

<p>This document summarizes changes in <i>Policy 204 Levels of IRB Review and Criteria for IRB Approval of Research</i> (referred to as Policy 204 in this document) that NIH investigators should be aware of, from the SOP(s) mentioned below.</p> <p>The policy describes the levels of ethical review and criteria for approval of human subjects research by the National Institutes of Health (NIH) Institutional Review Board (IRB) (i.e., review by the convened IRB, expedited procedures, limited IRB procedures, or exempt procedures) and describes investigator responsibilities when submitting research to, or interacting with, the NIH IRB.</p> <p>NIH investigators are responsible for reviewing Policy 204 and complying with the requirements of the policy.</p> <p><b>Note:</b> Text from the policy and other policy titles are italicized.</p>	
<p><b>Policy 204 Levels of IRB Review and Criteria for IRB Approval of Research:</b></p>	<p><b>SOP Superseded by Policies:</b></p>
<p><b>Policy 204 fully supersedes</b></p>	<p><b>SOP 5 NIH Research Activities with Human Data and Specimens</b> When inactivated, this SOP will be archived in the Policy Archive.</p>
<p><b>Policy 204 fully supersedes</b></p>	<p><b>SOP 6 Determinations, Including Exemptions Made by the Office of Human Subjects Research Protections (OHSRP)</b> When inactivated, this SOP will be archived in the Policy Archive.</p>
<p><b>Policy 204 fully supersedes</b></p>	<p><b>SOP 7 Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)</b> When inactivated, this SOP will be archived in the Policy Archive.</p>
<p><b>Policy 204 fully supersedes</b></p>	<p><b>SOP 7A Requirements for Expedited Review of Research by NIH Institutional Review Boards</b> When inactivated, this SOP will be archived in the Policy Archive.</p>
<p><b>Applicability of Policy 204 - This policy applies to:</b></p> <ul style="list-style-type: none"> <li>• NIH investigators when the NIH IRB is the reviewing IRB or when the human subjects research may be exempt from IRB review.</li> <li>• Non-NIH investigators when the NIH is the reviewing IRB.</li> <li>• The NIH IRB, including those experienced IRB members designated to conduct expedited review and limited IRB review.</li> </ul>	
<p>Policy 204 applies to the levels of ethical review by the NIH Institutional Review Board (IRB) or IRB Office (IRBO). These terms will be helpful to understand when reviewing this table:</p> <p><b>Exempt research</b> – research exempt from compliance with the full requirements of 45 CFR 46. Exempt research must be minimal risk and fall within one of the allowable exempt categories in 45 CFR 46.101 of the pre-2018 Common Rule or <a href="#">45 CFR 46.104 of the 2018 Common Rule, as applicable</a>.</p> <p><b>Limited IRB review</b> – review by limited IRB procedures to ensure exempt research meets the requirements under certain categories described in <a href="#">45 CFR 46.104 of the 2018 Common Rule</a>.</p> <p><b>Expedited research</b> – some minimal risk research may be reviewed by expedited procedures, such as minor changes to previously approved research; or research that presents no more than minimal risk to subjects and involves only procedures which are listed in one or more <a href="#">allowable categories</a></p>	

