National Institute of Environmental Health Sciences

Human Subjects/Clinical Trial Research

Worker Training Program

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Discussion Topics

- Definitions
- Human Subjects Research
- Exemptions
- Clinical Trials
- Resources

Definition of Research and Generalizable Knowledge

Research: a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

Generalizable Knowledge: information is expected to expand the knowledge base of a scientific discipline or other scholarly field of study and results are applicable to a larger population beyond the site of data collection or the specific subjects studied

Definition of Secondary Analysis

Research use of information or biospecimens collected from:

- Research studies other than the one proposed, or
- Non-research purposes (e.g., clinical care, public health, education)

Definition of a Human Subject

Human subject: a living individual about whom an investigator conducting research

1. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

2. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

- Not human subjects research:
  - Data/samples from deceased individuals.
  - Samples obtained from commercial source (without identifiers)
  - Data / Samples publicly available

What is the Common Rule?

The Common Rule is a baseline standard of ethics to which U.S. government-funded biomedical and behavioral research involving human subjects research is held.

- Requirements
  - assures compliance by research institutions
  - researchers to obtain and document informed consent
  - Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.
- Provides additional protections for certain vulnerable populations:
  - pregnant women, in vitro fertilization, and fetuses
  - prisoners
  - children

What Does Identifiable Mean under the Common Rule?

Applies to Identifiable private information / Identifiable biospecimens

- Identifiable if the identity of the subject is or may readily be ascertained by the investigator or is associated with the data or biospecimens
- Identifiability impacts on whether or how secondary research* is regulated under the Common Rule

*If anyone on the research team has access to identifiers, even if the identifiers will not be provided to other members of the team, the project is human subjects research.

Continuing IRB Review

- Under Revised Common Rule, certain minimal risk studies will no longer require continuing IRB review if not required by the Common Rule or other federal, state or local law; unless specified in the Funding Opportunity Announcement:
  - Research eligible for expedited review
  - Research that has completed interventions and now includes only
    - data analysis
    - accessing follow-up clinical data from clinical care procedures

What Does Exempt Research Mean?

- Research activities that meet the conditions for an exemption category are exempt from the requirements of the Common Rule, i.e., IRB review and approval according to the regulations
- Exemption determinations should be made by IRB
- Exemption determinations ≠ IRB review and approval
- The revised Common Rule introduced concept of limited IRB review
  - Ensures privacy/confidentiality protections are in place for exemptions that involve collection or use of sensitive identifiable data for E2 and E3
  - Ensures data was obtained under Broad Consent for E7 and E8

Exemptions

- **E1** – research is conducted in an educational setting involving normal educational practices
- **E2** – research uses cognitive, diagnostic, aptitude or achievement tests; interviews; or observations of public behavior, unless subjects are identifiable and disclosure could place them at risk. If subjects are identifiable, limited IRB review is required.
- **E3** – research using benign behavioral interventions in adults. If subjects are identifiable, limited IRB review is required. NEW
- Example: Members of community receive text messages on ozone levels each day. Survey of self-reported outdoor exercise frequency/duration on orange versus green ozone days.

Inclusion Enrollment Records Required

Exemption code E4

- Research involves the collection or study of existing data, documents, records or pathological or diagnostic specimens:
  - if the identifying information is publicly available, or
  - the information is recorded so subjects cannot be identified*, or
  - the data are already protected under HIPAA**, or
  - the data were collected by the government for non-research purposes and is already protected by another federal privacy rule.

*provider is not a member of research team and identifying information will not be made available;

**identifiers may be retained; project should be reviewed by Privacy Board

Do NOT Submit Inclusion Enrollment Records

Exempt Human Subjects Research

8 Exemptions

Consider

1 Meets the definition of human subjects research.

Exempt studies involve human subjects research: research involving a living individual about whom data or biospecimens are obtained/used/studied/analyzed through interaction/intervention, or identifiable, private information is used/studied/analyzed/generated

2 Meets the criteria of one of the following exemptions:

Exemption 1: conducted in an educational setting using normal educational practices*

*Cannot include any other procedures, such as collection of clinical data or biospecimens

Exemption 2: uses educational tests, surveys, interviews, or observations of public behavior*

*Limited IRB review may be required.

