

Questions about NCATS Prior Approval Process for Human Subjects and Vertebrate Animals

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POLICY QUESTIONS:

Why does NCATS have the prior approval process for pilots and KL2 projects that involve human subjects research?

This is an NIH policy as described in NOT-OD-15-128. **July 2015:** Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval: Updated Notice: [NOT-OD-15-128](#)

What value does the NCATS prior approval process provide over that of the institution's IRB and scientific review process?

IRB and scientific review serve the institution.

NCATS' assessments are done on behalf of the agency as required by the Common Rule at 46.120:

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the Federal department or agency through such officers and employees of the Federal department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal or enter into negotiations to develop an approvable one.

These assessments would be conducted whether or not a single IRB is used.

The primary purpose of the review is to comply with NIH policy and Human Subjects research regulations. The review of the materials provided to NCATS is limited to assessing the safety of the study. A standard process is followed by the NCATS Clinical Studies Group (CSG), a group of 7-10 members of MDs, clinical trial specialists and subject matter experts in regulatory and project management. Materials are reviewed by all CSG members and a consensus is reached. Any projects that are determined not to be safe are vetted by leadership in the NCATS Division of Clinical Innovation.

Common Issues:

1) Category 2:

- Submission of a Category 2 study (minimal risk or exempt) that is assessed not to be a Category 2 study by the CSG members.
 - The study is an NIH-defined clinical trial and thus is a Category 1 study (greater than minimal risk, clinical trial and/or contains a foreign component)
 - The IRB determination letter does not provide a statement of minimal risk.
 - Information provided or later requested is not consistent with a determination of minimal risk.

2) Category 1:

- Study is greater than minimal risk but this is not adequately represented in the Informed Consent.
- Submission proposes a therapeutic trial for which the drug (most commonly) may be approved but “manner of use” is not, (i.e., new indication, population, route of administration, formulation, etc., which impacts safety). An IND or IND waiver is needed from FDA and is missing.
- COI: Study is greater than minimal risk but all safety assessments are done by the PI or other member of the study team. An independent medical monitor is recommended for inclusion in the Data Safety Monitoring Plan (DSMP).
- There are alternatives to the proposed treatment, Standard of Care or other aspect of study that have not been considered or included in the protocol or informed consent.

COMMUNICATION QUESTIONS:

How and when does NCATS notify institutions that Category 2 research has been approved?

Category 2 does not receive official notification from the NCATS Grants Management Specialist as this would constitute official communication and this is not required.

Recall:

A Category 2 can start when all materials are submitted to the eRA HHS system and the documents are being reviewed by NCATS staff BUT if materials are not complete, are not clear, and/or the safety of the Human Subjects appears to be compromised in the study, the study may have to be paused while we are acquiring additional materials. NCATS will communicate this to you through your AOR. Failure to submit all the required documentation prior to initiating the pilot project study will result in non-compliance enforcement actions.

Why doesn't the eRA Human Subjects System automatically email NCATS when the study and documents have been entered?

There is an automatic email from eRA alerting NCATS when a study is submitted or updated in HSS. NCATS requires the following additional emails to be sent to assist us with conducting efficient review, processing and tracking of NCATS processes.

Category 1: deemed by the IRB to be Greater than Minimal Risk, meet the Definition of a Clinical Trial and/or include a Foreign Component:

- NCATSPriorApprovalRequest@mail.nih.gov
- This is received by NCATS Grants Management Staff that are tracking and processing these packages.

Category 2: deemed by the recipient institution IRB to be minimal risk or exempt studies and are not NIH-defined Clinical Trials:

- [NCATS CTSA Pilot HS@mail.nih.gov](mailto:NCATS_CTSA_Pilot_HS@mail.nih.gov)
- This is received by NCATS Staff that are tracking and processing these packages.

If NCATS needs additional information from a Category 2 study, does the research need to stop until NCATS reviews and accepts the responses?