<p><a href="#">authorized by the Secretary of HHS</a>. Expedited reviews are carried out by the IRB chairperson or designee who is an experienced IRB member.</p> <p><b>Convened IRB review</b> – a review conducted by the full IRB. Generally, the convened IRB reviews which is more than minimal risk and do not fall within one of the allowable expedited categories, or that do not meet the criteria for exemption from IRB review.</p>	
Policy Requirement	SOP Requirement
<p><b>Section C.1. – Application of the DHHS Common Rule (45 CFR 46)</b></p> <p><i>a. Research initially approved by the IRB, or for which IRB review was waived or determined to be exempt prior to January 21, 2019, is subject to the requirements of the <u>pre-2018 Common Rule</u>;</i></p> <p><i>b. Research initially approved by the IRB, or for which IRB review was waived or determined to be exempt on or after January 21, 2019, is subject to the requirements of the <u>2018 Common Rule</u>;</i></p> <p><i>c. Research subject to the pre-2018 Common Rule may only be transitioned to the 2018 Common Rule if it is determined and documented that transition will occur and that it satisfies the 2018 Common Rule requirements (e.g., as related to exempt research).</i></p>	<p>Not applicable (NA).</p> <p>A revised version of the Common Rule (45 CFR 46) regulations was published in 2018, effective January 21, 2019. The revised Common Rule is described throughout this table as the “2018 Common Rule.”</p> <p>The 2018 Common Rule (45 CFR 46) was not in effect at the time of publication, and was not relevant to SOPs 5, 6, 7, or 7A.</p>
<p><b>Section D.9. Human Subject (2018 Common Rule) – A living individual about whom an investigator (whether professional or student) conducting research:</b></p> <p><i>a. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or</i></p> <p><i>b. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.</i></p> <p>The definition of human subject is revised in the 2018 Common Rule. The definition now references biospecimens and to using, studying, or analyzing information or biospecimens.</p> <p>The new definition of human subject applies only to research approved under the 2018 Common Rule (effective January 21, 2019).</p>	<p>Pre-2018 Common Rule definition of Human Subject:</p> <p><b>SOP 5, Section 5.3.D. - Human Subject – A living individual about whom an investigator (whether professional or student) conducting research obtains:</b></p> <p><i>(1) Data through intervention or interaction with the individual, or</i></p> <p><i>(2) Identifiable private information.</i></p> <p>The 2018 Common Rule (45 CFR 46) was not in effect when the SOPs were published. Only the pre-2018 Common Rule definition of Human Subject applied at that time.</p> <p>The pre-2018 Common Rule definition applies only to research that approved prior to the implementation of the 2018 Common Rule (effective January 21, 2019).</p>

<p><b>Section C.2.a.</b> – <i>All review of exempt and non-exempt human subjects research will be conducted in accordance with federal regulations and policies.</i> AND <b>Section E.1.a.</b> – <i>NIH Principal Investigators (PIs) are <b>responsible for being knowledgeable as to whether their research activities meet the definition of human subjects research</b> and whether the research is eligible for an exempt determination or requires IRB review.</i></p> <p>Policy 204 clarifies that NIH PIs are responsible for being knowledgeable about whether their research activities constitute human subjects research, and whether an exempt determination or IRB review are required. See Policy 204 for additional information.</p>	<p><b>SOPs 5, 6, 7, and 7a</b> only specified procedures for complying with the pre-2018 Common Rule. Policy 204 combines exempt and non-exempt human subjects research into a single policy. Policy 204 applies to exempt research approved under the pre-2018 and the 2018 version of the Common Rule.</p> <p><b>SOPs 5, 6, 7, and 7A</b> discussed the types of research requiring IRB review or an Exempt determination but did not address the PI’s responsibility for knowing when their research activities met the definition of human subjects research.</p>
<p><b>Section C.5.a.i.</b> — <i>Only designated exempt reviewers may make determinations that human subjects research is exempt under 45 CFR 46.</i> AND <b>Section C.5.a.ii.</b> — <i>Investigators do not have the authority to determinate that human subjects research is exempt.</i> AND <b>Section C.6.a.</b> – <i>In order to be exempt, certain human subjects research subject to the 2018 Common Rule may require limited IRB review. Limited IRB review may be conducted by a designated limited IRB reviewer using expedited procedures.</i></p> <p>There is no change the authority to conduct exempt reviews, though Policy 204 is more explicit.</p> <p>Only designated exempt reviewers have the authority to conduct exempt reviews – including those exempt reviews which also require limited IRB review.</p> <p>Refer to Policy 204 for additional information.</p>	<p><b>SOP 6, section 6.5.</b> – <i>OHSRP has sole NIH authority to make the determination that a research activity is exempt from the DHHS requirement for IRB review under 45 CFR 46.101(b).</i></p>
<p><b>Section E.1.b.</b> – <i>NIH PIs are responsible for submitting all exempt and non-exempt human subjects research for review</i></p>	<p><b>SOP 8</b> required PIs complete and submit applications electronically.</p>

