no more than minimal risk. While we recognize that there is no minimum level of radiation exposure that is guaranteed to be totally free from risk, the University of Rochester uses about two weeks of background radiation as a rule-of-thumb. We suggest allowing common diagnostic testing techniques, such as a standard x-ray series (e.g., chest x-rays, a bone x-ray (e.g., ankle films) or other “plain films” of a limited part of the body), dexa-scans, dental x-rays, MRI, and CT scans that deliver an effective dose of less than 3 Rem to adults and 0.3 Rem to children (ref: 21CFR361.1(b)(3)(i-ii)). Because radiation exposure is cumulative over a lifetime, it is difficult—but not impossible—to establish “safe” exposures. Investigators must always be cognizant that individual thresholds and risk should be viewed in relation to cumulative exposure; exclusion criteria may need to limit persons with multiple exposures from enrolling in some studies.

<p>Given that the FDA has regulations about the use of radiation and radioactive materials in research in 21CFR361(b)(3), including the use of a separate committee with specialties in nuclear medicine, radioactive drugs, and radiation safety, it seems that this institutional committee could make determinations about types and categories of exposure to radiation that could be considered to be minimal risk. Guidance documents issued across agencies on generally accepted standards would be useful in making institutional policies.</p>
<p>Question 9: How frequently should a mandatory review and update of the list of research activities that are minimal risk that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently?</p>
<p>The expedited review list has only been revised once since it was implemented in 1981. If the list is retained, preferably as guidance, it should be revised every five years; more frequent revision would be difficult for institutional training programs, published training guides and texts, etc., and could cause investigator confusion. The University of Rochester believes that this list should be subject to careful review and updating by a convened, multidisciplinary task force or by a body such as SACHRP. Input from the Common Rule agencies should be solicited in the review process.</p>
<p>Question 10: Which, if any, of the current criteria for IRB approval under 45 CFR46.111 should not apply to a study that qualifies for expedited review?</p>
<p>For minimal risk research, the IRB's consideration of risk mitigation/minimization (111(a)(1)(i)), informed consent (111.a.4-5), privacy and confidentiality (111(a)(7)), and special concerns for vulnerable populations (111(b)) are sufficient to provide adequate protection.</p> <p>The following sections in section 111 are not necessary for minimal risk research that qualifies for expedited review:</p> <ul style="list-style-type: none">a.1.ii (risk minimization by procedures already being performed is not relevant)a.2 (adequate risk-benefit balance can be presumed to exist in minimal risk research)a.3 (subject selection and vulnerable populations are adequately covered by 111(b))a.6 (data monitoring is not relevant for minimal risk research and is covered by (a)(7)) <p>The University of Rochester believes that, rather than change the regulations and create a potentially confusing two-tier system, this realignment of review emphasis and documentation should be accomplished through guidance.</p>
<p>Question 11: What are the advantages [and disadvantages] of requiring that expedited review be conducted by an IRB member? Would it be appropriate to instead allow [expedited] 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?</p>
<p>The University of Rochester supports the change to allow appropriately trained and qualified IRB staff to review minimal risk studies under expedited procedures. We believe that the main advantage to member-review is maintaining the long-standing mechanism of peer review, which promotes respect for the advice and counsel in safeguarding the rights and welfare of human subjects. The main disadvantages are the time demand on faculty/staff</p>

members and IRB chairs and the occasional lack of timeliness when reviewers are busy. Also, IRB members are typically less attuned to the regulatory requirements of expedited review than are IRB chairs, who in turn may be less experienced with federal human subject protection regulations than professional IRB staff; so the quality of review may be variable within the institution depending on the assigned reviewer.

The Common Rule regulations presume convened meeting IRB review by peers as the default; the expedited review mechanism was developed to allow a board review process that did not require a meeting. Underlying the whole ANPRM is the question of whether it is time to update the almost 40-year-old regulations to account for the way research is conducted today. When the regulations were first drafted, the widespread assumption was that the IRB would exist only as a peer committee, that there would be no, or minimal, staff support; today, the IRB support infrastructure has grown to the point that, at least in academic research centers, IRB office staff often outnumber committee members. In these settings, rather than having a few hours of the IRB chair's secretary's time, dedicated full-time IRB staff are now typically well trained in the regulations, often have professional degrees, and increasingly are certificated (CIP) in IRB operations and regulations.

If the ANPRM results in removing studies eligible for expedited IRB review from the IRB committee portfolio (i.e., allowing review by non-members), that would be a major departure from the current expectation that an "ethics" review needs a peer-review committee or at least a peer representative from a committee. The current regulations require that expedited review be conducted by the IRB chair or an experienced member; this experience requirement ensures not only that the regulations are taken into consideration when reviewing, but also that the global sense and sensitivities of the IRB are considered as well as the obligations and capabilities of investigators, which are drawn from the reviewer's own experience. It takes some time to learn which issues are of concern to members and the institution. This sense of the board and institution can be acquired by IRB staff as they attend and participate in supporting IRB meetings. In fact, the IRB staff is often more attuned to local context and regulatory requirements than are members because of longer service, more actual experience, and greater regulatory knowledge. One area where IRB staff may be less qualified is in designing and conducting research studies, so an IRB staff member with only administrative experience may not be sufficiently qualified as a "peer" reviewer. If studies are allowed to be reviewed by appointed IRB staff, then institutions will need to set standards as part of the assignment of duties. Designation of reviewers by an IRB chair, institutional official (IO), or institutional human research protection program director should be based upon experience and knowledge of the regulations. We believe that no further elaboration needs to be made in the regulations. Federal guidance might offer some examples that institutions could use in formally designating reviewers.

An additional potential disadvantage stems from the reality that not all research is conducted by major centers staffed with IRB professionals. Many small facilities and clinical sites conduct research, so the 1970s model of the independent investigator is still at play; for these research sites, the availability, expertise, and knowledge of IRB staff may be highly variable. For that reason, it may be important to limit the staff-review to institutions with an accredited human research protection program or to certified IRB professionals.

It might be useful to maintain some degree of peer review in the expedited review process, so this part of the regulation (110) might be worded to say something such as (inserts underlined): “Under an expedited review procedure, the review may be carried out by the IRB chairperson, by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB, or by one or more experienced IRB staff members designated by the IRB chairperson. Designations should be based upon qualifications, competence, IRB experience, and knowledge of the regulations. Copies of such written designations should be kept as with other IRB documentation per §46.115.”

The University of Rochester believes that the effort to make sure that such persons are appropriately trained would not outweigh the benefits from making this change, if the regulations are not overly specific and do not require reporting/filing with federal agencies. Procedural detail is not appropriate for regulations; federal guidance should be developed to inform the implementation of institutional procedures to meet regulatory requirements.

Question 12: Are there other specific changes that could be made to reduce the burden imposed on investigators 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 [expedited] protocols or consent forms? Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated? Are there specific additions to [expedited] 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?

The ANPRM correctly states that “investigators typically must submit the same documents including a detailed protocol, informed consent documents, and any other supporting documents, regardless of whether the study will be reviewed by a convened IRB or be approved by the expedited review process.” The University of Rochester believes that submitting detailed protocol and informed consent documents is essential for making the required determination whether research qualifies for expedited review and this process does not add significantly to the investigator’s burden because these documents must be developed in order to conduct the study. We believe that IRB review of these documents does enhance human subject protection. We also believe that for minimal risk studies, other documents such as recruitment materials, flyers, business cards, screening tools, etc., should not be required to be reviewed by the IRB; the investigator should have the responsibility for ensuring that any document that the subject comes into contact with is appropriate. Review of such materials could be an optional service offered by the IRB if institutions so desire.

The University of Rochester believes that the OHRP guidance that IRBs must review grant/funding applications as part of the approval process should be immediately rescinded. This review rarely provides any additional information beyond what is requested and collected in the IRB application for review and is a major burden for IRBs and an unnecessary inconvenience for investigators.

Although investigator-developed measurement tools may need to be submitted, standard validated measures (e.g., MMPI, Beck Depression Scale, and Mini-Mental Status) should not be required to be submitted to IRBs.

In 2000, the University of Rochester began to refuse to consider individual adverse event reports and instead accepts a summary at continuing review. If continuing review for minimal risk studies is no longer required, as the ANPRM suggests, then this annual summary would be eliminated, but it could be submitted with the investigator's IRB close-out request.

Regarding mandatory review frequency, we agree with the elimination of mandatory annual continuing review for minimal risk studies. We suggest that section 109(e) should be changed to allow IRBs the authority to decide how frequently to review approved research (i.e., continuing review) for all research, regardless of risk. The interval of review could be one year, a shorter period of time, a longer period of time, or not at all depending upon the level and nature of risk posed by the research. Thus, the continuing review cycle would be set for each study based on the IRB's assessment of risk not as a *pro forma* action. We note that section 103(b) will need a conforming amendment, and possibly 45CFR46.502(e)(2) as well, because protocols will be active without a continuing review during the preceding twelve months (i.e., is the number collected from institutions to be reflective of research activity by investigators at the site or just IRB review activity, or both).

We believe that the OHRP guidance that forces investigators and IRBs to put excessive detail in consent forms should be eliminated. Although we understand that the absolute numbers of pages in a consent form may not change, we suggest that the subject signature form need only be a summary of the information provided in the consent discussion, i.e., consent signature forms do not need to contain the exact wording provided in the consent discussion. Additional information would be appended to the shorter signature form. In the regulations, section 116 lists the elements of information that must be conveyed in the consent discussion; section 117 requires consent forms to embody the elements in 116. It is the OHRP interpretation of the word "embody" that contributes to the length and excessive detail in consent forms—both minimal risk and greater than minimal risk. The sheer size of a consent form is intimidating to potential subjects and family members who are considering research. Especially for people whose language/reading skills are limited, such a lengthy consent form unnecessarily increases the perception of secrecy and risk. It is our experience that family members sometimes use the sheer size of the consent form as negative leverage against the potential subject: "Look at that big form; they are obviously trying to hurt you with that drug." The demand that every part of the consent discussion be included in the written signature document is a deterrent to subject consideration of research and participation. This is a problem that could be solved by re-enforcing that investigators are responsible for complying with section 116. IRBs should not be required to review and approve every fact, comma, and period. IRBs can and should review the signature form (consent form) that will be used to meet the section 117 signature requirements, but that form should not automatically include the detail that is required to be provided by investigators in compliance with section 116. Section 116 and 117 need to be de-linked in everyone's minds. Investigators need to provide subjects with the detailed elements of consent, but the subject signature form need only be a summary of the information provided, i.e., consent signature forms need not contain all of the wording provided in the consent process/discussion, which is the case now. If this de-linking approach is used, then consent forms can be significantly shortened and improved, even consent forms for greater than minimal risk studies. If

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sections 116 and 117 are de-linked, it would be possible to use a fairly standard template or boilerplate style signature/consent form for minimal risk studies, as the ANPRM suggests. To that end, we believe that section 117(b)(1) should be revised to replace the word “embodies” with the word “summarizes.” Thus, the revised regulation would be: “A written consent document that summarizes the elements of informed consent required by §46.116. This form”

The de-linking of sections 116 and 117 should be accomplished largely by change in guidance, with only the general permissions/standards in the regulations themselves. Federal guidance should make it clear that, for purposes of the documentation of the subject’s or representative’s signature, the summary need not be and should not be a detailed summary, but rather general statements about the informational elements.

In the spirit of harmonization, OHRP should be the lead agency and publisher of standard format guidelines, but input from other Common Rule agencies and the research community should be obtained.

Question 13: 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 Section B(1) [no continuing review for studies in data analysis phase or clinical follow-up only]? Should IRBs have to report instances in which they require continuing review [B(2)(b)] or convened IRB review [B(2)(a)(ii)] 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?

While the University of Rochester understands the desire for federal agencies to gather information about the types of studies that cause IRBs to override the defaults, we believe that the burden of mandatory periodic reporting outweighs the possible benefit. Typically, IRBs are more than willing to share experiences, so establishing a voluntary internet-based site to collect voluntary reports would seem a more appropriate way to achieve the federal goal. Also, national meetings and input sessions at OHRP-sponsored regional meetings would allow for the collection of input from IRB professionals from around the nation.

Revising the Exempt Categories

Question 14: Are expansions in the types of studies [removal of limitations and addition of certain types of social and behavioral research with competent adults] 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?

The University of Rochester does not support creating an “excused category.” The term “excused” or “partially excused” needs to be abandoned. If a new term is needed to convey that there is regulation, even if minimal, of this type of human subject research, then perhaps the term “registered” might be more appropriate. Rather than rename the exempt category of studies, we believe that it is best to retain the exempt categories and to add conditions for

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permitting the exemption to 101(b) including, for example, the requirement to register the studies with an institutional entity. Additional conditions might include security protections for data in cases where potential breaches of confidentiality have real, definable consequences for human subjects (rather than just theoretical ones) and some level of informed consent or permission where there is the potential to negatively affect subjects if consent is not obtained. We agree that research that is of such low risk should be “exempt” from the three major protections in the Common Rule, i.e., these studies should not require an assurance (FWA) for funding, nor IRB review (i.e., application of the section 111 approval criteria), nor research consent (i.e., inclusion of all section 116 elements and signature per 117). However, we believe they should not be exempt from ensuring adequate protections for research subjects by adhering to ethical standards, such as those in the Belmont Report and professional ethics codes.

The University of Rochester supports expanding the exempt categories to provide more examples/categories, e.g., research tool/measurement development, psychometric research, cognition research, speech and childhood development research, word association tasks, anonymous “internet research” (including web-based, email, tweeting, texting, etc.) and epidemiology, to name a few. Also, we suggest adding a new exempt category for research that uses “activities of daily living” as the research procedures, e.g., walking, talking, viewing/seeing, listening, answering questions, filling out forms, etc.

The regulations and/or guidance should not use the term “competent adults”; instead, it should use the phrase “an adult who is able to give legally effective informed consent.” Guidance should explain the definition of “incapacitated.” In addition, changes to exempt studies should be tracked (through amendment filing) in case the proposed change would require either expedited or full board review because of increased risk.

Subjects are not aware of the review level that is attached to the study, so changes in exempt categories would be unlikely to discourage individuals from participating in research. However, if there isn’t a clear understanding that data is de-identified or protected, subjects may not participate when sensitive information is collected.

In our experience, investigators have difficulty judging both the category of review and the risk level of studies. The problem with allowing the investigator to determine a level of risk and assess strategies to address that risk is that there is an inherent conflict that is not present when the determination is made by an independent review process (e.g., IRB, institutional committee, etc.). The University of Rochester agrees that the review process should be more streamlined, but if the regulations or guidance give investigators this responsibility, then there needs to be some institutional accountability for investigators. Non-proscriptive federal guidance could be developed that harmonizes, for all investigators, the expectations placed in recent FDA guidance (Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009).