Exemption 3: benign behavioral interventions in adults*

*Limited IRB review may be required.

Exemption 4: involves the collection/study of data or specimens if publicly available, or recorded such that subjects cannot be identified*

*May be identifiable in limited cases. See §46.104(d)(4)(iii) and (iv)

Exemption 5: public service program research or demonstration projects

Exemption 6: taste and food quality evaluations

Exemption 7: storage of identifiable information or biospecimens for secondary research use. *Broad consent* and *limited IRB review* are required.

Exemption 8: secondary research use of identifiable information or biospecimens. *Broad consent* and *limited IRB review* are required.

NIH Requirements:

- HS education
- Inclusion tracking for all except 4.

45 CFR 46 Requirements:

- Limited IRB review for 7 & 8, and some study designs under 2 & 3.
- Broad consent for 7 & 8.

Cannot involve **prisoners**, unless includes a broader population that happens to include prisoners.

Cannot involve **children** in:

- Exemption 2 if investigators participate in the activity being observed or includes identifiable info, OR
- Exemption 3.

For more information see the NIH OER Human Subjects Research website.
Send questions/comments to OER-HS@nih.gov.

NIH-Defined Clinical Trial

- A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
- Behavioral outcomes can include:
  - Measures of behavioral change
  - Change in knowledge about health-related topics
  - Intent to change a behavior
- Must submit to a Clinical Trial Allowed or Optional FOA or through Revision Application

Allowable Exemptions for Clinical Trials

- **E1** - research on normal educational practices in a commonly accepted educational setting.

- **E3** - research involving a benign behavioral intervention and collection of information from adults.

What this means for the WTP FOA……

- If you are just testing your product to see if it works, it is not an NIH defined clinical trial
- BUT, if you use language such as behavioral change or behavioral outcomes, testing the effect of the product or product efficacy, measuring knowledge, developing an intervention, etc. then your application may be drifting into the NIH defined clinical trial territory, and if found to be a clinical trial would be withdrawn before Peer Review.

Scenario 1

This project will develop education modules to teach safe practices for clean up of contamination following a chemical spill. Participants will receive training using a new virtual reality tool that places a person at the site of the spill and walks through tasks to clean up the spill. The purpose of the tool is to demonstrate participants can safely clean up a site.

Evaluation of the tool:

1. Is the scene realistic?
2. Is the headset comfortable?
3. Does the imagery flow smoothly?
4. How easy/difficult is the tool to use? Recommendations for improvement?
5. Is this a clinical trial? Why/Why not?

Scenario 1 Answer

- Is this a clinical trial? No.

  Why? The test only asks questions on the usability/function of the scenario and tool.

- Is this research? No.

Scenario 2

This project will develop virtual reality (VR) learning modules for clean-up of a nuclear contamination site. The evaluation will compare the VR model versus standard education. The goal is to increase knowledge, critical thinking and decision-making skills to avoid personal exposure to the contamination during the cleanup. The evaluation includes pre- and post-tests that will be used to measure, report and analyze performance to the behavioral learning objectives.

Post-test Evaluation:

- Was there a difference in knowledge gained between the two groups?
- Did the VR learning demonstrate improved decision-making skills over the standard education model?
- Is this a clinical trial?

Scenario 2

- Is this a clinical trial? Yes.
- Why? The purpose of the training is to increase critical thinking and decision-making skills to avoid exposure to the nuclear contamination. The evaluation is to determine the effectiveness of the training on the behavioral endpoints, which includes decision making skills. So, this is an NIH-defined clinical trial.