A Category 2 can start when all materials are submitted to the eRA HHS system and the documents are being reviewed by NCATS staff BUT if materials are not complete, are not clear, and/or the safety of the Human Subjects appears to be compromised in the study, the study may have to be paused while we are acquiring additional materials. NCATS will communicate this to you through your AOR. Failure to submit all the required documentation prior to initiating the pilot project study will result in non-compliance enforcement actions.

Will NCATS tell us if the Category 2 study needs to stop while they review responses to their questions?

Yes, NCATS will send an email to your AOR if we think it needs to stop while we review materials.

If NCATS does not communicate that the study needs to be paused, does that mean the study is ok to continue?

For Category 2 studies, the study can start (at risk by the institution) and will not receive official notification that the pilot project is approved from NCATS.

Can emails be sent directly from the hub personnel instead of the institute's AOR?

For Category 1 studies requiring prior approval and Category 2 studies requiring clarification NCATS is required to use official channels of communication.

PROCESS QUESTIONS:

What is the timeline for processing from NCATS for Category 1 studies?

NCATS has developed internal processes using a risk stratification to meet the 30-day window for review and approval. If the study submitted is missing documentation or requires revisions/clarifications before an approval is provided, the 30-day window resets when materials have been received by NCATS.

What constitutes the start of a study: is it the actual recruitment/work with human subjects? Does prework/preparing for the study count as starting the study?

A study starts when the first participant is enrolled.

Must the study begin on the same date NCATS approves it? Or can it start any date AFTER the NCATS approval?

The study can start after the NCATS approval is received.

However, recall:

Process for new pilot projects and KL2 projects involving humans subjects research:

Category 1: deemed by the IRB to be Greater than Minimal Risk, meet the Definition of a Clinical Trial and/or include a Foreign Component:

- The study may not start until receipt of NCATS' Grants Management Specialist official notification that the pilot project is approved.

Category 2: deemed by the recipient institution IRB to be minimal risk or exempt studies and are not NIH-defined Clinical Trials:

- Studies may not begin until all required documentation has been submitted into the eRA HHS system. Failure to submit the required documentation prior to initiating the pilot project study will result in non-compliance enforcement actions.
- Study can start (at risk by the institution) and will not receive official notification that the pilot project is approved from NCATS.

Can a pilot project cross over budget periods? Regardless of the start date, is the funding period is unchanged?

The pilot project activity may cross over budget periods. However, per NIH Grants Policy and the Notice of Award, the institution CANNOT carry over funds from one budget period to another without NIH prior approval. Repeated prior approval requests to transfer funds from one budget period to another for the same/similar program costs will be denied. Please work with your Office of Sponsored Programs to establish your pilot program in a manner that complies with NIH Grants Policy and avoids setting up a need for continual carryover requests for pilot program funds. While the period can remain unchanged, the impact of the start date on the pilot project crossing budget periods must be factored in.

If a project has an aim or component that does not involve human subjects, can that aspect be initiated while awaiting prior approval for the human subjects aim or component?

There is nothing prohibiting funds from being expended on the portion of the project that does not contain human subjects or vertebrate animals research while the project is undergoing prior approval. This must be done in accordance with your institutional cost principles and the responsibility to ensure no funds are expended for human subjects work rests with the recipient institution.

What is the process for diversity supplements?

Applications for diversity supplements should submit the required documentation in their application as per the instructions: <https://ncats.nih.gov/ctsa/funding/pa-2016-guidance>

If applicable, attach PDF documents in the "Other Attachments" field indicating that the proposed research experience was approved by the Institutional Animal Care and Use Committee (IACUC) or human subjects Institutional Review Board (IRB) at the grantee institution. Name the documents "IACUC Documentation.pdf" and/or "IRB Documentation.pdf". Adherence to the NIH policy for including women and minorities in clinical studies must also be ensured, if additional human subjects' involvement is planned for the supplement.

If they did not have the materials in the original application and later propose to conduct research not covered by their mentor's IRB or IACUC approval then yes, the AOR would need to submit information as described for the NCATS Prior Approval Process for New Projects with Human Subjects Research.