On a cautionary note, however, students and new investigators typically begin their careers with exempt-level research; therefore, they do not have the experience to make decisions on whether their research qualifies. Beginning investigators who work in healthcare

<p>organizations and can access PHI of patients and employees for what they perceive as non-research activity are particularly susceptible to this error. The independent pre-review system currently in place allows for education and training to occur, which gives these new investigators a better understanding of the categories, how their research fits or not, and how the human subject protection program works.</p>
<p>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?</p>
<p>The University of Rochester believes that switching to an “excused” category is not necessary and the exempt categories should be retained. Exempt Category-2 studies involving adults capable of giving legally informed consent should not require prospective review, even if they include sensitive data and are identifiable. Vulnerable populations (e.g., individuals with diminished capacity and children) may require prospective review to make a determination that the study risk is commensurate with the exempt category, but we believe that is an institutional policy decision. We believe that each institution is best suited to determine when and if a procedure that falls within Category 2 for children, and this flexibility should be allowed by removing overly restrictive, complex, and detailed wording from the regulations (see SACHRP Letter to HHS Secretary, September 18, 2008).</p>
<p>Question 16: Should research involving surveys and related [methods] 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?</p>
<p>Assuming that the concern is that investigators will inappropriately assign studies to the exempt categories, examples in federal guidance of which topics are considered “emotionally charged” would be helpful to institutions in designing procedures to comply with regulatory expectations and for investigators when designing studies. While it is not always the case, one could expect that the investigator should know the cultural norms of the subjects in the study better than reviewers.</p>
<p>Question 17: What specific social and behavioral research study [methods] 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? How should “deception” be defined?</p>
<p>A problem with adding new categories for social and behavioral studies is that there may not be a common language when defining these areas.</p> <p>The University of Rochester believes that a deception study (one that, because of scientifically-based justification, intentionally misleads subjects or that withholds full information about the purpose or nature of the research until the subject has completed the experiment) should not qualify for an exemption; it should be reviewed at least as expedited or even perhaps under full board review if the risk is unique. Specific deception studies may even justify a continuing review if they present a potential for unrecognized unanticipated problems, for example.</p>

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Question 18: How should determinations regarding whether clinical results should be returned to study participants 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)?

The University of Rochester believes that research results may or may not (if information is from tests and/or procedures that do not use standard diagnostic tests) be appropriate to be given to the subjects. We believe that if the investigator can make the determination of the risk/review of an exempt study, then they should be able to determine on their own if the results should be shared with the study subjects. We also believe that there may need to be some discussion in the consent process about the relevance or non-relevance to the individual that would share that responsibility for making the decision and should help the subject not to misinterpret the information that is received.

The standard that the University of Rochester uses is that only test results that are conducted by a qualified clinician, are performed in a clinically certified laboratory, have clinical relevance, and can be used to determine a course of clinical care may be returned to subjects. All four conditions must be present. Typically, information generated in clinical trials meets this standard, but most other research does not.

In some small studies, the publication of overall results may allow study subjects to infer their personal results on non-clinical tests. In this circumstance, under the principle of respect for persons, the University supports and encourages providing those results to subjects prior to study publication, even though the results do not meet all four of our usual conditions.

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?

Although there is not a direct ANPRM question on the proposed one-page registration form, the University of Rochester believes that such a detailed requirement should not be a regulatory requirement. We might be supportive of an internal institutional system that used a process similar to that of filing a Form FDA 1572. That is, the investigator would provide contact information and basic information about the research (study title, other investigators/staff, expected enrollment, etc.), indicate under which exempt category the research falls, and then formally commit to following good research practices (similar to the list of expectations contained above the signature line on the 1572). Federal guidance could be developed that could propose a format and explain the possible institutional use and suggest simplified review mechanisms for the exempt category, e.g., the 1572-like form submitted to the IRB or “registered” with some institutional office.

The University of Rochester does not support a waiting period because, rather than “allow” time for institutions to look at registration forms, a waiting period would devolve into requiring institutions (and most likely via the IRB) to determine whether the proposed studies should be exempt. In other words, a waiting-period-review would erase any decrease in burden that the registration process would achieve.

We believe that procedural detail is not appropriate for regulations (i.e., page limits and one-week waiting period). The creation of procedures is an institutional responsibility. Federal guidance is the best way to inform the development of institutional procedures to meet regulatory requirements.

Question 20: The term “Excused” may not be ideal 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 suggestions for an alternative label that might be more appropriate.

As stated above, rather than rename this category of studies, the University of Rochester believes that it is best to retain the exempt categories but to add conditions for permitting the exemption in 101(b), including the requirement to register the studies with an institutional entity. Additionally, the regulations could require, as conditions for exemption, security protections for data in cases where potential breaches of confidentiality have real, definable consequences for human subjects. Research that is of such low risk should not require an assurance (FWA), IRB review, or research consent (i.e., inclusion of all section 116 elements and 117 documentation requirements).

The University of Rochester believes that the current conditional model that 101(b) uses could be refined and clarified to add additional informational risk protections into the regulations themselves. We believe that Category 2 can be simplified as the ANPRM suggests and combining Categories 2 and 3 would help further simplify the regulations. Also, we support clarifying Category 4 in line with the ANPRM suggestion, to include the secondary use of material collected for purposes other than the exempt research activity. Because biospecimens are somewhat different from documents and records, we propose that a new category could replace the current Category 3, which would include collections of biospecimens. Also, Category 5 should be expanded to include public health activities and all governmentally directed research in this area, whether federal, state or local. This will be especially important if the application of the regulations is expanded to cover non-federal research based on receiving any funds from Common Rule agencies. We suggest a revised section 101(b) could read:

“(b) Unless otherwise required by department or agency heads, research activities that are registered with the institution and in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices.
- (2) Research involving the use of educational tests (e.g., cognitive, diagnostic, aptitude, and achievement), survey procedures, interview procedures or observation of public behavior, if:
 - (i) the human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) one or more federal statutes require without exception that the confidentiality of any personally identifiable information will be maintained throughout the research and thereafter; or
 - (iii) the confidentiality of any personally identifiable information will be maintained throughout the research and thereafter under the following data security standards:[insert new privacy and data security standards].

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- (3) [delete current 3 and replace with:] Research involving the secondary use of biospecimens (pathological, diagnostic or banked specimens) if the confidentiality of any personally identifiable information will be maintained throughout the research and thereafter under the following data security standards:[insert new privacy and data security standards].
- (4) Research involving the secondary use of material (data, documents and records) collected for purposes other than for the exempt research activity, if the source is publicly available or if the confidentiality of any personally identifiable information will be maintained throughout the research and thereafter under the following data security standards:[insert new privacy and data security standards].
- (5) Research and demonstration projects which are conducted by or subject to the approval of federal, state or local governments, and which are designed to study, evaluate, or otherwise examine: (i) public health, benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- (6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.”

Again, we remind HHS that procedural detail is not appropriate for regulations (i.e., listing examples as is done in the first category now). Federal guidance should provide examples and suggestions for implementing the regulations for determining exemptions; this guidance will be critical given the ANPRM recommendation that investigators make these determinations themselves. The University of Rochester believes that the SACHRP recommendations (SACHRP Letter to HHS Secretary, January 31, 2008) on clarifications to the exempt categories are appropriate and should be incorporated in federal guidance.

Question 21: Is it appropriate to require institutions holding an FWA to conduct retrospective [registration form] 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?

The University of Rochester believes that audits of the ANPRM-suggested registration forms alone would only ensure that investigators are properly completing the form, but looking at forms would do nothing to determine if the investigators are in fact assigning the appropriate level of review for their research. Mandatory form-audit requirements would be an economic and administrative burden on IRBs, institutions, and investigators with no benefit. It is not even clear what standards such audits could use. An audit (or pre-review) where research documents are compared to the protocol is the only way to determine if the investigator’s decision is correct.

The problem with conducting retrospective audits is that they do little to address actual protection of subjects because audits are an after-the-fact compliance evaluation of the institution and its investigators. Prospective review can identify potential problems before they occur, thus protecting human subjects; retrospective audit finds problems that have occurred and can only offer mitigation of harm.

The University of Rochester is concerned that the ANPRM does not address another particularly vexing problem that would accompany a system based on retrospective audits: how institutions would be expected to deal with findings of misapplication of the categories. We are adamantly opposed to treating these findings as “non-compliance” in the regulatory sense, which trigger federal reporting requirements and so forth. *Post hoc* monitoring for exempt studies should be implemented by institutions only as an educational and operational activity to assess experience with investigator classifications and to make adjustments and appropriate corrections where necessary, but with no federal penalties or reporting. Non-proscriptive federal guidance might suggest ways to track such findings so that, if requested, an institution could provide a summary of its audit experiences over a defined time frame.

Institutions should have the authority to determine procedures, such as auditing, and what level of quality improvement activity is appropriate based on the types of studies conducted at the institution and its experience with these studies. Random selection is an acceptable audit method, and while it would be helpful to have general guidance on methods to use to set the minimum percentage to be audited, that level of procedural detail is not appropriate for regulations (i.e., specifying a required minimum percentage). The creation of procedures is an institutional responsibility. Federal guidance works best to inform the development of institutional procedures to meet regulatory requirements. One area that non-proscriptive guidance could cover is what institutions might consider when audits uncover incorrect determinations or a pattern of incorrect determinations, i.e., should investigators demonstrating a lack of knowledge or skill at applying the categories be required to have training, be prohibited from further self-determinations, or other sanctions.

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 investigators possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category? By allowing investigators to make their own determinations, without prospective independent review, will protections for some subjects be inappropriately weakened? If allowing investigators 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? Will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the [registration form] audits?

If the investigator’s exempt determination was incorrect, they could be inappropriately conducting research for months or years. If there is no pre-review, a full audit where research documents are compared to the protocol is the only way to determine if the investigator’s decision is correct.

The form-audit mechanism suggested in the ANPRM would be less work for both the investigator and the IRB than the current system, but it will do nothing to determine if the investigators are assigning the appropriate level of review for their research. We believe that the burden from this proposed method will result from investigators making an incorrect determination and then having to take after-the-fact corrective actions for harm done.

Prospective review catches problems before they occur, thus protecting human subjects; retrospective audit finds problems that have occurred and can only lead to mitigation of harm. As Benjamin Franklin said, “an ounce of prevention is worth a pound of cure.” Audits can be a large burden on the IRB office and the investigators as well. More resources would need to be put into auditing and monitoring these minimal risk studies, when IRBs should be auditing and monitoring the studies with greater than minimal risk. In these times of decreasing budgets and scarce resources, the federal government should be particularly cognizant of unfunded mandates.

The problem with allowing the investigator to determine a level of risk and assess strategies to address risk is that there is an inherent conflict that is not present when the determination is made by an independent review process (e.g., IRB, institutional committee, etc.). The University of Rochester, like other academic institutions, has had instances where investigators (typically students or trainees) have conducted research without IRB approval because they did not understand that their study did not fit into an exempt category; they only find out when they go to publish and the manuscript is rejected because it did not have an IRB approval.

Students and new investigators often begin their careers with this level of research (exempt); therefore, they do not have the experience to make these decisions, which can put the institution at risk. The independent pre-review system currently in place allows for education and training to occur, which gives these new investigators a better understanding of the categories, how their research fits, and how the human subject protection program works.

Streamlining the process by using a simple form placing the burden on investigators to require them to justify the claim that the research falls under an exempt category would be potentially beneficial. However, the form must be well thought out and provide specific criteria that the investigator must show to ensure the determination of exempt category is indeed justified. If the form is developed as described above it may be appropriate to conduct an audit of the form and the study plan to ensure that the proper category was selected, but that would not be able to ensure that the research is being conducted according to the protocol.

Question 23: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens as described in Section 3(a)(3) [the secondary use of data or biospecimens collected for other purposes]? Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? Should a request to waive informed consent trigger a requirement for IRB review?

The University of Rochester believes that it should be permissible to not obtain additional consent if the existing data and biospecimens are de-identified because it meets the definition of “not human subject research.” This presumes there is no intention of the investigators to identify individuals in order to contact them. It is important to note, for harmonization purposes, that neither IRB review nor consent can be waived for FDA studies.

For identified existing data and biospecimens, we believe that the focus should be avoiding harm to individuals and identifiable communities of individuals. Therefore, as long as the published results cannot be traced to any individual or community and identifying links in the data are destroyed, consent should not be required. We believe that it does not matter if the data/specimens were originally collected for research or non-research purposes; however, the IRB should ensure the proper protections are in place and that the waiver is justified, i.e., that this should not be left up to the investigator.

De-identified biospecimens with or without annotated data by definition cannot be traced back to the subjects by the investigators using the data. This ensures that the subjects are protected from inadvertent psychological or social risk from scientific findings from novel analysis of their biospecimens and data by a wall of anonymity. Therefore, a waiver of consent should be permissible in research using de-identified biospecimens with annotated data and should not trigger a requirement for IRB review.

Rather than requiring a waiver procedure, the University of Rochester believes it would be more efficient and less burdensome for research involving the secondary use of biospecimens (pathological, diagnostic, or banked specimens) if the new privacy and data security standards were made a condition of exemption eligibility.

Question 24: Are there specific types of studies [e.g., quality improvement, public health, and program evaluation] for which the existing rules (even after the changes proposed in this Notice) are inappropriate? If so, should this problem be addressed through modifications to the exemption (Excused) categories, or by changing the definition of “research” used in the Common Rule to exclude some of these studies, or a combination of both? If the definition of research were to be changed, how should the activities to be excluded be defined (e.g., “quality improvement,” [“public health,”] or “program evaluation”)? Are there some such activities that should not be excluded from being [regulated under] the Common Rule because the protections provided by [the Common Rule] are appropriate and no similar protections are provided by other [federal] regulations? With regard to quality improvement activities, might it be useful to adopt the distinction made by the HIPAA Privacy Rule (45 CFR 164.501(1)), which distinguishes between “health care operations” and “research” activities, defining “health care operations” to include “conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities”?

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The University of Rochester believes that it is inappropriate to modify the exemption categories in an attempt to identify all the possible ways of obtaining information that should not be covered by the Common Rule. The Common Rule was not intended to apply to non-research activities, such as program evaluation, public health, or program improvement. These non-research activities should not require IRB oversight. This is also true for non-human subject activities, such as research with anonymous data and biospecimens. Modifying the exempt categories would be more confusing for investigators. Guidance can list examples of activities that are not research; the regulations cannot. We believe that changing the definition of “research” to more clearly indicate that these types of studies do not qualify for research is a laudable approach.

The University of Rochester believes the definition of research works most of the time to separate the activities that are research from those that are not; however, the definition could be improved and simplified for clarity. For example, the term “generalizable knowledge” has always been difficult to explain to investigators and IRB members because the word “generalizable” has a different meaning in the scientific lexicon, i.e., the extent to which research findings and conclusions from a study conducted on a sample population can be applied to the population at large. A recent demonstration of this confusion at the federal level was in the original draft of the HIPAA regulations where section 164.504 was proposed to include an elaboration on the definition of research to include: “‘Generalizable knowledge’ is knowledge related to health that can be applied to populations outside of the population served by the covered entity.” The University of Rochester suggests that the term “generalizable knowledge” in the definition of research be replaced with “scientific/scholarly literature or otherwise designed for dissemination for scientific/scholarly use.”

Also, the clause “including research development, testing and evaluation” has caused confusion and variability in the application of the regulations. The University of Rochester believes that it would decrease the burden on the research enterprise if that clause were deleted along with the last two sentences in the definition (“Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.”). These explanations are more appropriately placed in federal guidance where more detail and clarification is possible and more appropriate.

We agree, as the ANPRM suggests, that the definition of research should exclude “conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities.” These activities are intended to benefit a department, an institution, or an organization as opposed to adding to scientific/scholarly knowledge. The activities may use methods or collect data as do research projects, but they should not require IRB review and approval. Federal guidance can be developed to give more detail and explanation for these types of activities, to make it easier for these activities to be classified as not governed by the Common Rule, and to be conducted and, if desired, published without triggering an IRB review.

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Therefore, the University of Rochester believes that the definition of research should be changed to (inserts underlined): “*Research* means a systematic investigation designed to develop or contribute to scientific/scholarly literature, or otherwise designed for dissemination for scientific/scholarly use.” Because the HIPAA regulations also have a definition of research that follows the Common Rule, the HIPAA definition would also need to be changed to this more useful definition.

Question 25: Are there certain fields of study whose usual methods of inquiry were not intended to be covered by the Common Rule (such as classics, history, languages, literature, and journalism) because they do not create generalizable knowledge and may be more appropriately covered by ethical codes that differ from the ethical principles embodied in the Common Rule? If so, what are those fields, and how should those methods of inquiry be identified? Should the Common Rule be revised to explicitly state that those activities are not subject to its requirements?