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<p>AND</p> <p><b>Section E.1.c.</b> – <i>NIH PIs are responsible for assuring all submissions are entered into the NIH electronic IRB system for routing to the NIH IRB, whether evaluated by the convened IRB, expedited reviewer, exempt reviewer, or by the limited IRB. (See Policy 205 Requirements for IRB Submissions.)</i></p> <p>The policy is more explicit about the NIH PI’s responsibility, and what type applications must be submitted <i>into the electronic IRB system</i>. Previously, non-exempt activities were submitted via multiple IRB systems which are now combined into one electronic IRB system. Further, exempt activities were submitted via a separate electronic system.</p>	
<p><b>Section C.2.b.</b> – <i>NIH investigators may not commence research activities until all required approvals have been obtained (e.g., institutional approvals, as applicable, and approvals from IRB, and ancillary committees).</i></p> <p>AND</p> <p><b>E.1.f.</b> – <i>NIH PIs must ensure that research is not initiated until all required approvals have been obtained (e.g., institutional approvals, such as IC and ancillary reviews, approvals from the IRB, and exempt determinations).</i></p> <p>These requirements are unchanged.</p>	<p><b>SOP 5, Section 5.4.B.2.</b> – “... research cannot begin until the PI has obtained a formal determination from OHSRP that the activity is excluded from IRB review.”</p> <p><b>SOP 5, Section 5.8.</b> – <i>An NIH researcher does not have the authority to make his or her own exemption determination and must obtain OHSRP’s approval prior to beginning any research activity.</i></p> <p><b>SOP 6, Section 6.5.</b> contained similar language.</p>
<p><b>Section C.2.c.</b> – <i>The convened IRB or expedited reviewer, limited IRB reviewer, or exempt reviewer will review the submission materials in order to determine that the regulatory and policy requirements for approval of research are met. (See Policy 205 Requirements for IRB Submissions.)</i></p> <p>AND</p> <p><b>Section C.2.d.</b> – <i>Non-exempt human subjects research may be approved by the NIH IRB only when all required regulatory and policy criteria are met, (e.g., 45 CFR 46.109 and 46.111 of the pre-2018 Common Rule or the 2018 Common Rule, and, when applicable, 21 CFR 56.111).</i></p> <p>These requirements are unchanged, except that this policy adds specificity for clarity.</p>	<p><u>Convened IRB</u>: SOP 7A, Section 7A.6. addressed requirements that regulatory criterion be met.</p> <p><u>Expedited Reviews</u>: SOP 7, Section 7.6.1.B. required the IRB to ensure all regulatory and NIH policy requirements were addressed.</p> <p><u>Limited IRB Review</u>: The 2018 Common Rule was not in effect at the time of publication.</p> <p><u>Exempt reviews</u>: SOP 5, SOP 6, and SOP 6 Appendix 2 addressed regulatory and policy requirements under the Common Rule.</p>

