

OHRP/OSTP ANPRM (HHS-OPHS-2011-005)  
 Prepared by Gary L. Chadwick, PharmD, MPH  
 for the University of Rochester based on published ANPRM

ANPRM Question	Response
<b>Streamlining Documentation Requirements for Expedited Studies</b>	
1. Question 1: Is the current definition of “minimal risk” in the regulations appropriate? If not, how should it be changed?	
2. Question 2a: Are 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?	
3. Question 2b: What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?	
4. 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?	
5. Question 4: Should the regulations be changed to indicate that IRBs should only consider “reasonably foreseeable risks or discomforts”?	
6. 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?	
7. Question 6a: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk?	

<p>8. Question 6b: How should the characteristics of the study population (e.g. mental health patients) be taken into consideration in the risk assessment?</p>	
<p>9. Question 7a: 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?</p>	
<p>10. Question 7b: Should any of the existing activities on that list be removed or revised?</p>	
<p>11. Question 8: Should some threshold for radiological exams performed for research purposes, that is calibrated to this background level of exposure, be identified as involving no more than minimal risk?</p>	
<p>12. Question 9a: 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?</p>	
<p>13. Question 9b: Should the list be revised once a year, every two years, or less frequently?</p>	
<p>14. 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>15. Question 11a: What are the advantages [or disadvantages] of requiring that expedited review be conducted by an IRB member?</p>	
<p>16. Question 11b: 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?</p>	
<p>17. Question 11c: If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review?</p>	
<p>18. Question 11d: If so, what would qualify as being “appropriately trained”?</p>	

<p>19. Question 11e: Would the effort to make sure that such persons are appropriately trained outweigh the benefits from making this change?</p>	
<p>20. Question 12a: Are there other specific changes that could be made to reduce the burden imposed on researchers and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects?</p>	
<p>21. Question 12b: Are there specific elements that can be appropriately eliminated from [expedited] protocols or consent forms?</p>	
<p>22. Question 12c: Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated?</p>	
<p>23. Question 12d: 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?</p>	
<p>24. Question 12e: What entity or organization should develop and disseminate such standardized document formats?</p>	
<p>25. Question 13a: 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]?</p>	
<p>26. Question 13b: 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?</p>	

<p>27. Question 13c: 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?</p>	
<b>Revising the Exempt Categories</b>	
<p>28. Question 14a: 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?</p>	
<p>29. Question 14b: Would these changes be likely to discourage individuals from participating in research?</p>	
<p>30. Question 14c: Might these changes result in inappropriately reduced protections for research subjects, or diminished attention to the principles of respect for persons, beneficence, and justice?</p>	
<p>31. Question 15a: Beyond the expansions under consideration, are there other types of research studies that should qualify for the Excused category?</p>	
<p>32. Question 15b: 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>33. Question 16a: 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?</p>	

<p>34. Question 16b: If so, what entity should be responsible for determining whether a topic is or is not emotionally charged?</p>	
<p>35. Question 17a: What specific social and behavioral research study [methods] should fall within the Excused category?</p>	
<p>36. Question 17b: Under what circumstances, if any, should a study qualify for the Excused category if the study involves a form of deception?</p>	
<p>37. Question 17c: How should “deception” be defined?</p>	
<p>38. Question 18a: How should determinations regarding whether clinical results should be returned to study participants be made if the study now fits in the Excused category?</p>	
<p>39. Question 18b: 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)?</p>	
<p>40. 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?</p>	
<p>41. Question 20: The term “Excused” may not be the ideal term to describe the studies that will come within the proposed revision of the current category of exempt studies, given that these studies will be subject to some protections that are actually greater than those that currently exist. Might a term such as “Registered” better emphasize that these studies will in fact be subject to a variety of requirements designed to protect participants? We welcome suggestions for an alternative label that might be more appropriate.</p>	

<p>42. Question 21a: Is it appropriate to require institutions holding an FWA to conduct retrospective audits of a percentage of the Excused studies to make sure they qualify for inclusion in this category?</p>	<p>.</p>
<p>43. Question 21b: Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements?</p>	<p>.</p>
<p>44. Question 21c: Should some other method besides a random selection be used to determine which Excused studies would be audited?</p>	
<p>45. Question 22a: 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?</p>	
<p>46. Question 22b: Might this new audit mechanism end up producing a greater burden than the current system?</p>	
<p>47. Question 22c: Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category?</p>	
<p>48. Question 22d: By allowing researchers to make their own determinations, without prospective independent review, will protections for some subjects be inappropriately weakened?</p>	
<p>49. Question 22e: If allowing researchers to make such determinations without independent review would generally be acceptable, are there nonetheless specific categories of studies included in the proposed expansion for which this change would inappropriately weaken protections for subjects?</p>	