All of the fields mentioned in the question should be excluded from the Common Rule, in addition to program evaluation, public health, or program improvement activities. The University of Rochester believes that it is not possible to modify the exemption categories to identify all the possible ways of obtaining information from/about individuals that should not be covered by the Common Rule. The determination that an activity constitutes research involving human subjects or identifiable information about living subjects is not dependent on the scholarly discipline or occupation of the investigator. However, federal guidance can list examples of the types of activities that are not research and give examples of when these cross the line and become research; the regulations should not and cannot.

Question 26: Is the circumstance that a particular demonstration project generates “broad” knowledge incorrectly being used as a reason to prevent certain activities (including section 1115 waivers [experimental, pilot, and demonstration projects] under Medicaid) from qualifying for exempt category 5? If so, how should this exemption (as part of the new category of Excused research) best be revised to assure that it will no longer be misinterpreted or misapplied? Is there a need to update or otherwise revise the “OPRR Guidance on 45 CFR 46.101(b)(5)”?

For activities that evaluate public health, public benefit, or service programs such as Medicare and Medicaid; procedures for obtaining those benefits or services; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services, the University of Rochester believes these are not designed for the purpose of dissemination for scientific/scholarly use and to regulate them as research is inappropriate. These activities are not research, and they should be recognized as not meeting the definition of research.

The fact that a particular demonstration project generates “broad” knowledge (i.e., knowledge that can be used by the public sector) does not meet the standard for “generalizable knowledge” (i.e., knowledge that is intended to be used by scientists, scholars, and professionals) and should not be used as a reason to prevent such activities from qualifying for exempt Category 5. The University of Rochester believes that the clarification of not meeting the definition of research should hold true for both federal programs, such as Medicare, as well as state programs, such as Medicaid (i.e., state programs should not be forced into IRB review and consent waiver (116(c)) just because they are not federally conducted or sponsored activities).

As a research-intensive institution, the University of Rochester does understand that, unlike the “not research” situation above, it is possible for an investigator to design a study that evaluates public health, public benefit, or public service programs that does qualify as research involving human subjects (systematic investigation designed to develop or contribute to scientific/scholarly knowledge where data is collected through intervention or interaction with individual, or identifiable private information is recorded); this research should continue to be exempt under the current Category 5 as it is now. Federal guidance should be developed that will help investigators understand what is research that is governed by the Common Rule and what activities are not—either by virtue of being exempt or by not meeting the federal definition of research, even though the investigator, funders, and some departments, etc., consider the activity to involve “research” in common parlance.

Question 27: Do IRBs correctly interpret [45 CFR 46.111(a)(2)] as meaning that while they should be evaluating risks to the individual subjects participating in a study, it is not part of their mandate to evaluate policy issues such as how groups of persons or institutions might object to conducting a study because the possible results of the study might be disagreeable to them? If that is not how the provision is currently understood, is there a need to clarify its meaning?

The University of Rochester believes that our IRBs and, to our knowledge, other IRBs correctly interpret 45 CFR 46.111(a)(2).

Question 28: Should the Common Rule include a requirement that every institution must provide an appropriate appeal mechanism [for determinations]? If so, what should be considered acceptable appeal mechanisms? Should such appeal mechanisms, or different ones, be available for appeals asserting that the investigation is not research, or that the research does not require IRB approval?

The University of Rochester believes that an appeal mechanism should not be mandated in the Common Rule. An appeal mechanism implies an adversarial relationship between investigators and IRBs. As the regulations now state, IRBs should develop a system where its advice and counsel is respected. Most institutions, including the University of Rochester, have policies for appealing IRB determinations and have a mechanism for investigators to be able to seek reconsideration of IRB decisions and/or clarify IRB concerns that may be reflected in those decisions.

We believe that providing investigators an opportunity to respond in person or in writing is adequate. Mandatory mechanisms for appeals asserting that the investigation is not research or that the research does not require IRB approval would complicate the process and make more work for everyone. As part of the protocol or application, the investigator should justify why the project is not research or does not require IRB approval. If the justification is not accurate, then the IRB can educate the investigator and work with him/her to make a determination. If the justification is accurate but the IRB has misunderstood, then the investigator can educate the IRB, and it can make a new determination.

Question 29: Would it be helpful, in furtherance of increased transparency, to require that each time an IRB [engages in review activities beyond those that are required by the regulations], it must specifically identify that activity as one that is not required by the regulations?

The University of Rochester does not believe that identifying certain review procedures as institutionally driven versus federally mandated would serve any useful purpose, and certainly it would not help “transparency.” It would be extremely burdensome to require institutions to flag all of its policies to the type/source of the mandate. It would also inhibit institutions from promoting cultures of research integrity and excellence by setting higher standards or developing human research protection programs that are eligible for accreditation, which requires procedures that go beyond simple regulatory compliance.

Streamlining IRB Review of Multi-Site Studies

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?

The University of Rochester does not support federally mandated review by a single reliance-IRB for all domestic, multi-site research at institutions receiving federal funds. We believe that mandating an operational function in the regulations can cause more regulatory complexity and confusion and add to the burden on institutions and investigators. While there are some studies where one IRB of record may be reasonable, to mandate this will take away an institution’s autonomy to decide how they will review research.

We absolutely support the concept of relying on a single IRB in multi-site studies; however, it is the mandate to use a single IRB that is problematic. We contract with an independent IRB to review industry-sponsored multi-site clinical trials because we recognize that inefficiencies exist in multiple reviews of standardized and well-written protocols. The University of Rochester has been using an independent IRB for 15 years. In fact, we were the first university to do so and have the relationship recognized in our FWA. Clearly, our concern is not with the concept of single IRB review, but rather with the mandated nature as proposed in the ANPRM. A journal article by University of Rochester investigators Ravina, *et al.*, reporting on an experience with a multi-site study with 52 local IRB reviews states in the summary, “Multicenter clinical research involves parallel Institutional Review Board (IRB) reviews based on the premise that local review reflects aspects of the research environment. We examined the costs and effects of local IRB review of the consent and protocol in a multicenter clinical trial in Parkinson disease. Seventy-six percent of changes to the consent reflected standard institutional language, with no substantive changes to the protocol. The costs of this process exceeded \$100,000. These findings support initiatives by the Office of Human Research Protections (OHRP) and the National Cancer Institute (NCI) to facilitate centralized reviews.” (American Neurological Association, “Local Institutional Review Board (IRB) Review of a Multicenter Trial: Local Costs without Local Context,” February, 2010.).

To encourage the use of single-IRB review, there must be a federally recognized change in the accountability and regulatory liability of IRBs and institutions. The IRB of record must be solely responsible for compliance with IRB review requirements of the Common Rule, which will require a change to the assurance regulations (section 103). The individual institutions and investigators must be responsible for the oversight and actions of the conduct of research and other elements of human subject protection at the research site.

If a single IRB is responsible for reviewing each site participating in a multi-site study, the designated IRB must be familiar and account for each institution’s policies. In addition,

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depending on how the IRB of record is chosen, there may be delays that result in trying to process each site's approval if the IRB of record does not have the staff or resources to handle that kind of volume.

If the single IRB is only responsible for reviewing the protocol and "model" consent, each institution will still need to review the protocol and consent form to ensure compliance with institutional policies and standards (e.g., compensation for injury, financial conflicts of interest, site specific training requirements, ancillary committees, etc.). The information that is provided by these institutional reviews adds to the information that an IRB needs to consider in granting final approval and should not be conducted after the fact.

Tracking IRBs of record and updating assurances appropriately is also concerning because of the administrative burden. Under the current OHRP web-based system, IRBs are required to amend their FWAs to designate another site; it should suffice that the institution maintains accurate records, available for inspection, regarding the sites and the IRB of record for studies.

Advantages:

- The most obvious advantage is that the review process could be consistent for all sites with uniform concerns being articulated and a single "decision" on points of contention within the clinical research protocol.
- If delays in study initiation were in fact reduced, this would most benefit industry sponsors from a time and financial standpoint; federal sponsors may derive some benefit, however, time is rarely of the essence in federal grants. It should be noted that many studies are never completed, often due to inadequate enrollment, so rapid initiation would achieve little. Studies would still require a contract/grant review process at each institution, and this sometimes is the limiting factor for sponsored-research initiation, not local IRB review.
- Another potential advantage would be a greater willingness to place clinical research at domestic sites rather than going outside of the U.S. where more rapid initiation is the norm because of less strict regulatory environments (i.e., fewer regulations, formal guidance, and governmental oversight mechanisms).

Disadvantages:

- There is a potential loss of local considerations, such as investigator qualifications, facility limitations, investigator history (including previous compliance and corrective action plans), unique population or community concerns, etc.
- There is a possible lack of appropriate consideration when research involves vulnerable populations or unique population or community concerns, etc., as defined in the Common Rule and further protected by special HHS subparts, such as pediatric research that needs to be reviewed by IRBs with experience in the medical, psychological, social, and emotional needs of children.
- IRB shopping could be a significant problem if not managed.
- There is the potential for negative impact on established HRPPs, resulting in reduced ability for coordinated oversight and implementation of systems and safeguards to protect human subjects at the local level.

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- IRBs that review for sites across state lines would need to be conversant with all those state laws, which would seem to require the operation of a regulatory division within the single IRB.
- A loss of operating funds for those IRBs that charge for review services is possible because the review would be provided (and presumably charged for) by the single reliance-IRB.
- There is the risk of losing or having a restriction placed on the FWA, whether the institution operates the single reliance-IRB or is a site that uses a single off-site IRB when a study becomes a compliance case.
- Using a single IRB now requires filing FWA amendments to add sites/IRBs, developing inter-institutional agreements, and tracking IRB approvals and other documentation overhead. This process needs to be eliminated or at least streamlined.

Given the range of institutions that would need to comply with this requirement and the vastly different types of studies this might entail, we believe that the use of a single IRB should not be mandated. While we tend to think of multi-site medical clinical trials first and foremost, epidemiology, anthropology, psychology, and education studies often involve multiple institutions too. Rather than a regulatory mandate, federal guidance should encourage the use of a single IRB of record for multi-site research. Streamlining unnecessary, duplicative review would help to prevent multiple changes that have no bearing on human subject protection to multi-site clinical research protocols. However, beyond this narrow scope, mandated single IRB review does not serve the best interest of human subjects because it diminishes the flexibility required to permit institutions to identify—on a study-by-study basis—local issues that may be relevant to human subject protections. Importantly, because the overall responsibility for protection of research subjects vests with the local site, the University of Rochester, along with many local sites, prefers to review each research project, ensure compliance in the consent process, and ensure that the conduct of the research complies with local policies, procedures, and norms. If the regulations or, preferably, guidance were changed to make the reliant IRB responsible for compliance with IRB review requirements of the Common Rule for research occurring on site, while allowing for some type of local notice and administrative feedback (but not full review or sharing review duties or responsibilities), this would be less of a problem.

It should be noted that IRB review is just one step in the local review and approval process. The University of Rochester, like many research-intensive academic centers, has developed an accredited comprehensive Human Research Protection Program (HRPP) comprised of multiple components that apply across the institution. While the University's IRBs have a pivotal role, overall protections are provided to subjects through coordinated interaction with other regulatory review entities within the institution, e.g., the coordination between the IRBs and the research administration office in assuring consistency of compensation for injury payment language between the informed consent document and the clinical trial contract. IRBs receive information and feedback from other components of the HRPP that work in coordination with other human research protections (e.g., radiation safety reviews, contract negotiation, conflict of interest committees, investigational drug service, biosafety committee review, etc.). It is difficult to achieve full integration when using a remote IRB.

If there is an extension of the Common Rule to institutions that receive some federal funds, the impact of this mandate would reach beyond biomedical research to social, behavioral, and education research. Much of this type of research would not benefit from single reliance-IRB review, and the difficulty of arranging and conducting a single review system might in fact add delay.

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 [central] IRB may not have adequate knowledge of an institution's specific perspective or the needs of their population, or that [it] may not share an institution's views or interpretations on certain ethical issues?

There is no guarantee that instituting a mandate for single reliance-IRB review will add to human subject protection. In fact, there may be a risk to the individual subjects when a protocol conflicts with institutional policy and procedures. At the University of Rochester, many of the site-specific requested changes in multi-site studies relate to conflicts that arise between institutional policy and the protocol as drafted.

The following examples relate specifically to protocols that were revised at the local level to account for University of Rochester policies. In a study of subjects with dementia, the Rochester site did not enroll into one of the study groups because of the University's policy that greater than minimal risk research without the prospect of direct benefit cannot be conducted with individuals who lack the capacity to consent for themselves. In another case, the time frame for randomization into the study was shortened (24 hours to 12 hours) because of the University's policy on administration of a specific treatment. These changes were, of course, accepted by the sponsor before they were approved by the IRB and implemented, but without the first-hand knowledge of institutional policy, these could have been easily overlooked to the detriment of subject rights and safety.

The ANPRM assumes that all domestic sites are sufficiently similar so that a single reliance-IRB could assess the research appropriately for Common Rule purposes. We know that some domestic sites have subject populations and risks attendant to the research that are radically different, e.g., large immigrant minorities with cultural differences and language issues.

Differences in conflict of interest policies and related management strategies and the level of compensation for injury provided can vary by protocol, by institution, and by study. Ensuring that the subject is completely informed and that the IRB has reviewed and approved this information is important in ensuring that the subjects have all pertinent information to make an informed decision about participation in a study. Experiences with the "single IRB model" have been less than satisfactory when ensuring that subjects are presented with accurate institutional information because of unfamiliarity with institutional policy.

We also note that mandated review by a single IRB of record would not be appropriate for "Exception from Informed Consent" studies conducted under 21CFR50.24. Many of those studies are multi-site, federally funded protocols to which the proposed mandate could apply inappropriately (i.e., Rapid Anticonvulsant Medications Prior to Arrival Trial - RAMPART). These are high-risk studies with complex regulatory requirements, including coordinated

local community outreach efforts. Such studies have the potential to create divisiveness and controversy within a local community, necessitating a coordinated local solution.

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

Liability is a huge concern when an IRB considers taking the responsibility to review for another site. Under the current structure, the IRB of record puts its FWA and thus their institution's federal funding at risk by taking on this responsibility. In addition, given the variability in the quality of IRB reviews, institutions may be hesitant to rely on other IRBs, although this may not always be justified. For an IRB to adequately conduct the review of multiple sites in a large multi-site study, it would need the resources to do this effectively, including extra IRB staff to manage the approval process, the continuing review—including collecting and assessing unanticipated problem reports and other required notices and potentially increased oversight/auditing function to ensure that the research is conducted appropriately. The institution would either need to bear this financial responsibility itself—which would only be possible for a small study or a one-time study—or else it would need to charge each site for review. Given that only industry-sponsored studies routinely provide for payment of IRB review fees, this is another major impediment that will have to be addressed.

Regulatory liabilities (i.e., potential loss/restriction of FWA, federal compliance investigations, and negative public relations) and legal liabilities are both important issues to consider in determining when to rely on another IRB or accept responsibility for review of activities at another facility. Clarification is needed to delineate roles and liability between the IRB, sponsor, institution, and investigator (not to mention other entities such as sub-contractors, contract research organizations, or site management organizations). It is current reality that institutions will be held accountable in some way for any and all problems that take place at their facilities. We believe that, on the behavioral/educational/social science side of research, that shifting all regulatory and legal liability to the IRB of record would impede the willingness of academic institutions from serving as IRB of record for community-based research networks; legal counsel and institutional risk managers would be hard pressed to justify the institution risk with what would be an altruistic service.

