Compliance and Reporting in Human Subjects Research and the Human Subjects System (HSS) Troubleshooting

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National Institutes of Health
Office of Extramural Research

Compliance and Reporting in Human Subjects Research

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National Institutes of Health

45 CFR 46 Subpart A: The Common Rule and Subparts B, C, and D

- Harmonizes protection of human subjects among different U.S. Federal departments and agencies
- Outlines regulations for:
  - IRB review and approval
  - Informed consent
  - Federalwide assurance
- *Subpart B* – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- *Subpart C* – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- *Subpart D* – Additional Protections for Children Involved as Subjects in Research

Determining if a Proposed Activity is Non-Exempt Human Subjects Research

IS THE ACTIVITY **RESEARCH**?

DOES THE RESEARCH ACTIVITY INVOLVE **HUMAN SUBJECTS**?

IS THE HUMAN SUBJECTS RESEARCH **EXEMPT**?

1. Is the Activity Research

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

45 CFR 46.102(l)

Deeper Dive: Is the Activity Research?

Is the activity a systematic investigation?

- Are there plans using a methodical approach?
  - Is there a hypothesis? A research question? Plans to systematically collect and analyze data?

Is the activity designed to develop or contribute to generalizable knowledge?

- Will the activity add information and contribute to generalizable knowledge?
- Note- plans to share results with the larger community does not determine if the evaluation is designed to develop or contribute to generalizable knowledge.

2. Does the Research Activity Involve Human Subjects

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

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

Obtains, uses, studies, analyzes, or generates **identifiable private information** or **identifiable biospecimens**

45 CFR 46.102(e)(1)

Are Human Subjects Involved in the Research?

Identify who is the subject

- A human subject is the person that the information is about or from whom the specimen was taken

Is there an interaction or intervention? *OR* Does the investigator have

- Identifiable, private information about the subject or
- Identifiable biospecimens?

3. Is the Human Subjects Research Activity Exempt?

Research activities that meet the conditions for an exemption category are exempt from the typical requirements of the Common Rule (i.e., IRB review and approval according to the regulations)

Institutions generally designate experienced individuals (IRB member or in the IRB office) to make exemption determinations

NOTE: If the proposed human subjects research activity is exempt under one or more categories, **STOP.** The activity is ***not*** nonexempt human subjects research.

45 CFR 46.104

Exempt Categories of Research

Exemption 1: Normal educational practices in established or commonly accepted settings*

Exemption 2: Interactions involving educational tests, surveys, interviews, or observations of public behavior

Exemption 3: Benign behavioral interventions in adults if information is sensitive and identifiable*

Exemption 4: Secondary research use of identifiable, private information or identifiable biospecimens

Exemption 5: research or demonstration projects designed to study, evaluate, improve, or examine an NIH public benefit or service program*

Exemption 6: taste and food quality*

Exemption 7: Storage or maintenance of identifiable private information or identifiable biospecimens for secondary research

Exemption 8: Secondary research using identifiable private information or identifiable biospecimens

**Exempt categories that may include an NIH-defined clinical trial*

See Common Rule Exempt Research and NIH OER Definition of Human Subjects Research websites