<p>50. Question 22f: Will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?</p>	
<p>51. Question 23a: 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) above [the secondary use of data or biospecimens collected for other purposes]?</p>	
<p>52. Question 23b: Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes?</p>	
<p>53. Question 23c: Should a request to waive informed consent trigger a requirement for IRB review?</p>	
<p>54. Question 24a: 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?</p>	
<p>55. Question 24b: 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?</p>	
<p>56. Question 24c: 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”)?</p>	
<p>57. Question 24d: Are there some such activities that should not be excluded from being subject to the Common Rule because the protections provided by that rule are appropriate and no similar protections are provided by other regulations?</p>	

<p>58. Question 24e: 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”?</p>	
<p>59. Question 25a: 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?</p>	
<p>60. Question 25b: If so, what are those fields, and how should those methods of inquiry be identified?</p>	
<p>61. Question 25c: Should the Common Rule be revised to explicitly state that those activities are not subject to its requirements?</p>	
<p>62. Question 26a: 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?</p>	

<p>63. Question 26b: 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?</p>	
<p>64. Question 26c: Is there a need to update or otherwise revise the “OPRR Guidance on 45 CFR 46.101(b)(5)”?</p>	
<p>65. Question 27a: Do IRBs correctly interpret this provision 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?</p>	
<p>66. Question 27b: If that is not how the provision is currently understood, is there a need to clarify its meaning?</p>	
<p>67. Question 28a: Should the Common Rule include a requirement that every institution must provide an appropriate appeal mechanism [for determinations]?</p>	
<p>68. Question 28b: If so, what should be considered acceptable appeal mechanisms?</p>	
<p>69. Question 28c: 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?</p>	
<p>70. 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?</p>	

**Streamlining IRB Review of Multi-Site Studies**

71. 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?	
72. Question 31a: How does local IRB review of research add to the protection of human subjects in multi-site research studies?	
73. Question 31b: How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects?	
74. Question 31c: 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?	
75. Question 32a: To what extent are concerns about regulatory liability contributing to institutions' decisions to rely [only] on local IRB review for multi-site research?	
76. Question 32b: Would the changes we are considering adequately address these concerns?	
77. Question 33: How significant are the inefficiencies created by local IRB review of multi-site studies?	
78. Question 34a: If there were only one IRB of record for multi-site studies, how should the IRB of record be selected?	
79. Question 34b: How could "IRB shopping"-intentionally selecting an IRB that the investigators think is likely to approve the study without proper scrutiny- be prevented?	

### **Improving Informed Consent**

80. Question 35a: What factors contribute to the excessive length and complexity of informed consent forms?	
81. Question 35b: How might [these factors] be addressed?	
82. Question 36a: 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?	
83. Question 36b: What modifications or deletions to the required elements [of consent] would be appropriate?	
84. Question 37: Would the contemplated modifications improve the quality of consent forms? If not, what changes would do so?	
85. 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?	
86. 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?	
87. Question 40a: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required?	
88. Question 40b: Should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?	

<b>Waiver of Informed Consent or Documentation of Informed Consent in Primary Data Collection</b>	
89. 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?	
90. Question 42a: In circumstances where the regulations would permit oral consent, what information should investigators be required to provide to prospective subjects?	
91. Question 42b: Are all of the elements of informed consent included at 45 CFR 46.116 necessary to be conveyed, or are some elements unnecessary?	
92. Question 42c: If some elements should not be required for oral consent, which ones are unnecessary?	
93. 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?]	
94. Question 44a: Are there types of research involving surveys, focus groups, or other similar procedures in which oral consent without documentation should not be permitted?	
95. Question 44b: What principles or criteria distinguish these cases?	
<b>Consent Protections Related to Reuse or Additional Analysis of Existing Data and Biospecimens</b>	
96. Question 45a: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent?	
97. Question 45b: Should consent requirements [for future research use] vary based on the likelihood of identifying a research subject?	