Is prior approval for TL1 human subjects studies also required? If so, what is the process?

Yes. Generally, TL1-supported trainees will work on projects supported by other research grants rather than being funded through the TL1 award. If a trainee supported on the TL1 embarks on an independent research project funded through the CTSA Program hub that includes human subjects and/or vertebrate animals and is independent of the mentor's research projects, prior approval may be required. In this instance, it is the grantee institution's

responsibility to confirm with the assigned Program Official and Grants Management Specialist whether prior approval is required.

Reference: <https://ncats.nih.gov/ctsa/funding/prior-approval-paga>

QUESTIONS ABOUT THE QA/QC GROUP:

Do hubs need a minimum amount of time left on current award to qualify for a QA/QC supplement?

Per the NOSI ([NOT-TR-20-014](#)), eligible hubs need to either have 18 months remaining on the CTSA award or to have received new CTSA funding in FY20 and have subsequent years. Additionally, there is a requirement that the QA/QC personnel dedicate 9CM effort to the grant, so they would need to have at least 9CM remaining on the current budget period in addition to the other previously mentioned eligibility requirements.

Can a hub have a representative on the QA/QC group if you don't qualify to apply for the administrative supplement?

Yes! If interested in joining the QA/QC Group please reach out to Monica L. Carter-Donerson (monica.carter@nih.gov) to receive registration information for the meetings, be added to the QA/QC Listserv, and have access to the QA/QC Group Discussion Forum. Our intent is to have QA/QC representatives at every hub.

How will we know we are getting accurate advice in the Discussion Forum? Is there a "validation" from NCATS staff on topics?

The Discussion Forum will be monitored by NCATS Staff and depending on the question, answers will be provided or the questions will be re-directed to the appropriate staff member with a notation on the forum. As a reminder, for technical and policy related questions about the prior approval process please send them to: NCATSDOPInquiry@mail.nih.gov.

MISCELLANEOUS

Who are considered Key Personnel?

Unless otherwise specified in a FOA, senior/key personnel are defined as all individuals who devote measurable effort and contribute in a substantive, meaningful way to the scientific development or execution of the project, whether or not salaries are requested. Individuals with effort listed as zero percent or "as needed" may not be considered Key Personnel. (Reference: [NIH Grants Policy Statement section 1.2, Definition of Terms, Senior/Key Personnel](#))

How do I learn more about the NIH Human Subjects System?

The following resources are available for the NIH Human Subjects System:

NIH Human Subjects System <https://era.nih.gov/help-tutorials/hss>

- Overview of Human Subjects System <https://era.nih.gov/help-tutorials/hss/overview.htm>
- Online Help https://era.nih.gov/erahelp/HSS_External/
- User Guide https://era.nih.gov/files/HSS_user_guide.pdf
- FAQs <https://era.nih.gov/faqs.htm#XXIII>
- Training <https://era.nih.gov/help-tutorials/hss/era-training-hss.htm?q=help-tutorials/era-training-hss.htm>

For assistance with the eRA HSS, please contact the eRA Service Desk

<https://grants.nih.gov/support/index.html>

Toll-free: 1-866-504-9552 (Press 1 for eRA Commons or ASSIST)

Phone: 301-402-7469 (Press 1 for eRA Commons or ASSIST)

Hours: Mon-Fri, 7 a.m. to 8 p.m. ET (closed on federal holidays)

Who can I provide comments to about the functionality of the NIH Human Subjects System?

NCATS Staff of the QA/QC Group can receive these comments and provide them to NIH Staff that oversee the NIH Human Subjects System. Please send your comments to: Monica L. Carter-Donerson (monica.carter@nih.gov)

What should I do if I have a question about whether the proposed research is considered an amendment or is a sub-study/ancillary study to an IRB-approved parent protocol?

NCATS Staff will address your question at NCATSDOPAInquiry@mail.nih.gov.