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<p><b>Section C.2.e.</b> – <i>The expedited reviewer, the limited IRB reviewer, or the exempt reviewer, may refer any protocol for review by the convened IRB.</i></p> <p>The reviewers’ authority to forward submissions to the convened IRB is unchanged.</p>	<p><b>SOP 7A, Section 7A5.C.2.</b> – Authorized expedited reviewers to forwarded proposed research to the convened IRB.</p>
<p><b>Section C.7.a.</b> – <i>When reviewing research that includes federally defined vulnerable populations (i.e., prisoners, pregnant women, fetuses, neonates, and/or children), the convened IRB, expedited reviewer, limited IRB reviewer, or exempt reviewer, shall make all required determinations as specified under 45 CFR 46 subparts B, C and/or D, as well as 21 CFR 50 subpart D, and will consider whether adequate provisions have been made to protect the safety, rights, and welfare of the subjects and to minimize research risks unique to the population.</i></p> <p>AND</p> <p><b>Section C.7.b.</b> – <i>When reviewing research that includes other populations determined by NIH policy as vulnerable, such as decisionally impaired adults or NIH staff participating in research, the convened IRB or expedited reviewer shall assure that additional NIH policy requirements are met.</i> AND</p> <p><b>Section C.7.c.</b> – <i>When reviewing research that includes other populations determined by NIH policy as vulnerable, such as decisionally impaired adults or NIH staff participating in research, the convened IRB or expedited reviewer shall assure that additional NIH policy requirements are met consistent with Policy 403 Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation and Policy 404 Research Involving NIH Staff as Subjects.</i></p> <p>AND</p> <p><b>Section C.7.d.</b> – <i>Additionally, when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as economically or educationally disadvantaged persons, additional safeguards may be required by the IRB.</i></p>	<p><u>Exempt reviews:</u> <b>SOP 6, section 6.7.</b> described considerations for special populations under 45 CFR 46.</p> <p><u>Expedited Reviews:</u> <b>SOP 7A, Section 7A.2.</b> – <i>Like review by the convened IRB, expedited review must fulfill all the requirements of review found at 45 CFR 46.111 and subparts B, C, and D, if applicable.</i></p> <p><u>Convened IRB:</u> <b>SOP 7, Appendix A, section 5</b> referenced obligations to include additional safeguards for vulnerable subjects (e.g. pregnant women, prisoners, etc.)</p>

<p><i>There is no change in the IRB’s obligation to include additional safeguards as appropriate.</i></p> <p>Policy 402 references specific policies which may be helpful in designing studies involving vulnerable populations.</p>	
<p><b>Section C.2.f.</b> – <i>When the NIH IRB is the reviewing IRB, it will notify the NIH PI in writing of its decision – including conveying the approval period. Expedited, limited IRB, and exempt reviewers will also convey their decisions to the NIH PI in writing.</i></p> <p>These IRB actions are unchanged. See Policy 204 for additional information.</p>	<p><b>SOP 6 and SOP 7</b> stated that the IRB’s decision was to be conveyed to the investigator in writing.</p> <p>For example, PIs received an IRB approval letter or stipulations etc.</p>
<p><b>Section E.1.d.</b> – <i>For multi-site research when the NIH IRB is the Reviewing IRB, the NIH PI is responsible for communicating IRB determinations and approvals to the PI/Lead Site Investigator of the ceding institution consistent with Policy 105 IRB Reliance.</i></p> <p>There is no change in NIH PI responsibility regarding communicating IRB determinations and approvals when the NIH IRB is the reviewing IRB.</p>	<p>NA</p> <p>Previously these SOPs did not address requirements for multi-site research.</p>
<p><b>Section E.1.e.</b> – <i>When the NIH is relying on an external Reviewing IRB, the NIH PI must first submit the protocol for review and confirmation of compliance with institutional requirements in the NIH electronic IRB system, prior to submitting to the external Reviewing IRB. (See Policy 105 IRB Reliance.)</i></p> <p><i>1. In addition, the PI must also follow the submission requirements of the external Reviewing IRB. (See Policy 105 IRB Reliance.)</i></p> <p>There is no change in NIH PI responsibility to first submit the protocol in accordance with Policy 105 IRB Reliance.</p>	<p>NA</p> <p>Previously these SOPs did not address requirements for use of an external Reviewing IRB.</p>
<p><b>Section C.2.h.</b> – <i>For non-exempt human subjects research, PIs will submit protocols for CR (Continuing Review) at an interval established by the IRB.</i></p> <p>For studies requiring CR there is no change in the process of determining the continuing review interval.</p>	<p><b>SOP 7, Section 7.10.1.</b> – <i>At the time of initial and continuing review, the IRB will make a determination regarding the frequency of review of the research studies. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but not less than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required.</i></p>