Delayed Onset

When human subjects research is anticipated within the period of the award but definite plans for involvement of human subjects cannot be described in the application or proposal (referred to as "delayed onset human subjects research"),

- Check Delayed Onset Box
- Include One Study with Study Title
- Identify if study will be a Clinical Trial or Not a Clinical Trial

Delayed Onset versus Delayed Start:

- Community-based Research Project to be conducted with University researchers: community will select and help develop project
  - Know there will be an HS study, but it can't be described
- PI plans a human study based on mechanistic research to be conducted in mice in first two years of the grant; needs the mechanistic data before he can develop and describe the study
  - Know there will be an HS study, but it can't be described
- PI plans a study using sensors to collect biological and exposure data in 200 children, 100 living in rural versus 100 living in urban environments; needs to develop the sensor first
  - Know there will be a study in year 3 and can describe it – delayed start NOT delayed onset; requires full HS section/IERs
- Must be determined in the application

Martha Contact Info

Email: barnes@niehs.nih.gov

- Include grant number in subject line
- Provide a list of questions
- If a Human Subject System issue, include screen shots and/or copies of error messages

Resources

Resources for Training and Finding an IRB

- OHRP Human Research Protection Training - https://www.hhs.gov/ohrp/education-and-outreach/online-education/index.html
- NIH Human Subjects Information - https://grants.nih.gov/policy/humansubjects.htm
- Use Advanced Search to find an IRB https://ohrp.cit.nih.gov/search/search.aspx?styp=bsc

HS Specific Training – Available on youtube.com

- PHS Human Subjects and Clinical Trials Information Form Walk Through- https://www.youtube.com/watch?v=FNgOHqmk0rY
- How to View, Edit and Submit Study Records - https://www.youtube.com/watch?v=8E5RX0HLI0M
- Entering Inclusion Data Using the Participant Level Data Template - https://www.youtube.com/watch?v=lHYrdlPfKVo

Additional NIH Human Subjects Resources

- NIH Human Subjects Website - https://grants.nih.gov/policy/humansubjects.htm
- 45 CFR 46.104 - https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects#p-1366
- Exempt Human Subjects Research Graphic: https://grants.nih.gov/sites/default/files/exemption_infographic_v7_508c-4-4-19.pdf
- Inclusion Across the Lifespan: https://grants.nih.gov/grants/funding/lifespan/lifespan.htm
- Annotated Forms Set for NIH Grant: https://grants.nih.gov/grants/how-to-apply-application-guide/resources/annotated-form-sets.htm

NIH Human Subjects System

Comprised of two parts

- ASSIST
  - System used by PIs to enter data
  - A copy of the latest data is always accessible to PI or delegates
  - NIH staff cannot see changes until submitted
- Reporting Database
  - Used by NIH Staff
  - Where submitted data resides
  - Includes all versions of data submitted to the system

Accessing ASSIST

- Competing Application or RPPR
  - Use Human Subjects Link
- At any other time:
  - Locate Active Record through Status Tab of eRA Commons account
  - Click on Human Subjects link under Actions Column

Accessing the Human Subjects System

- SO: Status tab > General Search screen > Specific Award >Action column > Human Subjects Link
- PI: Status tab > Status — PI Search screen > Status Result — List of Applications/Awards screen > Specific Award >Action column > Human Subjects Link
- Both: RPPR tab > Manage RPPR > Specific Grant > RPPR Menu screen > Edit button > Inclusion Section (G.4.b) > Human Subjects Link

Clicking on Human Subjects Link takes you to ACCESS – the tool used to add info to HSS