The University of Rochester believes that the proposed changes do not sufficiently address the concerns associated with assuming regulatory responsibility for research conducted at another institution; we encourage this more full consideration and the removal of impediments to single-IRB review. There must be a consideration of changes in IRB accountability. The IRB of record must be responsible for compliance with IRB review requirements of the Common Rule, and the individual institutions and investigators must be responsible for the actions and oversight of the conduct of research and other elements of human subject protection at the site.

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

The University of Rochester believes that it is inefficient for each site in a multi-site trial to reconsider all of the components of a complex interventional research trial. However, in order to properly centralize the research review process, there would need to be substantive changes in regulations, guidance, and enforcement in areas such as liability. It is also

important to remember that variation does not necessarily mean that IRBs are not doing the job properly. Research is not simple; studies often are complex and nuanced. Therefore, it seems understandable that depending on the site, there can be inefficiencies created by local IRB review, but there are a significant number of inefficiencies that are created because of the quality of the consent forms that are distributed to the local IRBs for review by many of the cooperative groups and large study groups. For example, the University has received consent forms from a government-run central IRB that just lists the risks as reported in an adverse event reporting system, rather than writing the risks so that the subjects will understand what they may experience; it has taken additional time for our local IRB to negotiate with the central IRB to revise the consent form appropriately. Many industry and government cooperative group consent forms list a welter of risks, but do not provide any symptoms to describe what the subject will experience or what this will mean for the subject. When protocols are unclear or poorly written, reviews take longer. For example, we recently were given the following consent form risk language, which was approved by a federal central IRB: “fast heartbeat usually originating in an area located above the bottom pumping chambers of the heart (ventricles) that may not have a regular rhythm.” While this accurately describes a physiological risk, where the fast heart beat originates makes no difference to the subject and provides no meaningful information about the effect on the subject’s health.

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

The University of Rochester believes that allowing an investigator, contract research organization, or sponsor to select the single reliance-IRB would risk a process of “IRB shopping” to secure the most lenient or permissive IRB. Speed is often the major determinant in selecting IRBs, and too often, speed varies inversely with quality and thoroughness. If the regulations mandate a single IRB of record for all multi-site studies, the IRB of record must be selected through a process that is independent from the research to help prevent “IRB shopping.” A system of accreditation (e.g., the AAHRPP program) or some type of federal certification may need to be part of the required selection criteria.

The process of selecting a single IRB of record for a multi-site study is extremely difficult. If the investigator is the individual who will select the IRB of record, then there is little to prevent the investigator from selecting the IRB that he/she deems the best for whatever reason, whether it is the quickest turnaround time or because the IRB has let the investigator do something that another IRB would not allow. There could be a federal audit procedure or central tracking of selected IRBs of record to look for trends on which investigators select which IRBs. If a certain IRB is selected to be the IRB of record more often than what is expected, that IRB would be audited more often. The liability of risking more frequent auditing may prevent an IRB from taking on the added responsibility of being the IRB of record for a multi-site study.

Another option would be setting standards for who could undertake the role of IRB of record for multi-site studies. If standards are initiated, then the risk of IRB shopping would be minimized. Unfortunately, setting standards may prevent some of the smaller institutions from being an IRB of record, even for a smaller study.

Improving Informed Consent

Question 35: What factors contribute to the excessive length and complexity of informed consent forms? How might [these factors] be addressed?

Although it is true that studies have gotten increasingly complex and clinical research often involves difficult-to-describe procedures and risks, the University of Rochester believes that the complexity of consent forms now is driven less by the need to provide useful information to subjects and more by institutional risk determinations, which are driven in large part by OHRP, FDA, and other federal guidance (some of which is contained in “compliance letters” to specific institutions or provided in unpublished presentation material). Concern about complying with all these interpretations and the institutional tendency to be risk adverse have led to “IRB mission creep,” just to be on the safe side. The requirement for HIPAA authorizations has added pages and complexity to consent forms because, even though an authorization does not need to be combined with the consent form, institutions do so to ensure the wording is reviewed by an IRB to prevent sponsors, investigators, and others from using non-compliant authorizations.

The need to document that every possible risk and contingency (including data security) has been addressed and discussed with the subject contributes to the excessive length and complexity of informed consent forms. Reducing the documentation, along with standardization of data security requirements, would greatly reduce the length and complexity of informed consent forms.

The ANPRM states, “length and high reading levels may inhibit people from reading the full document and from understanding relevant information.” We believe that statement demonstrates the root of the problem—the expectation that a written consent form must be read and understood to satisfy the consent process. We believe that a better expectation, from both a practical and protective view, is that the consent form should only summarize the key elements, i.e., give the big picture of the important elements, and the detail (tailored to the level each individual potential subject desires) should be provided orally by the responsible investigator who is seeking to obtain consent. It is the purpose of the consent process to ensure that the information conveyed to subjects accurately and appropriately informs and aids subjects in the decision process. This should not be conflated with the need to obtain the subject’s signature when/if they have agreed to enroll in research.

The University of Rochester believes that to solve the “complexity” of consent forms, the Common Rule must de-link section 116 and 117 by changing the word “embodies” to “summarizes” in 117(b). This would allow investigators to develop an “Executive Summary” for the consent form that is to be signed. To aid the decision-making process, federal government agencies have been using Executive Summaries for decades that convey critical information in highly technical and complex reports. It seems reasonable to use this same technique for potential research subjects. Thus, the consent form could be a brief summary of the research and the elements that will be addressed in the consent discussion, plus one or more attachments. These attachments/appendices would contain more detailed information that would serve as reference materials for considering the initial decision at home or with advisors as well as for ongoing reference as the study proceeds. We believe the use of this model would facilitate true informed consent and human subject protection

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because subjects would have a concise description to read and understand and IRBs could continue to rely on the more complete information in the attachments to serve as a source of relevant information on the study presented from the subject's viewpoint, i.e., everything a reasonable person would want to know about the study.

The regulations (116a-b) currently require that consent include at least eight specific items of information and an additional six items if they apply to the study. The eight plus six item total is somewhat understated because several of the required consent elements have multiple parts, e.g., the first element contains five "sub-requirements": (1) a statement that the study involves research, (2) an explanation of the purposes of the research and (3) the expected duration of the subject's participation, (4) a description of the procedures to be followed, and (5) identification of any procedures which are experimental. So in reality, there are about 17 "always required" elements (116a) plus another 6 "sometimes required" (116b) for a total of 23. The extent of detail for each item must be gauged by (1) how much information the "average" potential subject might want, (2) the most detail any specific subject might need, (3) the legal liability for excluding any relevant informational item, and (4) the "institutional" standard of meaningful information per site policy. Current OHRP guidance to IRBs is that the consent form required by section 117 must contain the equivalent of a verbatim repetition of each of the elements required by section 116. Over the years, the default expectation of regulators, IRBs, and, increasingly, plaintiff's attorneys has become "more" not less information, thereby increasing the length of consent documents to the detriment of understanding.

One recommended method for lowering reading level is to use shorter sentences; however, shorter sentences generally translates to more actual words, thereby increasing the length of consent documents. At some point a longer document forfeits the gains to be had from lowering the reading level. Thus, it is essential to change the consent form into a briefer document, written at a level that fosters understanding and provides more complete information in attachments.

Often in medical research and sometimes in other types of research, there are scientific and technical terms that subjects will hear as part of the research procedures (e.g., "we are now going to do a functional MRI") and thus need to be explained in the consent. These common-term/scientific-term dyads also add to the length and complexity of consent forms and raise the reading level because of the scientific and technical terms.

Simply stated, you cannot provide full and complete information in a brief written form. To address the concerns regarding overly lengthy consent forms, the University of Rochester believes that section 116 and 117 need to be de-linked. Investigators need to provide the detailed elements of consent, but the signature form need only be a summary of the information provided, i.e., to improve consent, the elements of consent (the informational requirements) must be separated from the signature document that shows the consent of the subject was obtained.

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We recommend adding the word “orally” to 116(a), so that it becomes: “*Basic elements of informed consent.* In seeking informed consent, the following information shall be provided orally by the investigator/qualified designee to each subject.”

We also recommend adding the word “orally” to 116(b): “*Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided orally by the investigator/qualified designee to each subject.”

The University of Rochester believes that section 116 must be de-linked from section 117 by changing the word “embodies” to “summarizes” in 117(b) so it becomes, “Except as provided in paragraph (c) of this section, the consent form may be either of the following: (1) A written consent document that summarizes the elements of informed consent required by §46.116. This form may be read...” Alternatively, guidance could be written to state that the “short form” allowed in 117(b)(2) is to be considered the preferable/default method for obtaining signature of consent and that the required “written summary” is just that—a one- or two-page summary, not the excessively detailed written form that is so problematic today.

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

Again, we believe that the overarching issue is captured in the ANPRM statement of the problem, i.e., consent forms should not describe alternatives, even in concise and clear language; they should summarize or simply state that alternatives exist (if they do) and perhaps state where more information can be obtained. The University agrees that a description of alternatives to participating in the research study and why it may or may not be in a subject’s best interests to participate should be part of the consent process when it is appropriate. Typically, alternatives are important when clinical care is combined with research or when coercion or undue influence may be an issue (e.g., psychology student pools). As this question implies, it would be reasonable to change 46.116(a)(4) to: “A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and why it may or may not be in the subject’s best interests to participate.”

Three of the “required elements” of consent are conditional (46.116(4), (5), and (6)). Clearly, this acknowledges the fact that the information imparted in a study that presents no greater than minimal risk is different from that in a study with greater than minimal risk. It would be reasonable to move these three elements to “Additional Elements” and/or to address, in federal guidance, the required elements for consent for minimal risk studies and studies with greater than minimal risk separately (or, more radically, to even delete required consent elements for minimal risk studies and only address requirements studies with greater than minimal risk).

The University of Rochester believes that federal guidance should set the basic elements of informed consent for minimal risk studies to:

- a statement that the study involves experimentation/research and the expected duration of the subject's participation;
- a statement that the risks or discomforts to the subject are minimal;
- a statement that the expected benefits from the study are for scientific/scholarly knowledge;
- a statement that participation is voluntary—refusal to participate or discontinuing participation at any time will not lead to any penalty; and
- a contact for answers to pertinent questions about the research and research subjects' rights.

If this new standard were adopted, it can be seen that the signature document/consent form for minimal risk studies could be a standard form (all elements except the first and last above are “statements” that could be put in a national template).

Another option for minimal risk studies that the University of Rochester believes has merit would be to allow IRBs to determine the level and extent of consent similar to the way assent requirements are described in the regulations for research involving children (subpart D). This method would decrease burden on both investigators and IRBs and could be accomplished easily by adding a new section 108(c) to say, “When an expedited review procedure is used, the IRB shall determine that adequate provisions are made for obtaining and documenting consent.” Federal guidance could then describe considerations for IRB deliberation and mechanisms that would adequately safeguard human subjects while decreasing burden for investigators.

In the area of deletions to the required elements and in keeping with harmonizing agency requirements, the University of Rochester agrees with the Congressional efforts to provide subjects with information about how to access the results of trials in which they participated (FDA Amendments Act of 2007); however, that information should not be a required element of informed consent (21 CFR 50.25(c)). As we have stated before, the level of detail in the regulations should be general, with more detailed guidance informing institutions how to accomplish responsive compliance.

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

The University of Rochester believes that some of the modifications that HHS is considering may improve the quality of consent forms. Again, the ANPRM seems to confuse the elements of consent in 116 with the signature document requirements in 117. Section 116 and 117 need to be de-linked. Investigators need to provide the detailed elements of consent, but the signature form need only be a summary of the information provided.

Prescribing, with greater specificity, required content: If section 116 remains as is and investigators are held to those requirements, then it would be useful for section 117 to be modified to give greater specificity on the style of the content in the form used to obtain the subject's signature. This section could be rewritten to state that the “short form”

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currently allowed in 117(b)(2) is to be considered the expected method for obtaining signature of consent for minimal risk studies, i.e., a form that would state that information about the research has been discussed, that there has been a chance for questions and answers, and that the subject agrees to participate. The requirement for a witness should be removed for minimal risk research. For studies with greater than minimal risk, it should be clarified that the written signature document (117(b)(1)) should summarize (not “embody”) the elements of informed consent required by section 116.

Restricting content that would be *inappropriate*: Section 116 already carries a prohibition on wording that would be “exculpatory.”

Limiting the length of various sections of a consent form (akin to grant application page limits): This is not likely to be useful or possible because of the variability in research study methods, risks, populations, etc.

Prescribing how information should be presented in consent forms (formatting), including use of appendices: This has the potential to be very useful in improving subject comprehension of the information presented in the consent process/form. The government should agree on the use of a simplified summary document for the form on which to obtain signatures and allow supplementary information with greater detail to be placed in one or more appendices. Federal guidance should also be developed on alternate ways to obtain consent besides a written signed form, e.g., video consent and web-based consent (which would facilitate standardized assessments of understanding and tracking).

Reducing institutional “boilerplate”: This seems to be an unwarranted intrusion into institutional policy. Beyond what was said in item (2) above, it seems unlikely that this would either improve the consent process or be possible to implement. There are two sections where the University of Rochester has institutional boilerplate language in the consent form: compensation for injury and the HIPAA Authorization. The compensation for injury section is a statement of the compensation we provide to an injured subject (a vanishingly rare occurrence), which has been approved by the University’s senior leadership. We believe this is incumbent upon the University because there is no national pool for compensation for injury and the model consent statements we receive from sponsors often contain unacceptable legalese boilerplate with multiple conditional factors, such as the subject must “follow the protocol” [sic]. In the Ravina article previously cited, the most frequent local IRB change was for injury compensation.

The requirement for HIPAA authorizations has added boilerplate pages and complexity to consents because even though an authorization does not need to be combined with the consent form, institutions do so to ensure the wording is reviewed by an IRB to prevent sponsors, investigators, and others from using non-compliant authorizations. While the elements of HIPAA Authorization are standard, each institution creates its own template language to be either maintained as a separate document or incorporated into the consent form. There are so many elements that need to be addressed that, in many cases, this template language is at least a page. We believe that working with OCR to reduce the

<p>number of required elements or a shortened standard paragraph for research authorization would be extremely beneficial.</p> <p><u>Making available standardized consent form templates:</u> Standardized templates are useful for formatting, but the template must be modified for each study by adding study-specific information. Thus, there is little gain in either investigator or IRB time when using standardized fill-in-the-blank templates.</p>
<p>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?</p>
<p>Investigators should informally assess how well potential research subjects comprehend the information provided to them in studies with greater than minimal risk and when the potential subjects may not have the capacity to fully comprehend the information. When the research risks include death or irreversible harm, a formal assessment is warranted. It is also reasonable to expect that FDA-regulated phase 1 clinical trial investigators should assess how well potential research subjects comprehend the information provided to them. The University of Rochester does not support putting this requirement in federal regulations; procedural detail is not appropriate for regulations.</p>
<p>Question 39: If changes are made to the informed consent requirements of the Common Rule, would any conforming changes need to be made to the authorization requirements of the HIPAA Privacy Rule?</p>
<p>The University of Rochester believes the HIPAA rules for research do not provide a benefit to human subjects beyond that already provided by the Common Rule sufficient to justify the burdens imposed. Therefore, we suggest that the portion of HIPAA that regulates research should be rescinded, especially if the Common Rule is amended to strengthen privacy and security protections. Currently, healthcare research conducted in covered entities must be reviewed and conducted to a different set of rules, thereby increasing the complexity and confusion for investigators and IRBs. Given that removal of research from HIPAA is unlikely, the requirement for authorizations under the HIPAA Privacy Rule should be changed by stating that the rules only apply to studies with greater than minimal risk (whether due to physical, psychological, or informational risk) in healthcare. Alternatively, the elements required for research authorization need to be significantly decreased.</p>
<p>Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required? Should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?</p>
<p>To harmonize with FDA requirements and provide a mechanism to document that consent was signed on or before the day the research began, we suggest that section 117(a) be modified to require a signed and dated form. Also, to harmonize with FDA and ICH requirements, section 117(a) should be modified to require a description of payment and financial conflicts of interest. The University of Rochester believes that, for studies with greater than minimal risk when the institution has determined that a management plan is required, investigators should be required to disclose in the consent process only general information about any financial relationship/s they have with study sponsors. Disclosure during the consent process should be brief but should allow subjects to ask questions if they want. In the spirit of de-linking sections 116 and 117, consent signature forms for studies</p>

with greater than minimal risk should contain a simple statement about financial relationships, e.g., “x is paid by the sponsor of this study to give talks at professional meetings” or “x holds stock in the company that sponsors this research.” If the government were to develop standardized disclosure statements and publish these in a guidance document, it would be a valuable resource for investigators, IRBs, and conflict of interest committees.