<p>98. Question 45c: 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?</p>	
<p>99. Question 46a: Under what circumstances should unanticipated future analysis of data that were collected for a different research purpose be permitted without consent?</p>	
<p>100. Question 46b: Should consent requirements [for unanticipated future research use] vary based on the likelihood of identifying a research subject?</p>	
<p>101. 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>102. 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>103. Question 49a: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data?</p>	
<p>104. Question 49b: Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?</p>	

<p>105. Question 50a: 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?</p>	
<p>106. Question 50b: 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)?</p>	
<p>107. Question 50c: Should individuals have the option of identifying their own categories of research that they would either permit or disallow?</p>	
<p>108. Question 51a: 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?</p>	
<p>109. Question 51b: Should there be different rules for that setting, and if so, what should they be?</p>	
<p>110. Question 51c: Should [the rules] be based on the relevant requirements in the countries where the biospecimens were collected?</p>	
<p>111. Question 52a: Should the new consent rules be applied only prospectively, [or], should previously existing biospecimens and data sets be “grandfathered” under the prior regulatory requirements?</p>	
<p>112. Question 52b: What are the operational issues with doing so?</p>	

<p>113. Question 53a: 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?</p>	
<p>114. Question 53b: If so, what threshold number should constitute impracticability?</p>	
<p>115. Question 53c: Is the number of potential human subjects the only measure of impracticability?</p>	
<p><b>Strengthening Data Protections to Minimize Information Risks</b></p>	
<p>116. Question 54a: 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?</p>	
<p>117. Question 54b: 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?</p>	
<p>118. Question 54c: If [not], what standards would be more appropriate?</p>	
<p>119. Question 55a: What mechanism should be used to regularly evaluate and to recommend updates to what is considered de-identified information?</p>	
<p>120. Question 55b: 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?</p>	

121. Question 56a: How should Federal regulations manage the risks associated with the possibility of identification of [DNA from] biospecimens?	
122. Question 56b: Should a human biospecimen be considered identifiable in and of itself?	
123. Question 56c: What are the advantages and disadvantages of considering all future research with biospecimens to be research with identifiable information?	
124. 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)?	
<b>Standards for data security and information protection</b>	
125. Question 58a: 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?	
126. Question 58b: 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?	
127. Question 58c: How should the new standards be enforced?	
128. Question 59a: 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?	
129. Question 59b: Are [the HIPAA] standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research?	

<p>130. Question 59c: Might a better system employ different standards for different types of research?</p>	
<p>131. 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>132. Question 61a: Are there additional data security and information protection standards that should be considered?</p>	
<p>133. Question 61b: Should such mandatory standards be modeled on those used by the Federal government [e.g., NIST]?</p>	
<p>134. 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>135. 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>136. 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 researcher from disclosing the de-identified data to, for example, third parties who might not be subject to these rules?</p>	

<p>137. 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>138. Question 66a: What entity or entities at an institution conducting research should be given the oversight authority to conduct the audits, and to make sure that these standards with regard to data security are being complied with?</p>	
<p>139. Question 66b: Should an institution have flexibility to determine which entity or entities will have this oversight responsibility for their institution?</p>	
<b>Data Collection to Enhance System Oversight</b>	
<p>140. 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?</p>	
<p>141. Question 68a: 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?</p>	
<p>142. Question 68b: 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?</p>	
<p>143. Question 68c: To what types of research should such a requirement apply (e.g., interventional studies only; all types of human subjects research, including behavioral and social science research)?</p>	

<p>144. Question 68d: Are there other strategies and methods that should be implemented for gathering information on the effectiveness of the human subject protection system?</p>	
<p>145. 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?</p>	
<p>146. Question 70: Is the access to information on individual studies provided by [the publicly accessible database ClinicalTrials.gov.] sufficiently comprehensive and timely for the purposes of informing the public about the overall safety of all research with human subjects?</p>	
<p><b>Extension of Federal Regulations</b></p>	
<p>147. 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?</p>	
<p><b>Clarifying and Harmonizing Regulatory Requirements and Agency Guidance</b></p>	
<p>148. 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]</p>	
<p>149. Question 73a: 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?</p>	
<p>150. Question 73b: What are the most important differences influencing the conduct of research [domestically and internationally]?</p>	

<p>151. Question 74: If all Common Rule agencies issued one set of guidance [documents], would research be facilitated both domestically and internationally?</p>	
<p>“General” Question</p>	
<p>152. 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.</p>	