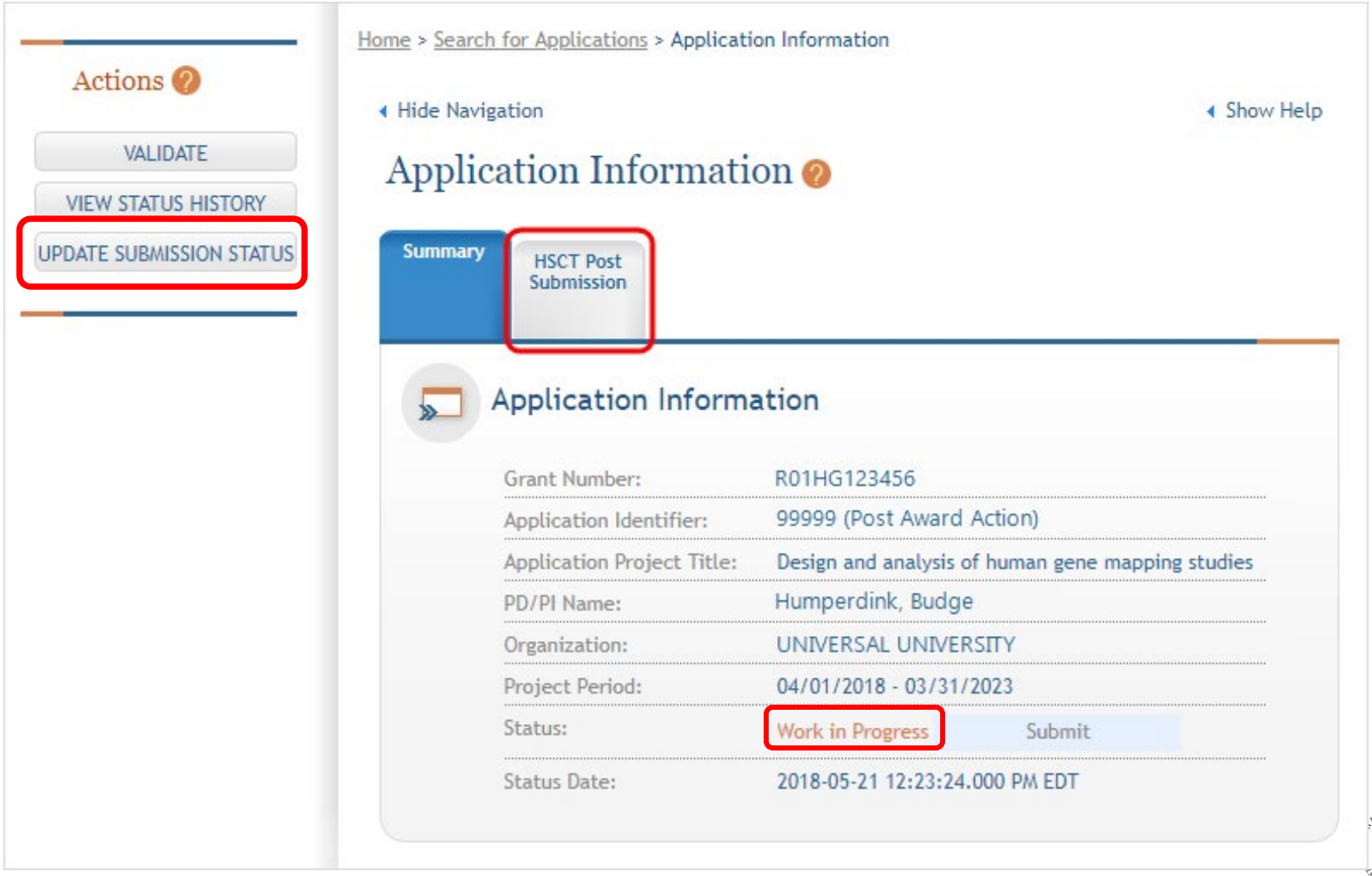
Record Status

- Records must be in Work in Progress to Edit
- Must be in Ready for Submission for SO to Submit
- On Summary Tab - Use Update Submission Status under Actions Column to change Status

Common System Issues

- Can't Edit
  - If not a New Application or RPPR, make sure accessing through Status Tab
  - Check Status
    - If not in Work in Progress – Use Update Submission Status to change
  - If Record is in Work in Progress, make sure last person to work on the record Released the Lock
- If none of the above fixes the issue, contact the eRA Help Desk: https://inside.era.nih.gov/era-service-desk.htm