A primary focus of the ANPRM is on data security. In response to this emphasis, the University of Rochester recommends that the consent process should better inform subjects about mechanisms to protect data confidentiality. Federal guidance could be developed to help institutions implement procedures to address this area.

Waiver of Informed Consent or Documentation of Informed Consent in Primary Data Collection

Question 41: What changes to the regulations would clarify the current four criteria for waiver of informed consent [45CFR46.116(d)] and facilitate their consistent application?

As 45 CFR 46.116(d)(1) appropriately requires, the waiver of consent, which provides the elements of information to subjects, should only be considered/allowed in minimal risk research. It is the next two conditions (46.116(d)(2-3)) that leave IRBs and investigators unsure of the permissibility of a waiver. Determining that a waiver or alteration will not adversely affect the rights and welfare of the subjects and that the research could not practicably be carried out without the waiver or alteration have always bedeviled IRBs and is fairly incomprehensible to investigators. SACHRP developed several recommendations regarding the interpretation of these waiver criteria (SACHRP Letter to HHS Secretary, January 31, 2008). The University of Rochester believes that, as the SACHRP letter suggested, OHRP should develop guidance, based on the suggestions in the letter, for the implementation of the provisions under HHS regulations at 45 CFR 46.116(d) for IRB approval of a waiver or alteration of informed consent elements. It might be preferable to have a separate regulation for waiver of consent and a new regulation addressing only waivers of single or multiple elements of consent, the latter of which could be simply that an IRB must document that any waiver of an element of consent does not increase risk to the subject and the reason that the element is inapplicable or unnecessary. Another option for minimal risk studies that the University of Rochester believes has merit would be to allow IRBs to determine the level and extent of consent similar to the way assent requirements are described in the regulations for research involving children (subpart D).

Question 42: In circumstances where the regulations would permit oral consent [without signature], 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 [in oral consent], or are some elements unnecessary? If some elements should not be required for oral consent, which ones are unnecessary?

In circumstances where the regulations would permit oral consent, i.e., no subject signature, the University of Rochester believes that the following information should be provided by investigators to prospective subjects: (1) A statement that the study involves

research/experimentation and the expected duration of the subject's participation; (2) a statement that risks or discomforts to the subject are minimal; (3) a statement that the expected benefits from the study are for scientific or scholarly knowledge; (4) a statement that participation is voluntary—refusal to participate or discontinuing participation at any time will not lead to any penalty; and (5) a contact for answers to pertinent questions about the research and research subjects' rights. Of course, we believe that the investigator or other person seeking to obtain consent must be able to expand on these areas at the request of the prospective subject (e.g., explaining what the research procedures entail).

The University of Rochester believes that the following consent elements are unnecessary:

- 46.116(a)(2) – risks that are minimal do not need to be individually identified;
- 46.116(a)(3) – a benefit does not need to be explained for minimal risk research;
- 46.116(a)(4) – alternatives are unnecessary, except possibly for vulnerable populations;
- 46.116(a)(6) – compensation for injury is not applicable;
- 46.116(a)(7) – contact for injury is not applicable; and
- 46.116(b)(1-6) – none of the additional elements are necessary in minimal risk research

Question 43: Are there additional circumstances [beyond those in 116(c) and (d) and 117(c)] under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent? [If so, what are they?]

The University of Rochester believes that it should be permissible to waive the usual requirements for documenting informed consent in behavioral and epidemiological research that involves rapid assessment (e.g., survey, finger prick blood draw, etc.) in community or street settings (e.g., street corners, gay bars, injection shooting galleries) because these settings are often not conducive to obtaining signed informed consent when investigators are attempting to remain inconspicuous and protect subjects' identities. We also believe that it should be permissible to waive the usual requirements for documenting informed consent when federally sponsored research is conducted in an international setting where, for cultural or historical reasons, signing documents may be viewed as offensive or inappropriate and in settings where consent and the permission of the authorized representative is not possible, i.e., to mirror FDA's 21 CFR 50.24. We are sensitive to the fact that any waiver must be ethically justified so reasonable conditions must be in place to ensure that subjects are appropriately protected.

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

Yes, there are limited types of research in which oral consent without documentation should not be permitted. For example, when it is contrary to other federal, state or local laws and regulations, e.g., the Family Educational Rights and Privacy Act (FERPA) (34 CFR Part 99) may require written permission from the adult student, or parent if the student is a minor, to release any personally identifiable information from student education records for research.

Consent Protections Related to Reuse or Additional Analysis of Existing Data and Biospecimens

Question 45: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent? Should consent requirements [for future research use] vary based on the likelihood of identifying a research subject? 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?

The University of Rochester believes that a requirement to obtain individual consent for each separate research study involving specimens or data collected for non-research purposes would create unmanageable logistical demands and impossible expectations for collecting choices and then tracking and complying with those options (yes/no/partial/exclusions), making valuable research in areas of public health, medical, behavioral, educational, and social concern impossible. We oppose requiring written consent for research on specimens and data collected for non-research purposes as long as the data or specimens cannot be identified. If the data or specimens cannot be identified, then no consent should be required. The costs associated with the logistical nightmare that would be created by requiring written consent would greatly exceed any benefits to subject protection.

The University of Rochester does not support the proposed universal consent requirement for research with all identifiable data and biospecimens. Under both the current Common Rule and the HIPAA Privacy Rule, if identifiers are removed, specimens and data that have been collected for purposes other than the proposed research can be used without informed consent or a HIPAA authorization. Regulatory disharmony is introduced when identifiers have not been removed because it is still possible to allow investigators in certain situations to obtain a general consent for future research with existing biospecimens and other information stored in databases under the Common Rule, but the HIPAA Privacy Rule has been interpreted to require study-specific authorization (or waiver).

Future research use of data initially collected for clinical non-research purposes should not require informed consent if properly de-identified and there is minimal risk to the subject (e.g., retrospective studies, quality assurance, and novel test validation). In these cases, the subject has already been diagnosed and has undergone or is undergoing treatment that will not be impacted by the results of the study. Imposing the burden of obtaining consent from patients for quality assurance or evaluation of clinical care procedures may introduce unnecessary bias that can impact overall patient care delivery. In the clinical setting, it may also increase healthcare costs by hampering efforts aimed at increasing patient safety and providing optimal patient care.

The University of Rochester is aware that some former research subjects have objected to research performed on biospecimens without consent and is sensitive to the dangers of a utilitarian approach to justifying research and research methods. We believe, however, that societal benefit does play a role in determining ethical acceptability and that risk of harm inherent with the likelihood of identifying a research subject should be a factor for deciding when consent would be required. We support the ANPRM suggestion for a federal public education campaign on the scientific and scholarly use of data and biospecimens.

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The University of Rochester agrees with the ANPRM that biospecimens and data that have been collected for purposes other than for the proposed research are often an important source of information and material for investigators, and the reuse of existing data and materials can be an efficient mechanism for conducting research without presenting additional physical or psychological risks to the individual. As the Institute of Medicine (IOM) stated in their 2009 report entitled *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research*, it is important to “facilitate important health research by maximizing the usefulness of patient data associated with biospecimens banks and in research databases, thereby allowing novel hypotheses to be tested with existing data and materials as knowledge and technology improve.”

Even if institutions could ask for consent universally, it is a recognized fact that research is skewed by individuals who refuse consent, undermining the scientific validity of the research. Obtaining research consent at the time of data collection in non-research activities is impracticable when sources can be identified and impossible when sources are yet to be identified in the future. The HIPAA Privacy Rule was not designed to address non-medical research involving secondary data (e.g., courtesy card data, cell phone usage data (tweets and text messages), voting records, etc.), and it arguably does a poor job even with medical research. There are many questions to explore, such as “Who would administer and oversee this?,” “What is the cost and who pays?,” “What is the burden?,” “What is the benefit?,” “How would proposed consent requirements apply to existing specimens and data sets collected/located in other countries?,” and “How would this affect the data-sharing requirements that NIH and NSF have for funded research?”

The ANPRM proposes the use of a standardized general consent form to permit future use of data and specimens; however, the “one-size-fits-all” approach will create more problems than it solves. For one thing, not all data and biospecimens that are used in research come from medical facilities where consent is a standard operating procedure. Schools, motor vehicle departments, hair salons, supermarkets, etc., would have no reason to institute consent for an event that may never occur.

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

The University of Rochester believes that so long as the data is properly de-identified and the data is secured using standard requirements, future analysis should be permitted without consent. The likelihood of identifying a research subject is usually based on criteria that disregard the subject’s identifiers. However, in the unlikely event that a subject identifier (e.g. zip code in localized epidemiologic studies) is necessary for research subject identification, the request should be reviewed by the IRB.

The University of Rochester believes that data collected for a different research purpose should be permitted to be used in a future analysis of data without consent if privacy and confidentiality are protected because subject identities are not disclosed to or discovered by the investigator. We believe, however, that societal benefit plays a role in determining ethical acceptability and that risk of harm inherent with the likelihood of identifying a

<p>research subject should be a factor for deciding when consent should be required. Given that risks vary based on the likelihood of identifying research subjects, the mechanisms to minimize the risk would also vary. The University of Rochester believes that for informational risk when data is being collected for non-research purposes, consent is not a reasonable, effective, or efficient protection against risk. At best, it might warn risk-adverse individuals to avoid research, but typically the data is collected for purposes other than research in settings that may have little to do with or identification with research. We support the ANPRM suggestion for a federal public education campaign on the use of data and biospecimens.</p>
<p>Question 47: Should there be a change to the current practice of allowing research on biospecimens that have been collected outside of a research study (e.g., “left-over” tissue following surgery) without consent, as long as the subject’s identity is never disclosed to the investigator?</p>
<p>The University of Rochester believes that the current practice of allowing research on biospecimens, which have been collected outside of a research study without consent, is proper as long as subject identities are not disclosed to the investigator. We do note that under current regulations and interpretations it is not permissible to waive IRB review or consent for FDA studies. We believe that it would foster research and harmonization without significantly affecting human subject protection if the current Common Rule standards and practice were adopted by the FDA, VA, and other Common Rule agencies.</p>
<p>Question 48: What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens?</p>
<p>The University of Rochester believes that the current practice of allowing research on biospecimens, which have been collected outside of a research study without consent, is proper, even for additional analysis, as long as subject identities are not disclosed to the investigator. We believe that it would simplify the regulations and improve compliance and thus human subject protection if the current Common Rule standards and practice were adopted by the FDA, VA, and other Common Rule agencies.</p> <p>For studies that are retrospective, have no risk or benefit to the subject, and use properly de-identified biospecimens, there should be no requirement to obtain consent for further analysis. This actually decreases the risk of unintentional privacy invasion that would arise from identifying subjects for the explicit purpose of obtaining consent. It also removes the risk of psychological harm of having the subjects relive possibly traumatic life events (e.g., cancer diagnosis, body-image altering surgery, etc.).</p>
<p>Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?</p>
<p>No, the new general consent forms would add unnecessary burden on the institution. It would result in more paperwork that runs counter to the aims of this reform. The University of Rochester believes that a requirement to obtain individual consent for this type of research would create unmanageable logistical demands and impossible expectations for collecting choices and then tracking and complying with those stated options (yes/no/partial/exceptions), making valuable research in areas of public health, medical, behavioral, educational, and social concern impossible. A public education campaign to</p>

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educate the public about the role of the biospecimens in research should be carried out under the close supervision of the Office of Biorepositories and Biospecimen Research. This would be a good way to counter misguided concepts regarding the scientific capabilities of biospecimen analysis.

Question 50: What is the best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research that might pose particular concerns for substantial numbers of research subjects beyond those presented by the usual research involving biospecimens? How should the consent categories that might be contained in the standardized consent form be defined (e.g., an option to say yes-or-no to future research in general, as well as a more specific option to say yes-or-no to certain specified types of research)? Should individuals have the option of identifying their own categories of research that they would either permit or disallow?

The University of Rochester believes that societal benefit plays a role in determining ethical acceptability and that risk of harm inherent with the likelihood of identifying a research subject should be a factor for deciding when consent would be required. Biospecimens and data that have been collected for purposes other than for the proposed research are often a vitally important source of information and material for investigators, and the reuse of existing data and materials can be an efficient mechanism for conducting research without presenting additional risks to individuals.

The University of Rochester believes that a requirement to obtain individual consent for research would create unmanageable logistical demands and impossible expectations for collecting choices and then tracking and complying with those stated options (yes/no/partial/exclusions), making valuable research in areas of public health, medical, behavioral, educational, and social concern impossible. There is no hope for successful implementation even for the proposed use of a standardized general consent form that would have a straight “yes” or “no” without specific options to allow certain specified types of research or identifying idiosyncratic categories of research that would be permitted or disallowed. Many subjects are undergoing a stressful situation at the time of biospecimen collection (e.g., new cancer diagnosis, risks of surgery, healthcare costs, lifestyle changes, etc.). It would be unconscionable to add additional stress by forcing them to comprehend and choose from a menu of choices regarding future research using their biospecimens. The University of Rochester believes that the blanket permission approach will create more problems than it solves.

Question 51: If the requirement to obtain consent for all research uses of biospecimens is implemented, how should it be applied to biospecimens that are collected outside of the U.S. but are to be used in research supported by a Common Rule agency? Should there be different rules for that setting, and if so, what should they be? Should [the rules] be based on the relevant requirements in the countries where the biospecimens were collected?