Non-Exempt Human Subjects Research

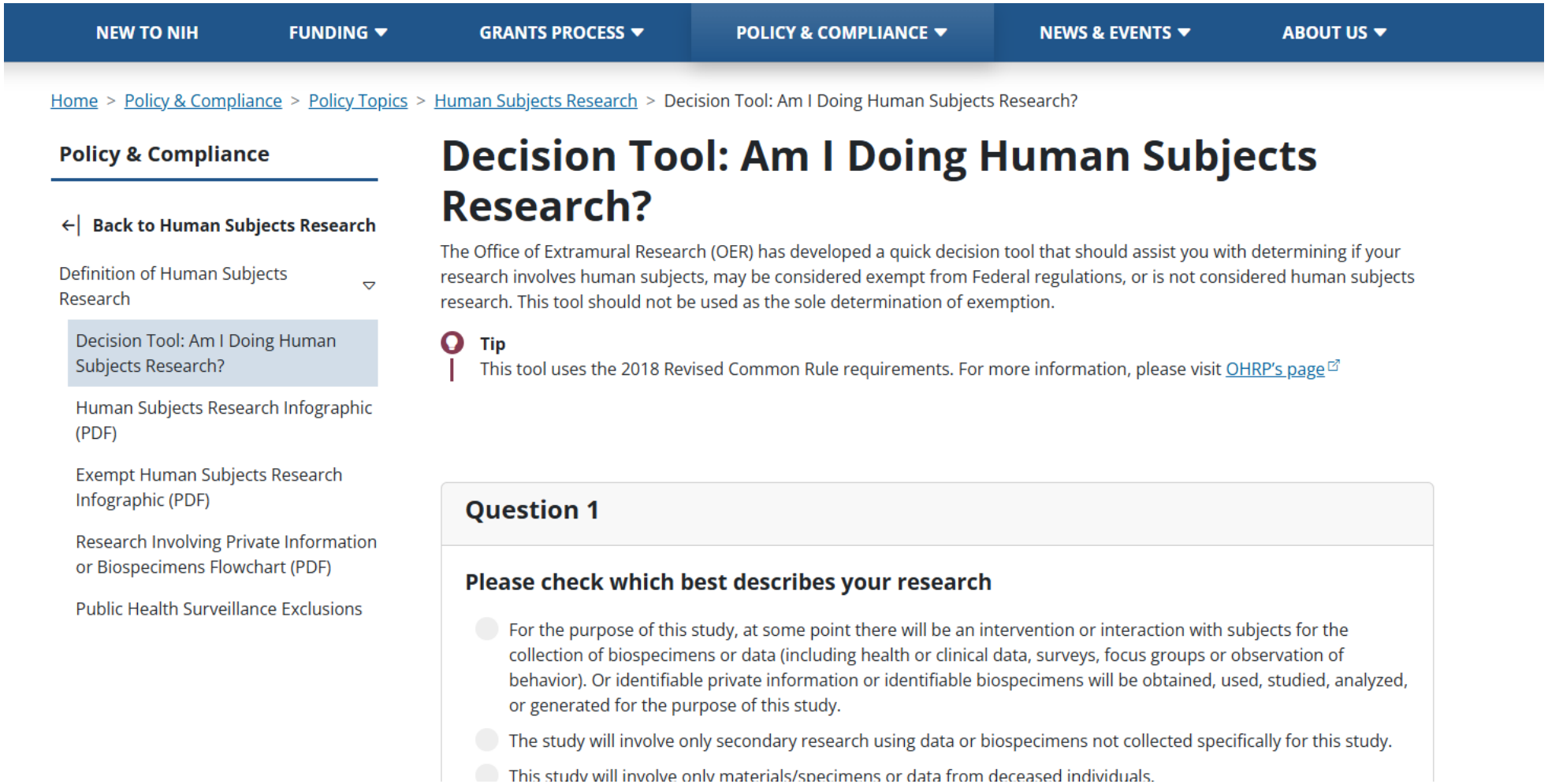
When the answer to the first two questions is yes, and the answer to the third question is no, the activity ***is*** non-exempt human subjects research and requires IRB review and approval.

1. Is the activity research?
2. Does the research activity involve human subjects?
3. Is the human subjects research exempt?

References and Resources:

- OHRP Human Subject Regulations Decision Charts
- NIH Human Subjects Research Infographic
- NIH Decision Tool: Am I Doing Human Subjects Research?