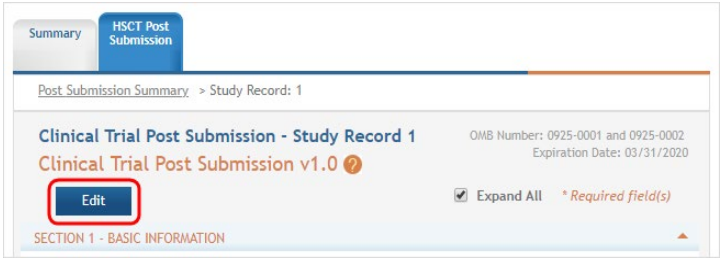
HSCT Post Submission



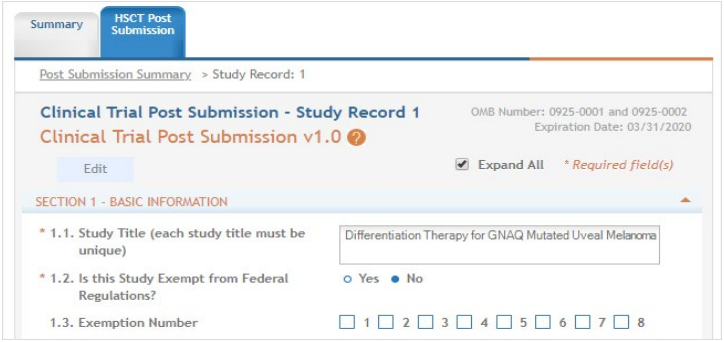
Editing Existing Studies

Clicking on HSCT Post Submission brings up a list of existing studies on that grant.