The U.S. government cannot directly impose requirements on foreign governments or citizens of those countries; therefore the only way to extend federal regulations is to require compliance when the material comes into this country or is otherwise in the control of the U.S. or regulated entity. This is the model that is used for HIPAA compliance. We believe that risk of harm inherent with the likelihood of identifying a research subject should be a

<p>factor for deciding when consent would be required; in the case of foreign biospecimens that risk of re-identification is small. It would be impossible to consent subjects in foreign countries, and not allowing the use of biospecimens collected abroad will hamper research into rare diseases and international cooperative studies. Thus, we believe that de-identified biospecimens from foreign sources should be considered de-identified when received in the U.S. and regulated as such. The University of Rochester believes that it would be overly complex and result in an unworkable system to base U.S. consent requirements on the unique requirements in the countries where the biospecimens were collected. It is impossible to know all the relevant details and the current standards in all these countries.</p>
<p>Question 52: Should the new consent rules be applied only prospectively, [or], should previously existing biospecimens and data sets be “grandfathered” under the prior regulatory requirements? What are the operational issues with doing so?</p>
<p>The University of Rochester believes that the proposed consent rules should definitely not be applied retrospectively; previously existing biospecimens and data sets should be “grandfathered” under the prior regulatory requirements. We do not support the requirement for obtaining consent for de-identified biospecimens. This would require biospecimens and data to be time-stamped to show date of collection. A potential crippling burden to institutions would be large projects that rely on biospecimen and data collected under the prior regulatory requirements. These studies should also be “grandfathered” and provided an automatic waiver of consent.</p>
<p>Question 53: In cases in which consent for future research use is not obtained at the time of collection, should there be a presumption that obtaining consent for the secondary analysis of existing biospecimens or identifiable data would be deemed impracticable, such that consent could be waived, when more than a specified threshold number of individuals are involved? If so, what threshold number should constitute impracticability? Is the number of subjects the only measure of impracticability?</p>
<p>The University of Rochester agrees that in cases where consent for future research use is not obtained at the time of collection, there should be a presumption that obtaining consent for the secondary analysis of existing biospecimens or identifiable data would be deemed impracticable and consent could be automatically waived. However, data and biospecimens should be properly de-identified to remove links to subjects and/or data security regulations should be followed to ensure information protection. Institutions may wish to set numerical and time parameters that would override the deemed impracticability and trigger an assessment, but that should be an institutional prerogative. Procedural detail is not appropriate for regulations (e.g., setting threshold limits that constitute impracticability).</p>
<p style="text-align: center;">Strengthening Data Protections to Minimize Information Risks</p>
<p>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 not, what standards would be more appropriate?</p>
<p>No. The University of Rochester believes that using the HIPAA standards will put a huge burden on institutions to construct a separate research IT infrastructure that will be prohibitively costly to implement. In some cases, HIPAA identifier information may be necessary for a study to be feasible (e.g., zip codes in epidemiologic studies).</p>

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The University of Rochester believes that the Privacy Rule's definitions for "individually identifiable health information," "de-identified information," "limited data set," and "data use agreement" would have to be so heavily modified to be useful in the broad scope that constitute research settings that it would render them almost unrecognizable. Take, for example, the definition of individually identifiable health information: "information that is a subset of health information, including demographic information collected from an individual, and: (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (i) that identifies the individual; or (ii) with respect to which there is a reasonable basis to believe the information can be used to identify the individual." First, we do not believe that any piece of demographic information can/should render data identifiable—certainly some do such as a street address or cell phone number, but some do not. Item 1 is only applicable when an investigator is also a healthcare provider in a covered entity and there is testing performed that goes into the clinical record. Item 2 only involves covered entities and data from them, which only leaves items (i) and (ii) that apply universally to all types of research. The definition of "de-identified" data is too rigid and would move a lot of data that is currently considered anonymized into the identifiable category with little subject protection gain.

The University believes it would be more useful to develop research standards *de novo*, or based upon research standards other than HIPAA, than to modify the HIPAA standards for research to be in line with good research practice. Likewise, the University of Rochester does not support the adoption of the HIPAA security and notification standards as a model for the proposed mandatory data security and information standards. The regulations require prompt notification to affected individuals of a breach, as well as the HHS Secretary and the media in cases where a breach affects more than 500 individuals. Even breaches affecting fewer than 500 individuals must be reported to the HHS Secretary on an annual basis. Encryption and destruction are the two methods that are recognized to render protected health information unusable, unreadable, or indecipherable to unauthorized individuals.

Although security standards are warranted in this technological age and used by most institutions, simplified, straightforward guidelines developed with the input of research institutions would help to unify the standards across institutions and would be more appropriate and flexible than a fixed regulatory requirement. The HIPAA Privacy and Security Rules include complex security standards with extensive enforcement rules and penalties for protecting health information; the number of pages required to proclaim the HIPAA regulations is an order of magnitude greater than the Common Rule. Again, we caution that guidelines should not be proscriptive, but should assist institutions in designing appropriate policies and procedures—in this case for research data security.

The extension of these standards to "all" research at institutions that receive federal funds assumes that HIPAA has been an effective tool for healthcare privacy protections involving research. This assumption is not correct. The Institute of Medicine (IOM) published a report in 2009 titled *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research*, which described the IOM Committee on Health Research and the Privacy

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of Health Information findings. The committee concluded that “the HIPAA Privacy Rule does not protect privacy as well as it should, and that, as currently implemented, it impedes important health research.”

The HIPAA standards are related to insurance and healthcare; therefore, they were specifically designed to protect medical information within a clinical setting, not as a way to manage research information. Granted, there is a carve-out for research and the management of research information, but HIPAA is not a standard that should be implemented for all research. Because of its orientation to protected healthcare information (PHI), HIPAA treats all PHI as equal (e.g., a blood pressure reading is as “sensitive” as a diagnosis of coronary disease), which runs counter to one key focus of the ANPRM, namely distinguishing between types and levels of risk to enable appropriate protections.

While there is a given familiarity with the HIPAA Privacy Rules at medical centers because many IRBs function as Privacy Boards, this does not mean that this should be the standard implemented for research across the board. The HIPAA Privacy Rules may be a place to start to develop definitions as the standard across research, but there are important modifications that must be made to facilitate research and decrease the burden on investigators and IRBs. For example, zip codes should be allowed, and dates should not automatically be classified as an identifier.

The HIPAA Privacy and Security Rules are not appropriate to minimal risk research of the type seen in social, behavioral, and educational studies. However, there are some established mechanisms for mitigation strategies, such as certificates of confidentiality. The purpose of the certificate is to protect identifiable research information from forced disclosure, allowing those with access to research records to refuse to disclose identifying information on subjects to any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, but they do not protect against voluntary breaches in confidentiality.

IRBs serve as the “HIPAA police” for biomedical research now. The University of Rochester does not support eliminating the need for IRBs to review information risks simply because new data security and information protection standards have been established. Institutions would need to establish policies and procedures to ensure adequate information protection.

The ANPRM suggests extending the applicability of the Common Rule to all research—including that which is not federally funded. The implementation of HIPAA requirements for all research at institutions that receive federal funds—whether those institutions are covered entities or not—would create a significant financial burden for faculty, student investigators, institutions, IRBs, and sponsors newly obligated to meet these standards. These costs are not justified nor balanced with the information risks that the standards are designed to minimize.

Implementation of some basic definitions and guidance regarding data security would be sufficient, rather than adopting a standard that is only appropriate for medical information. In this environment of ever-changing technologies for data security, guidance documents can

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be much more easily updated and to provide the most effective protections for human subjects. With IRBs already required to make the determination that “there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data [45 CFR 46.111(7)],” there are already best practices for ensuring that data is maintained in a confidential manner without imposing the HIPAA Privacy and Security Rules. If one set of guidance documents existed for all agencies, this could be more easily implemented.

Question 55: What mechanism should be used to regularly evaluate and to recommend updates to what is considered de-identified information? Beyond the 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?

The University of Rochester believes that regular periodic evaluation based on the passage of time (e.g., every five years) is the most useful way to update and assessments should be conducted based on evolutions in technology. If there were more frequent changes, implementation would be difficult in the field because rapid changes would make it difficult to educate investigators and IRBs and to ensure compliance. An evaluation of the current environment for data and specimen re-identification and data security mechanisms should be conducted by a federal—academic—industry panel and an updated guidance document should be issued promptly thereafter based on the panel recommendations. Using the guidance mechanism rather than rule-making or quasi-regulatory standards, if evolutions in technology, such as “cloud-computing” or the development of new security risks, compel providing guidance to the field, then an interim document could be quickly developed by a lead agency to address the concern.

Question 56: How should Federal regulations manage the risks associated with the possibility of identification of [DNA from] biospecimens? Should a human biospecimen be considered identifiable in and of itself? What are the advantages and disadvantages of considering all future research with biospecimens to be research with identifiable information?

Biospecimens that include DNA do not identify individuals without other linked information about individuals or their relations, or a large database that may contain the individual’s specific DNA sequences. Therefore, a biospecimen should not be considered identifiable if otherwise properly de-identified. The main risk is in inappropriate release of research subject genomic data, which new data security standards should minimize. Another protection required is from possible court or government orders that require specific biospecimens to be released from institutional repositories with linked data.

It is impossible to write stable regulations around changing technologies. The current standards (111(7)) allow IRBs to make the determination that “there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.” This strategy gives the IRBs the latitude to consider risks based upon changing technologies, because the issue is not really identifiability itself, but rather the informational risk level that identifiability poses. Written federal guidelines about issues to consider could assist the IRBs with making these decisions.

The University of Rochester believes that the federal regulations should not require biospecimens to be automatically considered as identifiable. The impact on basic and clinical science would be staggering. The ability to perform research with rare conditions and diseases would suffer. The requirement for informed consent would also negatively impact the use of pediatric samples when a child-donor becomes an adult, i.e., if all samples are considered identifiable and no waivers would be permitted, unless the child can be located and consent obtained, samples collected with parental permission could not continue to be used. This would obviously have consequences that would result in impossible barriers for the pediatric research community.

This is an era when the research enterprise and the federal government are faced with overwhelming financial challenges. Prudent decisions must be made to ensure that limited resources are used wisely. The resources required to implement a system to obtain written consent for subjects, maintain those varied subject responses (yes, no, some yes, some no), and track samples will be a significant burden and frankly not possible to accomplish with any assuredness. The research community will not be able to implement or sustain a consent-based system, which would then lead to elimination of vital research.

The Belmont Report outlines three ethical principles that must be balanced; none supersedes any other. Considering all human-derived specimens as identifiable clearly assumes that “respect for persons” should trump “beneficence” and “justice.” We believe that a rational analysis would conclude that other safeguards could adequately address respect for persons while recognizing the benefit to society that accrues from research with biospecimens that—to all intent and purposes—are not readily identifiable and for which there is no reason or desire to re-identify samples.

In practice, such a policy would not result in meaningful informed consent processes, and it will be prohibitively expensive to implement (in time, dollars, and personnel costs) and impede both clinical and basic biomedical research when we are trying to accelerate research through the translational science model. The technology is not currently available to automatically mean that having a biospecimen alone indicates that it is identifiable. In addition, a DNA databank is not available to make having a biospecimen identifiable. While there is some benefit to having rules in place before a problem arises, at this point, we do not truly understand when this could occur.

Question 57: Should some types of genomic data be considered identifiable and, if so, which types (e.g., genome-wide SNP analyses or whole genome sequences)?

The type of genomic test does not make a difference to how identifiable the biospecimen is because genomic data should not be considered identifiable for research. It is extremely unlikely that individual human genetic data will ever be placed in the public domain without the expressed written consent of the individual—making it effectively impossible to query a human genetic database in a way that would lead to re-identification of subjects. The only exceptions to this are likely to be rare individuals who elect to place their genetic information into the public domain for personal, medical, and scientific reasons—such as James Watson. These rare individuals can be deemed to have waived their right to privacy by making this personal information available to the public. The issue is not really identifiability, but rather the risk level that potential identifiability poses and how to scale protections to the risk.

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Standards for Data Security and Information Protection
<p>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?</p>
<p>The University of Rochester strongly believes that activities that occur before implementation of any rule (e.g., data previously collected) should not be held to the new standard. Unfortunately, if the federal position is that all biospecimens are identifiable in and of themselves, then the date of collection does not make a difference to that standard. We believe that the impact of that position and thus applying the rule to all data and specimens—existing and future—would be devastating. Currently, there are millions of samples collected nationwide and valuable data warehouses set up, which are used to conduct vital research. The administrative burden will be significant with these rules, regardless if they are applied to retrospective and prospective samples or just prospective samples.</p> <p>Any new data security and information protection standards should apply only to data and biospecimens collected after the implementation of new rules, not to all data and biospecimens. Not doing so would levy a heavy administrative burden in applying the rule to all data and biospecimens. Data security and information protection should be the responsibility of individual investigators and their institutions. Institutional standards should be promulgated to which individual investigators should adhere and which impose punitive action on those who fail to comply.</p> <p>The University of Rochester also believes that including biospecimens without identifiers within the human subject research provisions related to information risk would inappropriately expand the meaning of “human subject” and add unintended burden to the system of human subject research oversight.</p>
<p>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 [the HIPAA] standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research? Might a better system employ different standards for different types of research?</p>
<p>If investigators are required to adhere to a strict set of data security and information protection standards modeled on the HIPAA Rules, the system would be overly burdened with no corresponding, additional protection for subjects. The HIPAA standards were specifically designed for healthcare, medical insurance, and billing to protect medical information within a clinical setting, not as a way to manage research information. While some information collected during social and behavioral research is sensitive and requires strict protection, to implement a stringent HIPAA-based regulation for all social and behavioral research is unjustified.</p> <p>The HIPAA Security Rule provides an extensive list of requirements for data security (encryption, firewalls, access controls, etc.) and many other mechanisms, including risk</p>

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analysis and management, administrative safeguards, physical safeguards, technical safeguards, organizational requirements, policies and procedures, documentation requirements, implementation specifications, enforcement, and penalties for noncompliance. While some of these elements would be helpful in federal guidelines for educating and informing investigators regarding data protections, as regulatory mandates, they would not guarantee any more effective protection and would be inappropriately burdensome. It should be the investigator's responsibility to meet institutional standards for data security and information protection, and the institution should develop standards and procedures that are responsive to federal standards as described in guidance.

Whether or not HIPAA-like standards are implemented for research study subjects, grant compliance for FISMA cannot be overlooked moving forward as many government-contracted grants are increasingly requiring compliance with this standard. While not all research data is human subject data, for those that are, a stringent data protection schema such as FISMA is relevant in the protection of direct individual identifiers. Risk must be assessed based on the relevancy of the data collected to determine whether or not it falls into the specified framework of data protection instilled by such government regulations. Social and behavioral research involving human subjects, especially if de-identified, generally poses little need for adhering to such stringent regulations. IRBs should provide the risk assessment for such research and determination of adequate data protection.

Issues related to privacy and confidentiality have been a part of IRB review from the beginning of HHS regulation of research. The University of Rochester agrees that data security is an important step in minimizing information risks, but we do not agree that IRBs do not have the expertise or are unable to address security issues. IRBs are accustomed to dealing with these issues just as they are in any of the other section 111 approval criteria. The creation of a separate risk category—in addition to physical and psychological risk—is helpful in the analysis of risk, but removing this from IRB responsibility and managing it separately from IRB review may not serve to protect subjects. For research that presents solely informational risks (e.g., current Categories 2 and 4), it would be appropriate to allow exemption as long as the investigator has responsibility for ensuring data security standards are met and that the risks, considering data protections, are minimal.

Co-opting the HIPAA standards used for protected health information to apply across the range of disciplines and activities represented by the human subject research enterprise is an unjustified response to a yet-to-be realized problem. It is unclear what problems or incidents involving disclosure or breaches of confidentiality would be addressed with this proposed change. The information most at risk—protected health information—is already protected under HIPAA; other types of sensitive information are often protected under the provisions of other state and federal regulations.