<p><b>Section C.2.i.</b> – “... the convened IRB will conduct CR at an interval established by the IRB (not less than once per year). The IRB shall determine which projects require review more often than annually.”</p> <p><b>Section C.2.i.III.</b> – All research subject to Food and Drug Administration (FDA) regulation will undergo CR at intervals of not less than once per year, regardless of whether the research is subject to the pre-2018 or 2018 Common Rule.</p> <p>Some minimal risk protocols do not require continuing review under the 2018 Common Rule, but all other requirements, including submitting amendments to previously approved research, and submitting reportable events, still apply.</p> <p>Because the FDA has not adopted the Common Rule, FDA-regulated protocols generally require continuing review. This may change in the future.</p> <p>Refer to Policy 204 for a more information, including a detailed description of approval periods and anniversary dates in section C.2.g.</p>	<p><b>SOP 7, Section 7.10.1.</b> – At the time of initial and continuing review, the IRB will make a determination regarding the frequency of review of the research studies. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but not less than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required.</p> <p>For studies under the 2018 Common Rule, or transitioned to it, some minimal risk protocols do not require continuing review. However, all other requirements still apply.</p> <p>FDA-regulated studies <i>continue to require CR</i> at least once per year.</p>
<p><b>Section E.1.g.</b> – For non-exempt human subjects research, when CR is required, it is the PI’s responsibility to obtain CR prior to expiration to avoid lapse in IRB approval. Failure to allow sufficient time for IRB review may result in a lapse in approval.</p> <p>If CR is not obtained prior to the expiration date, the study will have a lapse in approval, and all study activity <u>must cease</u> - even if no notice of the lapse of approval is received.</p> <p><b>Section E.1.g.I.ii.</b> – However, when it is in the best interests of already enrolled subjects to continue in the research during the period of lapse in IRB approval, the IRB has the authority to, or the PI may request from the IRB permission to, continue the participation of already enrolled subjects during this period.</p> <p>AND</p> <p><b>Section C.2.i.VI</b> – If a study has lapsed due to the PI’s failure to obtain timely CR, the IRB may elect not to review other active or new</p>	<p><b>SOP 9</b> addressed the continuing review process and related PI responsibilities.</p>

<p><i>studies submitted by the PI until the CR is resolved.</i></p> <p>For studies that expire, there is no change in how CR is conducted. The policy is more explicit about the NIH PI’s responsibilities relating to CR. Refer to Policy 204 for additional information.</p>	
<p><b>Section C.2.V.i.</b> – <i>For protocols in which CR is not required, all other requirements still apply after initial approval, e.g. submitting amendments to previously approved research, submitting reportable events to the IRB, and obtaining other ancillary reviews, as applicable. (See Policy 205 Requirements for IRB Submissions, Policy 106 Ancillary Reviews and <a href="#">Policy 801 Reporting Research Events.</a>)</i></p> <p><b>Note the following exception at Section C.2.V.i.a.</b> - <i>Except that research that was determined to be category 8(b) or 9 (of the HHS Secretary <a href="#">list of categories</a> that may be expedited (v.1998)) , and therefore eligible for expedited review, will be required to submit a continuing review at intervals not less than once per year, consistent with <a href="#">OHRP Guidance – 2018 Requirements FAQs - IRB Review.</a></i></p> <p>All requirements relating to ongoing research continue to apply to all active/open studies. There is no change in this requirement. <u>However, PIs should be aware that these requirements apply regardless of whether CR is required.</u></p> <p>Note that Continuing Review by expedited procedures <u>will continue</u> for the following expedited review Categories:</p> <ul style="list-style-type: none"> <li>• 8(b)- for research previously approved by the convened Board, but no subjects have enrolled, and no additional risks have been identified), and</li> <li>• 9 - for research, <i>not</i> conducted under an IND or IDE, where expedited categories two (2) through eight (8) do not apply, but the IRB has determined and documented <i>at a convened meeting</i> that the research</li> </ul>	<p>NA</p> <p>The 2018 Common Rule (45 CFR 46) was not in effect at the time of publication, and was not relevant to SOPs 5, 6, 7, or 7A. However, all other requirements (such as submitting amendments, and submitting reportable events) applied throughout the course of all active studies.</p>