Click on View for study you want to edit – brings up view of study

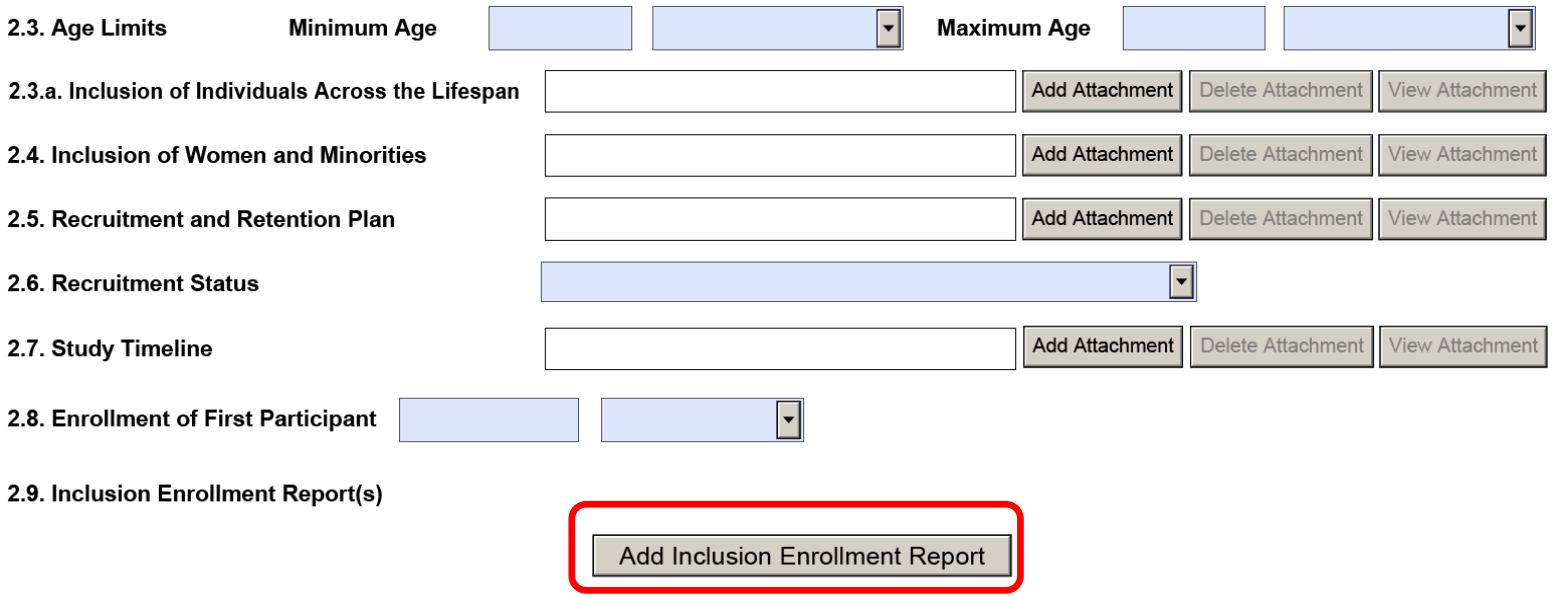


Then, Click on Edit button to make record editable



Add Inclusion Enrollment Record

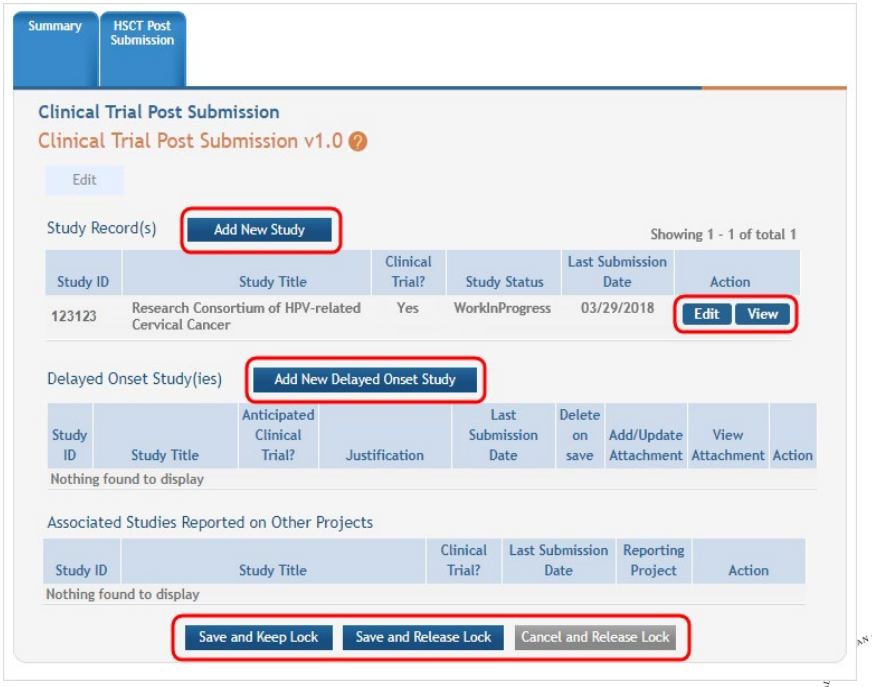
If you need to add a new population to the existing study, Add a New IER Button will be available in Section 2.9 (up to 20 IERs may be added to each study)



Add a New Study

Click on Post HSCT, then click EDIT

Opens options to Add New Study



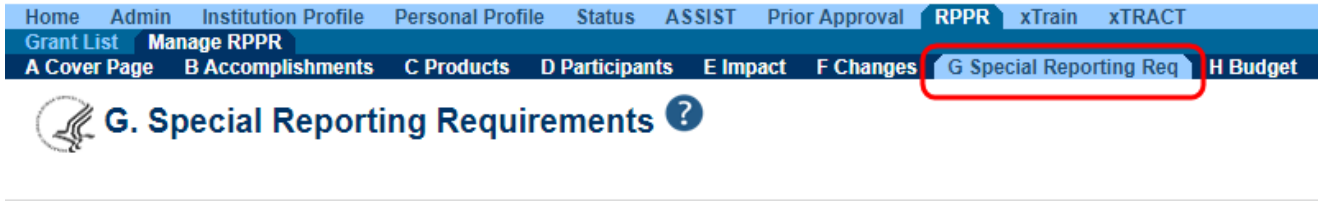
Keep Versus Release Lock

- Save and Keep Lock
  - If lock is ON, record cannot be edited by anyone else
  - Retains “Work in Progress” Status – saves work, application cannot be submitted