As the ANPRM states, the goal of information protection should be to prevent the breach of confidentiality through unauthorized access, inappropriate disclosure, or re-identification at either the individual or, in some cases, the subgroup level. The University of Rochester does not support the suggestion in the ANPRM that investigators should be required to adhere to breach notification standard modeled on those applied to HIPAA-covered entities for

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<p>breaches of individually identifiable health information. Information that contains direct identifiers of individuals poses the greatest informational risk, while limited data sets and de-identified information pose little risk. Different standards should be employed for the two categories of (1) information that contains direct individual identifiers and (2) limited data sets or de-identified information (i.e., these should be considered the same low-level risk)</p> <p>Implementation of basic definitions and guidance regarding data security would be sufficient rather than adopting HIPAA Privacy and Security Rules for all research. In this environment of changing technologies for data security and identification of samples, guidance documents can be much more easily updated and revised to provide protection for human subjects.</p>
<p>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)?</p>
<p>No.</p>
<p>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 [e.g., NIST]?</p>
<p>Standards for how data should be managed (encryption, firewalls, etc.), such as those contained in the Federal Information Security Management Act (FISMA), may not be appropriate for research involving little informational risk. FISMA emphasizes “risk-based,” cost-effective security standards; if additional federal guidance on security is modeled on these standards, the involvement of research institutions will be critical to arriving at standards that protect human subjects without unduly burdening investigators and institutions. If standard guidance for all Common Rule agencies is implemented, then these standards would be consistent.</p>
<p>Question 62: If investigators are subject to data security and information protection requirements modeled on the HIPAA Rules, is it then acceptable for covered entities to disclose limited data sets to investigators for research purposes without obtaining data use agreements?</p>
<p>Unfortunately, even if investigators are subject to data security and information protection requirements modeled on the HIPAA Rules, it will be unlikely that covered entities will find it acceptable to disclose limited data sets to investigators for research purposes without obtaining data use agreements because the covered entity will still have to comply with the HIPAA Rules. So this will not improve the existing inhibitory environment. Real change to facilitate research will only come when the HIPAA Rules are changed to exempt research from compliance.</p>
<p>Question 63: Given the concern that even with the removal of the 18 HIPAA identifiers, re-identification of de-identified datasets is possible, should there be an absolute prohibition against re-identifying de-identified data?</p>
<p>Yes. The prohibition against investigators re-identifying de-identified data could easily be communicated through the IRB approval letter. This should not prohibit third parties from maintaining a link to enable appropriate research results to be given to the subjects through their clinicians. Only with appropriate IRB approval in instances where dramatic discovery of life-impacting research is successful should there be the allowance of re-identification; otherwise, there should be a prohibition of re-identifying de-identified data.</p>

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<p>Question 64: For research involving de-identified data, is the proposed prohibition against a researcher re-identifying such data a sufficient protection, or should there in some instances be requirements preventing the investigator from disclosing the de-identified data to, for example, third parties who might not be subject to these rules?</p>
<p>The University of Rochester believes that it can enforce a prohibition against re-identifying data within the institution. For data shared with outside investigators, the removal of identifiers should be sufficient to protect shared data; however, we typically require an agreement not to re-identify data when that is appropriate. Control of re-identifying data should be managed at the institution level where tight control can be applied if necessary. Federal regulations are unnecessary as this action is better enforced locally at the institution. The University of Rochester does not support putting this requirement in federal regulations; procedural detail is not appropriate for regulations.</p>
<p>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?</p>
<p>Neither de-identified data nor biospecimens without identifiers should be considered research involving a “human subject.” The issue of registration as a means of auditing for unauthorized re-identification, while seemingly justifiable, should be locally instituted by the IRB as opposed to federally mandated. In rare cases where re-identification is needed, registration with the institution should be considered. The University of Rochester does not support including this requirement in federal regulations; procedural detail is not appropriate for regulations.</p>
<p>Question 66: What entity or entities at an institution conducting research should be given the oversight authority to conduct the [data security] audits, and to make sure that these 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?</p>
<p>Assigning oversight authority to conduct the data security audits is an institutional responsibility and could be assigned to anyone within the institution who is sufficiently trained and educated on the standards to conduct a meaningful audit. Conducting data security audits is time consuming and labor intensive, and requires specialized expertise (typically requiring participation of both an IT professional and compliance professional). In addition, an in-depth look at the computer hardware can require considerable time and effort, depending on the complexity of the data that has been collected and stored. It is unrealistic that these labor-intensive audits can be applied to all research regardless of which institutional entity is responsible for auditing.</p> <p>The University of Rochester strongly believes that institutions should have the flexibility to determine how to accomplish oversight responsibility. Institutions have different resources, infrastructure, and expertise, and therefore, only they can determine which group within their organizational structure should conduct audits. Procedural detail is not appropriate for regulations (e.g., specifying institutional entities and methods for audit selection). The creation of procedures is an institutional responsibility.</p>

Data Collection to Enhance System Oversight
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 University of Rochester believes that the current reporting system (i.e., individual letters to the regulatory agency/sponsor/institution) and required reports to federal offices are burdensome and offer little benefit. For example, required reporting of suspensions to federal agencies when investigating allegations and potential problems adds burden and may actually decrease human subject protection by delaying prompt investigator/institutional assessment and corrections to risks. It is also difficult to see any benefit from reporting unanticipated problems to federal regulatory authorities that justifies the burden.
Question 68: Should the number of research participants in federally funded human subject research be reported (either to funding agencies or to a central authority)? If so, how? What additional data, not currently being collected, about human subject research should be systematically collected in order to provide an empirically-based assessment of the risks of particular areas of research or of human subject research more globally? To what types of research should such a requirement apply (e.g., interventional studies only; all types of human subject research, including behavioral and social science research)? Are there other strategies and methods that should be implemented for gathering information on the effectiveness of the human subject protection system?
<p>This question revisits the difficulties in defining the scope of the information to be collected: how is a “research participant” defined? Are the subjects in a clinical trial counted the same as respondents to a survey or the number of records reviewed in a database study? How are subjects in epidemiology studies counted? Are “screening failures” counted as subjects, or those who are approached, but refuse participation? The burden of collecting the number of subjects would be significant for IRBs because each study would have to be examined for total number of subjects. Even for institutions with an electronic database system, this would be difficult. The University of Rochester believes that the burden of this proposal is not justified by any clearly achievable benefit. We believe it is important for the government to only collect information when there are clear and compelling reasons to do so, resources to analyze it in a timely manner, and the ability to act upon the analysis. We believe these seem to be absent for this broad-based federal reporting requirement. We do grant that it might be feasible and there might be value in obtaining such information from a limited set of research activities, i.e., multi-site, medical clinical trials that are conducted under a single IRB review.</p> <p>In order for IRBs to have any idea of numbers of individuals who have participated, investigators must submit that data, if not on continuing review reports, at least when the study is complete. If studies are allowed to commence without IRB approval (exempt category) or with no required continuing review (expedited categories), then some form of final report, which includes numbers of individuals who have participated, should be required. Federal guidance could be developed that would explain the expectation that investigators will file final reports to close out their studies. We believe that the burden to submit final reports for exempt studies presents an unreasonable and unjustified burden; however, for studies that have IRB approval, a final report should be required. This would</p>

require the revision of current OHRP guidance (Guidance on IRB Continuing Review of Research; November 10, 2010) which states: “OHRP is aware that many IRBs require investigators to submit final closeout reports when a research study is completed or no longer involves human subjects. Since [sic] the HHS regulations at 45 CFR part 46 do not require submission of such reports, institutions are free to decide whether and when such reports are required and what their content should include.”

Question 69: Is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?

While the University believes that this central collection is theoretically desirable, it could not be practicably carried out (to use regulatory wording). It is difficult to understand how the reporting of aggregate numbers from disparate sources and studies serves the purpose of managing unanticipated problems or adverse events. This is truly an apples and oranges situation, with needle-in-the-haystack implications. Report timing would also be a critical issue; to require reporting to the database before completing an evaluation is unlikely to be of any value.

One of the more difficult prerequisites that would have to be solved before such a universal reporting system could work effectively is the development of a dictionary of definitions and technical terms. It will be difficult to get the federal regulatory and funding agencies as well as industry sponsors and research sites to agree on basic terms such as “adverse event,” “serious adverse event,” and “unanticipated problems” (versus unexpected), let alone reach agreement on medical conditions and the range of reportable events that behavioral, educational, and social science research would need to standardize.

If a new federal office is established to review of all this data or this new responsibility is given to an existing office such as OHRP, the administrative burden on that office and financial cost to the public may far outweigh the benefit. The University of Rochester believes it is important to only collect data when there is a clear reason to do so and resources to analyze and act upon the analysis in a timely manner. We believe these to be absent, and it would seem to us that this proposed system would create not only an unmanageable burden and cost but also a huge agency liability.

A combined database raises a welter of procedural questions that include: Would IRBs be able to submit their reportable events through this database? If so, who would review them? Would the IRB receive some type of notification when the review is complete or if questions are required? Would the questions and responses be done directly within the database? Will the public have access to the database? How will the potential for identification of subjects whose cases are reported be prevented? How are corrections to inaccurate submissions to be handled? How will duplicate/multiple submissions of the same event be culled? Will only federally sponsored research be submitted, or will it be open to (mandated for?) industry-sponsored studies and others? In a multi-site study with many parties involved, who submits the event to the database, and at what point is it submitted?

It is also critical to remember that this enormous cost and administrative burden would add little value for minimal risk studies and would duplicate the current system for reporting and tracking adverse events and unanticipated problems. In clinical trials, adverse events that are

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not expected based upon the investigator’s brochure must be reported in an expedited fashion, and the sponsor is then required to distribute the details of that event to all research investigators participating in any trial with that specific intervention (e.g., any trial for the same drug). Thus, the benefits of central reporting for adverse events, especially those that might be newly identified problems with a drug or device, are already available within the current systems prescribed for the conduct of clinical research, so the creation of a new system would be expensive, burdensome, and entirely unnecessary.

Question 70: Is the access to information on individual studies provided by [ClinicalTrials.gov.] sufficiently comprehensive and timely for the purposes of informing the public about the overall safety of all research with human subjects?

No. Most research and even most clinical research is non-interventional, such as imaging studies, longitudinal epidemiology studies, biomarker studies, and questionnaires, and, of course, the bulk of social-behavioral research is not clinical. So if a listing of research is desired, looking on clinicaltrials.gov would only yield that small subset of clinical research that is interventional, i.e., clinical trials.

The clinicaltrials.gov database is not easy to use, and the information is often not current. It is unclear what the public thinks of it, or even if they know of its existence and the database is not easy to navigate—even for the professionals who are making entries. The database was not set up to inform the public about the overall safety of all research with human subjects and to presume that the public could complete the complex analysis required to make clinical sense of the data is not warranted. There is no possible way to maintain such a central web-based database without an enormous use of resources. Without significant changes to the design of the website, this database will not and cannot be an appropriate vehicle for this purpose.

On the other hand, this database is already in wide use by investigators and modification of the interface could increase the ease of use for the general public without creating new burdens for investigators and institutions. If the goal of redesign is to provide composite information at the conclusion of a trial when the clinical results are posted, then modest extra data input by the sponsor might allow a lay user to understand the types and severity of risk encountered during the clinical research study.

Extension of Federal Regulations

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?

The University of Rochester believes that extending the applicability of the Common Rule to all research—including that which is not federally funded—is an attractive goal. We wonder, however, if extending the Common Rule based on federal funding will actually fill the gap in protections because this extension will not affect non-federally funded institutions/research sites, e.g., contract research organizations; so the overall effectiveness of this proposal is questionable. The cost of extending the coverage is another consideration that must be carefully weighed and justified. We also wonder how long after the “qualifying” federal funding ends will the institution be covered under the extension, and what will be the effect on “mergers and acquisitions” and “hybrid” organizations?

Major research institutions with an FWA have generally applied the protections of the Common Rule to all research they conduct, regardless of funding source, because it is the ethical thing to do and it would be confusing to operate under two different standards for protection. Recently, however, while continuing to apply the protections of the Common Rule, many institutions have “unchecked the box” to limit the scope of their FWA to only federally funded studies because the requirements for reporting to federal agencies and federal compliance oversight can be onerous. If the Common Rule is expanded as suggested, it must be teamed with a realistic system for risk-appropriate oversight; to that end, it would be desirable to allow relief from federal oversight and reporting for non-federally sponsored studies, i.e., extend only the human subject protection mechanisms of IRB review and consent to all research, but do not require new assurances (or modifications to existing assurances) or federal reporting. As many have done in the past, institutions could develop appropriate human subject protection procedures that cover all research at their facility/s.

Another consideration if the Common Rule is extended is that institutions and parts of hybrid institutions that are otherwise not governed by the HIPAA regulations will become at least partially engaged if the new data security requirements are aligned with HIPAA requirements.

We are concerned that there are many questions that will have to be addressed before the Common Rule is extended, including how the requirements for IRB review, and consent will be applied to the range of non-federal research that would be included and how the assurance mechanism could be exempted. The effect of encompassing additional research (or research-like) activities under the regulations, including those that may be “politically” or “socially” sensitive such as family planning and stem-cell research, must also be carefully considered.

Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

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

There are more than 25 areas of difference in federal guidance (see list below), not counting the ICH standards, which have been adopted by the FDA as standards for good research practice. Obviously, it is hard to see how this many differences in guidance can all strengthen protections for human subjects. To the extent that these differences add burden without strengthening protections, they weaken the system by confusing and burdening investigators and IRBs. The multitude of differences also contributes to compromising the integrity of the oversight system because investigator non-compliance is increased when different requirements conflict or are applied in an inconsistent manner.

While common guidance across agencies is the best outcome, the University of Rochester believes that it would be a major step forward in terms of both protecting human subjects and relieving burden if the differences and complexities that exist just within the HHS offices can be removed or harmonized. We suggest that HHS harmonize guidance from OHRP, FDA, and OCR, even if the other Common Rule agencies require separate guidances.

Differences (ref: AAHRPP Evaluation Guide):

- Written procedures (HHS, FDA VA, DOJ, EPA)
- Education (VA, DOD/DON)
- Scientific review (VA, DOD, DOJ)
- Resources (VA)
- International research (HHS, FDA, VA, DOD)
- HRPP evaluation (VA, DOE)
- Reporting of serious or continuing non-compliance (HHS, FDA VA, DOD)
- Use of investigational test articles (FDA, VA)
- Emergency use (HHS, FDA, VA)
- IRB composition (HHS, FDA, VA)
- Threshold for financial interest reporting/COI (HHS, FDA, VA)
- Inclusion of children with disabilities (HHS, ED)
- Criteria for exemptions (HHS, FDA, VA)
- Convened meetings (HHS, FDA, VA)
- Review using the expedited procedure (HHS, VA, DOD)
- Report of unanticipated problems/AEs (HHS, FDA VA, DOD, DOE, DOJ)
- Multi-site research (VA, DOD)
- Plans for data and safety monitoring (HHS, FDA VA, DOD)
- Review of advertising (FDA, VA, DOD, DOJ)
- Protection of personally identifiable information (HHS, OCR, FDA, VA, DOJ, DOE)
- Research-related injury (HHS, DOD, DOJ, VA)
- Waiving or altering the consent process (HHS, FDA, VA, DOD, DOE)
- Planned emergency research (FDA, VA, DOD)
- Required records (HHS, VA)
- Investigator qualifications (DOJ, VA, DOE)
- Recruiting Study Subjects, Payment (HHS, FDA, VA, DOD)
- Consent (HHS, FDA, VA, DOD, ED)

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 differences influencing the conduct of research [domestically and internationally]?

Although we, like other academic medical centers, have learned to cope with the HIPAA regulation of research, clearly this is an area where regulations are overly burdensome and do inhibit the conduct of research—most notably with research that is minimal risk and presents promise to improve a wide variety of important societal ills.

While FDA and HHS have recently made significant strides in issuing joint guidance and should be applauded for these efforts, to the extent that differences exist between the FDA Centers themselves (most typically CDER and CDRH) as well as with the Common Rule guidance, research is, if not altogether impeded, at least slowed while potential differences are sorted out. These differences sometimes require extended communications between the investigator and the IRB and between the institution and the federal agencies. Sometimes telephone calls or emails can be used to resolve issues, but all too often, written questions

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and supporting materials must be sent and examined to ensure compliance with all potential interpretations (some of which are urban legend and others are found only in compliance letters) and written guidances.

It is the University of Rochester's experience that the Common Rule agencies most often at odds with HHS guidance are the FDA, VA, and DOD (especially the Department of the Navy). For example, the Navy does not fully accept an assurance filed with the other federal agencies and requires institutions to file a separate amendment; they also require completion of their own training in addition to other agency and institutional requirements. All these add burden and inhibit research with little or no benefit to subjects.