<p>involves no greater than minimal risk and no additional risks have been identified.</p>	
<p><b>Section C.2.j.</b> – <i>The PI will submit changes to previously approved research (referred to as “amendments”) for review and approval by the IRB, before these changes are implemented, except when necessary to eliminate apparent immediate hazards to a subject. (45 CFR 46.108)</i></p> <p>AND</p> <p><b>E.1.h.</b>— <i>NIH PIs must ensure that all changes (amendments) to previously approved research are submitted for IRB review and approval prior to instituting any change, unless that change is required to prevent an immediate risk of harm to subjects, (see C.2.i. above).</i></p> <p><i>I. When the PI has taken an action to eliminate an immediate hazard to a subject, the PI will notify the IRB within <u>7 days</u> (emphasis added) of such a change. Such an action is considered a “major deviation” for the purposes of reporting. (See <a href="#">Policy 801 Reporting Research Events.</a>)</i></p> <p><i>II. For research that has previously been determined to be exempt, PI’s must submit amendments for review and approval prior to instituting any changes.</i></p> <p>Policy 204 describes these requirements as PI responsibilities for clarity.</p>	<p>Obligations have not changed. SOP 10 and SOP 16 described these obligations.</p>
<p><b>Section C.2.k.</b> – <i>For any non-exempt human subjects research suspended by the IRB, the PI will comply with IRB requirements.</i></p> <p>AND</p> <p><b>Section E.1.i.</b> – <i>When the research has been suspended, if subjects are enrolled on the research, the PI must provide a plan to the IRB for its consideration that takes into account the continued rights, safety and welfare of enrolled subjects during the period of suspension</i></p> <p><i>I. The NIH investigator must obtain IRB approval before the research may be restarted.</i></p>	<p><b>SOP 11</b> described suspensions and IRB approval of the plan to resume the research.</p>

<p>These obligations have not changed. As before, PIs must obtain IRB approval prior to restarting the research.</p>	
<p><b>Section E.1.j.</b> – For non-exempt human subjects research, the NIH PI will close the research when all subjects have completed research interactions and interventions and primary data analysis is complete. This includes analysis of identifiable private information or identifiable biospecimens, consistent with the analyses described in the protocol (see C.2.k. below). AND <b>Section E.1.j.</b> – For non-exempt human subjects research, once all activities involving human subjects have been completed, and analysis of identifiable private information or identifiable biospecimens is complete, consistent with the analyses described in the protocol, the PI will close the research. I. Once the research is closed, all research activities will cease. II. Once the study is closed, any analyses using the identifiable private information or identifiable biospecimens from the study, will require prospective IRB review and approval.</p> <p>Obligations for study closure have not changed. Policy 204 is more explicit.</p>	<p><b>SOP 11A.2.</b> – Principal Investigators (PIs) are responsible for notifying the IRB whenever an IRB-approved study will be closed, regardless of the reason for closure. Data collection and analysis for the study are not permissible after study closure.</p>
<p><b>Section E.1.j. II.</b> – When the PI, Sponsor, or the IC prematurely closes the research, the PI must notify the IRB that the study will be closed prematurely. i. If research prematurely closes or the IRB terminates its approval and subjects are enrolled, the PI must provide the IRB for its consideration: • A plan for orderly closure that takes into account the rights, safety and welfare of enrolled subjects; and • The proposed correspondence to subjects regarding premature closure of the study, if not already approved by the IRB as part of an amendment.</p> <p>The PI responsibility to notify the IRB and develop a plan for orderly closure has not changed.</p>	<p><b>SOP 11A.5.F.</b> – If premature closure of a study is anticipated (e.g., the study is to be closed earlier than anticipated based on recommendation of the DSMB), the IRB should work with the PI to develop a plan to ensure that the rights and welfare of currently enrolled subjects are protected.</p>

<p><b>Section E.1.j. II.</b> – <i>The PI is responsible for maintaining study records after study closure consistent with Policy 300 Investigator Responsibilities.</i></p> <p>See Policy 204 for more detail.</p>	NA
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