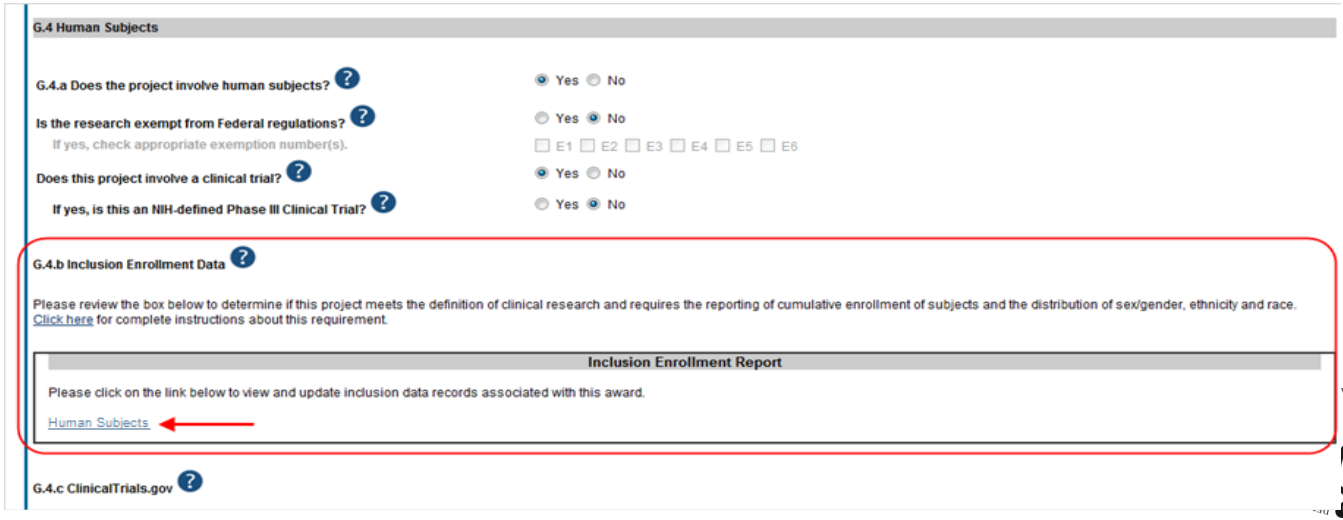
- Save and Release Lock
  - Allows others to edit the record
  - Able to set to “Ready for Submission”, application can then be submitted to NIH

RPPR

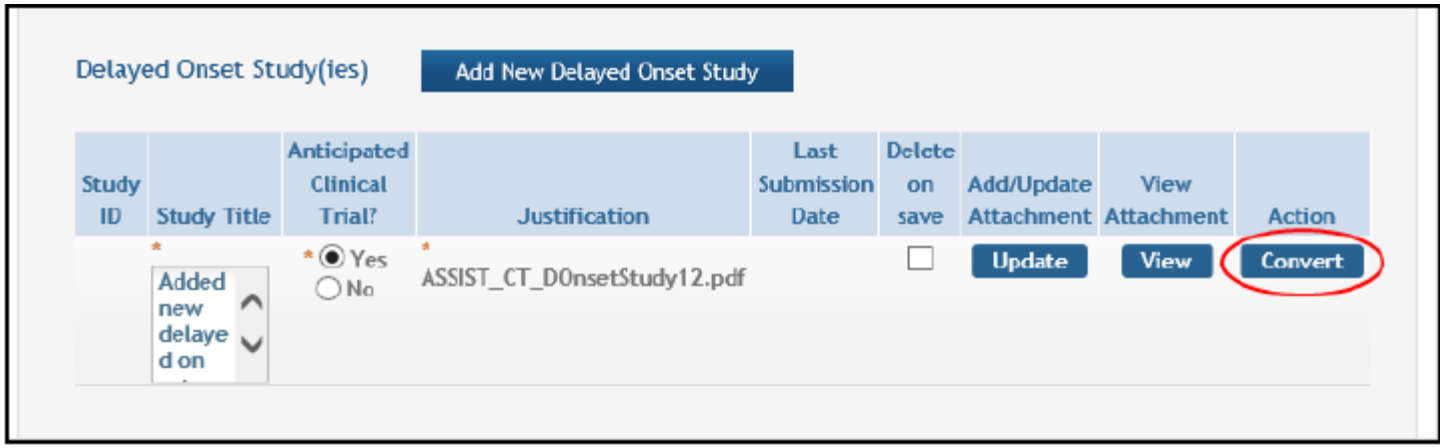
PI: Status tab > Status — PI Search screen > Status Result — List of Applications/Awards screen > Specific Award >Action column > RPPR>G. Special Reporting Requirements