The University of Rochester believes that it would be helpful to have guidance for U.S. IRBs that review research conducted in foreign countries, including when it is acceptable to rely upon a foreign IRB. As part of the guidance, a process should be developed for determining which countries have laws and regulations that are equivalent to the protections offered by the Common Rule.

Question 74: If all Common Rule agencies issued one set of guidance [documents], would research be facilitated both domestically and internationally?

If all Common Rule agencies issued one set of guidance documents, research would be facilitated to the extent that the guidance was not overly proscriptive and was useful in helping institutions and investigators comply with the regulations. The problem in issuing joint guidance is the same that has caused the different Common Rule agencies to adopt variations on the Common Rule, i.e., agency roles and responsibilities are different and thus, to an extent, they require different standards.

One issue that the University of Rochester believes must be addressed is that "guidance" should be guidance, i.e., clarification and instruction in the application of the regulations; it should not be used to extend the regulations, i.e., add new requirements that must be accomplished to comply with agency goals, which have not been vetted through the formal rule-making process.

Another concern is that "guidance" is often found in compliance letters (e.g., FDA's recent "Advice Letter" regarding "component analysis"). Again, this smacks of rule-making without the protections of advanced notice and comment that the formal rule-making and official guidance development require. Setting guidance/policy by letter also guarantees that there will be confusion and variance in application because the only sites that will know of the new standard or interpretation will be the recipient of the letter and those other sites that discover the letter through FOIA, web searches, the grapevine, etc.

Current system of protections for human research subjects

General comment is invited on the current system of protections for human research subjects as implemented through the Common Rule, the HIPAA Privacy and Security Rules, and any other regulations or guidance documents. In particular, comments are sought not only on ways to improve the efficiency of the current system, but about circumstances in which the protections provided by the current system might be inadequate and in need of supplementation or change in order to make sure that subjects are receiving appropriate protections.

The University of Rochester offers the following comments for consideration on the current system of protections for human research subjects as implemented through the Common Rule and the HHS human subject regulations:

1) The proposed “revisions” in the ANPRM largely do not address inherent deficiencies in the regulations, but rather the collective complexities introduced by written guidance, one-off compliance letters, and oral *ad hoc* interpretations from agencies. The University of Rochester strongly believes that the desirability of any federal regulation depends not only on the importance of the problems the regulation aims to address, but also on the regulation’s effectiveness in achieving those aims. Generally when proposing federal regulations, the least complex rules are preferred, as long as those measures achieve the important societal goals that have been identified as requiring regulation. The Office of Management and Budget (OMB) issued a bulletin in 2007 entitled “Final Bulletin for Agency Good Guidance Practices.” [<http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2007/m07-07.pdf>.] That Bulletin established policies and procedures for the development, issuance, and use of guidance documents by Executive Branch departments and agencies and is intended to increase the quality and transparency of agency guidance practices and the significant guidance documents produced through them. We suggest that drafters of the suggested guidance review the OMB document.

2) Some of the ANPRM suggestions deal with removing IRBs from their traditional review, approval and monitoring role or minimizing oversight activities, such as allowing investigators to self-certify some projects as exempt; continuing research over multiple years without annual IRB continuing review; and removing IRB review of data security plans. While we believe that there is merit in this shift of responsibility, it is appropriate only if the institutional obligations that IRBs now enforce are given to investigators as clear and direct duties under federal regulation. To be effective and efficient, responsibility should be placed on those who initiate and conduct research and are in the best position to protect human subjects (i.e., investigators). Therefore, the University of Rochester believes that the Common Rule regulations should be amended to include investigator responsibilities, which should cover at a minimum: (1) responsibilities of investigators (biomedical and non-biomedical); (2) qualification standards for investigators, i.e., training; and (3) investigator documentation/records. Regulations for investigators will become even more important if, as the ANPRM suggests, oversight shifts from local IRBs to central IRBs and more research is

covered by an expansion of the Common Rule applicability. We believe that it will be critical to the successful implementation of the proposals in this ANRPM to have effective investigator training programs. Thus, it may also be useful to amend section 103 to add a general requirement that research institutions provide investigators with training and education in investigator responsibilities, conflicts of interest, research integrity and scientific conduct as part of an institutional human subject protection program. The regulatory structure should, however, be sensitive to “unfunded mandates” so there should be reasonable latitude for institutions to develop responsive training programs. The regulations and supporting guidance would need to be sufficiently open and flexible for application to all institutions that engage in human subject research.

3) The University of Rochester strongly believes that institutions should have the flexibility to determine how to accomplish oversight responsibility. Institutions have different resources, infrastructures, and expertise, and therefore, only they can determine which procedures are appropriate to their organizations. Procedural detail is not appropriate for regulations. The creation of specific procedures is an institutional responsibility.

4) There are no financial conflict of interest regulations in the Common Rule for investigators. This could be added to the Common Rule by simply requiring that before conducting a research study, investigators certify to institutions/sponsors that they have no financial conflicts of interest or if conflicts exist that might bias or appear to bias the research or the reporting of results, these are appropriately managed. The definition of financial conflict of interest would need to be placed in the section 102 definitions and this should mirror the standards now endorsed by NIH and NSF. It may also be appropriate to have a somewhat more detailed regulation that would mirror the FDA regulations, i.e., “investigator shall provide the [institution or] sponsor with sufficient accurate financial information to allow [conflicts of interest to be appropriately managed]. The investigator shall promptly update this information if any relevant changes occur during the course of the [research] and for 1 year following the completion of the study.” Again, we stress that procedural detail (how institutions should review and manage) would not be appropriate for regulations and could in fact create disharmony and yet one more level of complexity for investigators conducting research with human subjects.

5) Section 113 states, *in toto*: “An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.” Although there is no written guidance stating so, OHRP staff have expressed that an IRB-directed suspension of “any” research activity is considered a suspension of the study under section 113 (and section 103(b)(5)(ii)) and must be reported. This has caused IRBs to be creative to the point of absurdity in getting enrollment in studies stopped to protect subjects while the IRB can explore with the investigator if the study is being conducted in accordance with the IRB's requirements or if it is associated with unexpected serious harm to subjects. The University of Rochester believes that this interpretation and federal reporting requirement hinders the ability to oversee studies and pursue appropriate internal procedures

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and negatively affects subject safety. Written federal guidance should be developed that clarifies that IRBs should be given the opportunity to investigate an allegation of non-compliance and be permitted to request an investigator to voluntarily stop enrollment (e.g., recruitment, new subject enrollment, halting a study arm) without triggering the reporting requirements. In other words, a temporary hold on enrollment pending an investigation should not be deemed a suspension. Only suspensions of all research activities on a protocol, occurring after an IRB investigation, should be deemed suspensions. The University believes that if IRBs are allowed to freely pursue issues of potential concern without being intimidated by automatic federal reporting requirements, subjects will be better protected and the oversight that IRBs provide will be more effective with fewer burdens on the institution, the IRB, and the system as a whole.

6) The Belmont Commission and subsequent federal ethics commissions since then have called for a national policy on compensation for injury. The University suggests that HHS explore, with the other Common Rule agencies, establishing a “national compensation fund,” “subject injury fund,” or “insurance pool” (or other standard approach to subject-injury) for research subjects who, in the rare instance, are injured as a result of participation in federally funded research. This would standardize on a national level the compensation-for-injury clause in the consent process and the signature form. We believe that establishing a government-backed insurance pool is essential to the goal of streamlining the consent process for multisite clinical trials; absent this, it will be very hard to get institutions to agree to use a single consent form without institutional changes.

7) Section 110 allows IRBs to use an expedited review procedure to review “minor changes in previously approved research.” The regulations do not contain a definition of “minor change”; however, they should. This is actually a point of difference in FDA and HHS interpretation and guidance. In our policies, the University of Rochester defines minor changes that are eligible for expedited review as those that do not change the risk/benefit ratio of the study; do not increase the risk presented by the study above minimal risk or, in and of themselves, do not expose more people to the risk; and do not present more than minimal risk.

8) The IRB documentation requirements in sections 103 and 115 (minutes, rosters, reports) should be decreased. The University of Rochester suggests that 103(b) be reduced to one sentence—the first sentence—and all other verbiage be placed in consolidated federal guidance. The level of detail regarding the content of an assurance in this federal regulation is overly burdensome. Deleting this unnecessary detail in the Common Rule would also help to harmonize with the FDA standards by eliminating the regulatory requirement to submit IRB membership rosters (assuming guidance would in fact eliminate that burden). Section 108(a) should be revised to state that IRBs shall “Follow written procedures for conducting its initial and continuing review of research and for ensuring prompt reporting to the IRB any unanticipated problems involving risks to subjects or others.” Procedural detail (e.g., how/when to review and report) is not appropriate for inclusion in regulations. The concepts in 103(b) can best be addressed in guidance, which would also allow flexibility and the ability to keep practice up to date with future changing conditions.

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9) Section 117 is entitled “Documentation of informed consent.” Unfortunately, the section does not address the commonly understood definition of the term “documentation” (i.e., providing evidence that a process, such as informed consent, has occurred), but rather it only describes requirements and mechanisms for obtaining the signature of the subject or legally authorized representative. This causes considerable confusion for investigators and study-team members, especially when waiver of documentation is involved, i.e., they think that they do not need to keep files or records that consent was obtained. The University of Rochester recommends that section 117 be re-titled “Signature Requirements for Informed Consent.” The body of section 117 should also be revised to carry the idea that this section addresses signature requirements, e.g., 117(a) could be changed to: “Except as provided in paragraph (c) of this section, informed consent shall require the signature and date of signature of the subject or the subject’s legally authorized representative on a written consent form approved by the IRB. A copy shall be given to the person signing the form.”

10) A focus of the ANPRM is on data security. The University of Rochester believes that implementation of basic definitions and guidance regarding data security would be sufficient rather than adopting HIPAA Privacy and Security Rules for research. We suggest that such federal guidance should recognize data encryption and/or other simple techniques as a “safe-harbor” for investigators when using computer-based technology to record and store data.

11) The University of Rochester suggests that the role of the Data Monitoring Committee (DMC) be codified in the Common Rule. Forming and operating a DMC is a subject safety mechanism for clinical trials that should be legitimized through regulations as an available technique in addition to other mechanisms that investigators should ensure are in place and effective. This could be accomplished by a brief new section in subpart A. This would be a step to harmonize the Common Rule with the FDA regulations without limiting the ability of the FDA to expand regulatory requirements in 21 CFR. A conforming amendment would need to be made to section 46.102 (Definitions) to add a definition for “clinical trial.” The definition used by NIH would be an obvious model and better than the FDA definition.

12) Simplification is needed in “engagement” determinations and the requirement for agreements and IRB approval for field sites such as schools and businesses that allows investigators to access records and/or interact with students/employees, etc. We recommend that FWAs not be required for such sites. The requirement to file updates of FWAs is one of the impediments to using single IRBs for multi-site studies, so revision of this policy could solve two problems at once.

13) In subpart B, “Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,” the word “neonate” is incorrectly used and causes considerable confusion in the applicability of the subparts (i.e., B versus D). The word “newborn” would better describe what is now defined as “a neonate of uncertain viability.” The definition in section 46.202(d) should be changed to: “Newborn encompasses the time immediately after delivery, but before a determination is made regarding viability.” It may also help to define, in this subpart, “Child” as a newborn who has been determined to be viable after delivery. The University of Rochester strongly suggests that, to reduce confusion, the misused word neonate be replaced in this subpart.

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14) Subpart C is entitled “Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.” For many years after the initial adoption of subpart C, institutions only reviewed research that targeted prisoners as the population to be enrolled and studied. Circa 1999-2000, institutions were informed by OHRP that it now interpreted the phrase “involving prisoners as subjects” as applying to “incidental prisoners,” i.e., those research subjects already enrolled in a research study who subsequently become prisoners. For the past ten years, this has led to the mandated re-review of ongoing studies—typically those that provide life-sustaining treatment—because one individual in a general population study is detained in a penal institution. The University of Rochester believes this has sometimes put subject safety at risk, is a total waste of time and resources, and has the unintended effect of decreasing respect for regulatory compliance. According to Chapter 6 on Prisoners in the OPRR Guidebook, which was published in 1993 (http://www.hhs.gov/ohrp/archive/irb/irb_chapter6ii.htm#g6), “the first question IRBs must ask when a protocol proposes to use prison inmates as a study population is whether that population was chosen simply out of convenience to the investigator.” The phrase “when a protocol proposes to use prison inmates as a study population” clearly shows that the original interpretation of the federal regulators was the subpart C applied to studies of prisons and targeted enrollment to prisoners. Historically, there was no intent to include incidental prisoners. The Guidebook further states, “the very fact of incarceration may make it difficult or impossible for prisoners to give voluntary, informed consent” and “the primary issue surrounding the participation of prisoners in research has always been whether prisoners have a real choice regarding their participation in research, or whether their situation prohibits the exercise of free choice.” Clearly, free choice is not an issue with a subject already enrolled as a non-prisoner. The Guidebook continues, “DHHS issued regulations governing research with prisoners, limiting it to studies with an independent and valid reason for involving this particular population.” Reading the “Additional duties of the Institutional Review Boards where prisoners are involved” that are listed in section 46.305, one can clearly see that the regulations were not written for individual subjects, to wit: “any possible advantages accruing to the prisoner ... are not of such a magnitude that [consent] is impaired; the risks are commensurate with risks that would be accepted by non-prisoner volunteers; procedures for the selection of subjects within the prison are fair (note: an old version of the regulations required that control subjects be selected randomly from a group of available prisoners); and the [consent] information is presented in language which is understandable to the [prison] population.” The regulations (45.305(c)) also require institutions to certify when prisoner research has been reviewed to OHRP, resulting in a reporting delay and burden on OHRP, which must then review the certification package and respond to the institution. There is no added human subject protection in this process, only delay, cost, and burden. The University of Rochester believes this situation can be quickly remedied by publishing federal guidance that states subpart C is only to be used in studies consisting mainly or exclusively of prison populations. We do understand that there is some legitimate concern about whether confidentiality of participation and data can be adequately maintained in the prison, so if OHRP truly believes that there is value in a re-review and can justify the burden, guidance could suggest that incidental prisoner involvement could use an administrative review (even if the study itself is greater than minimal risk) to detect such concerns and ensure they were adequately addressed. No certification by institutions to OHRP should be required for incidental prisoner involvement.

15) Subpart C – If the exempt categories are appropriate for children (subpart D), then they should be appropriate for prisoners as well. Thus, a new 301(d) should be added that is the same as 201(b): “The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.” This would also have the beneficial effect of conditioning the exemption even in those institutions that do not apply this subpart to its research.

16) Subpart D – the complicated restrictions in 401(b) should be deleted, instead adding the condition on surveys and interviews to 101(b)(2), i.e., allowing the exemption for children. Thus, 401(b) could be the same as 201(b): “The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.” This also would have the beneficial effect of conditioning the exemption, even in those institutions that do not apply this subpart to its research.

17) Subpart E will need an amendment to 46.502(e)(2) because protocols will be active without a continuing review during the preceding twelve months (i.e., is the number collected from institutions to be reflective of research activity by investigators at the site or just IRB review activity, or both). In order for IRBs to have any idea of numbers of active studies, investigators must submit that data, if not on continuing review reports, at least when the study is complete. Federal guidance should be developed that includes the expectation that investigators will file final reports to close out their IRB-approved studies.

18) The University of Rochester believes that the required IRB initial and continuing review for humanitarian use devices is inappropriate and HHS and FDA should work with Congress to pass legislation to reverse this requirement.