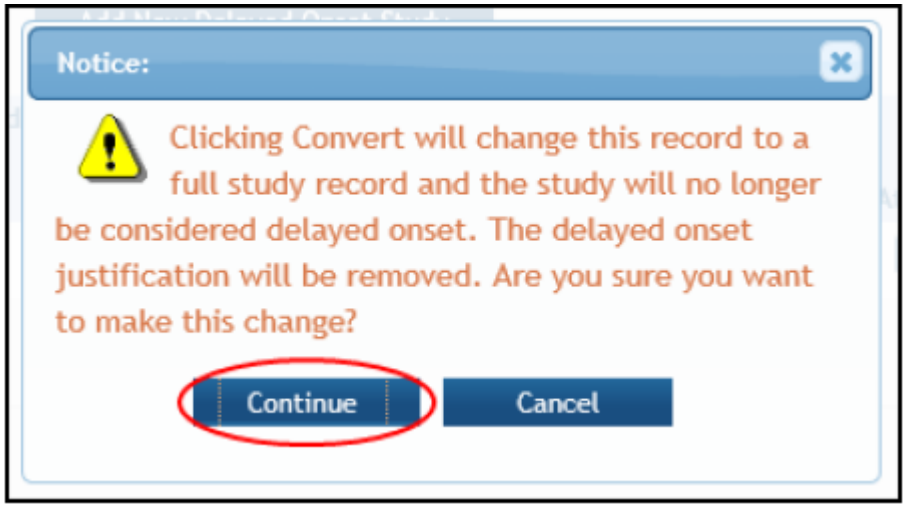


Click on Special Reporting Requirements - Under G.4 b. is Human Subjects Link to ACCESS



Convert Delayed Onset Study to Full Study Record





HSS – Things to remember

- System operates on Statuses
- If you cannot edit, check Status
  - Status must be set to “Work in Progress” to Edit
- Complete Edits and Validate Record before change to “Ready for Submission”
- Status must be “Ready for Submission” for SO to submit
- NIEHS staff cannot see until Records are Submitted
- Submit separately - HSS data first, then RPPR
- Submission task may be delegated to PI
  - Still must set status to “Ready for Submission” before can Submit

Participant Level Data

- Download template from ASSIST which is in .csv format
- Do not change any formatting on the template.
- ALWAYS save in the original .csv format.
- If there is an error in the data, the file can be uploaded as many times as needed.
- When all data is correct, it will be uploaded.

Correcting Participant Level Data

If in .csv format and not accepted, there is a data error.

To find data errors, suggest:

- Create a second copy of the completed .csv form
- Remove all but a small subset of data from copy 2 and submit.
- If file is accepted, then copy additional data from copy 1 to copy 2 and resubmit copy 2. If an error, it is in added data. Fix and resubmit.
- Continue by adding subsets of data and submitting until file is complete and data is accepted.
- The file can be submitted as many times as needed.