Decision Tool: Am I Doing Human Subjects Research



https://grants.nih.gov/policy-and-compliance/policy-topics/human-subjects/hs-decision

HHS Regulatory Requirements

Institutions engaged in NIH conducted or supported non-exempt human subject research must

- Provide **written assurance** that it will comply with the regulatory requirements
  - OHRP-approved Federalwide Assurance (FWA)
    and
- Certify to NIH that research was reviewed and approved by an **IRB** and that the research will be subject to continuing review by an IRB

45 CFR 46.103

Engagement in Human Subjects Research

In general, institutions are considered engaged in an NIH conducted or supported non-exempt human subjects research project when:

The institution's employees or agents obtain, for research purposes:

data about the human subjects through intervention or interaction;

or

identifiable private information about the subjects Informed consent

Multi-site Study Consideration

In general, Prime recipients of an NIH award (e.g., grant, contract, cooperative agreement) for non-exempt human subjects research are ***considered engaged in the research*** project, even when all activities involving human subjects are carried out by employees or agents of another institution.

All engaged sites must have:

FWA (can be covered under recipient's FWA) • Extending a FWA to Cover Collaborating Investigators	IRB Approval	U.S. sites to rely on one IRB under 45 CFR 46.114 • OHRP Institutional Review Board (IRB) Authorization Agreement

Required Education Protection of Human Subjects

All key personnel must have education on the protection of human research participants:

- Individuals responsible for design and conduct of the research
- Also applies to key personnel at performance sites

One-time training

- Also applies to investigators who conduct exempt human subjects research

See NIH Guide Notices

- NOT-OD-00-039 and
- NOT-OD-11-061

Just-in-Time Requirements-Human Subjects

Verify required information received

- Federal-wide Assurance Number (FWA)
- Certification of IRB approval (or exemption)
- Human subjects education for key personnel

Initiate policy requests (***rare***)

- Exemption 5 (HSS)
- sIRB exception request (email)
- Public Health Surveillance Exclusion (HSS)

NIH GPS Certification of IRB Approval

Recipients must provide a certification to NIH that all nonexempt research involving human subjects has been reviewed and approved by an appropriate IRB. The date of final IRB approval is the date that all protocols in the proposed research application received IRB review and approval.

NIH requires the date of final IRB approval; Conditional IRB approval is not sufficient.

See the NIH Grants Policy Statement (GPS) 4.1.15.2

Single IRB Requirements

NIH Single IRB Policy

- Multi-site domestic studies where each site will conduct the same protocol involving non-exempt human subjects research must use a single Institutional Review Board
- See Guide Notice NOT-OD-16-094

Common Rule Cooperative Research

- Any institution located in the United States that is *engaged* in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States
- See HHS Regulations at 45 CFR 46.114(a)

Resource: NIH website, Single IRB for Multi-Site or Cooperative Research

IRB Review

Institutional Review Board (IRB): committee charged with reviewing human subjects research to ***ensure*** that the ***rights*** and ***welfare*** of research participants ***are protected***.

Initial IRB review

- Convened review
- Expedited review
- Limited review

Amendments

- Expedited review
- Convened review

Continuing review

Continuing Review

Periodic review (annually or more frequently) of ongoing research, including study progress and if risks and benefits have changed. Evaluates if research still satisfies criteria for approval.

Not required for research eligible for expedited or limited IRB review, or for research where all interventions are complete and only accessing follow-up data or performing data analyses..

Continuing Review Requirements

No **NIH** requirement for annual review if not required by Common Rule unless otherwise specified in Notice of Funding Opportunity

- Examples: Studies eligible for expedited review, studies that have completed interventions

NOTE: Institutions/IRBs may have additional requirements

See the HHS regulations at 45 CFR 46.109(e)

Informed Consent Requirements

– Include Key Information

Concise and focused presentation of key information needed by a “reasonable person” to decide on participation

- 9 basic elements & 9 additional elements
- Obtain written informed consent from participant or legally authorized representative, unless consent waived or documentation of consent waived

Certificates of Confidentiality (CoC) Policy

Prohibits disclosure of names or information, documents, or biospecimens containing identifiable, sensitive information

- To persons not connected to the research
- In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding (unless with participants' consent)
- For any other purpose, with some exceptions

Deemed issued to all NIH-funded research that collects or uses identifiable, sensitive information as of December 13, 2016

Copies of research protected

Covered information protected in perpetuity

See Guide Notice NOT-OD-17-109

NIH Inclusion Policies

- Women and members of racial and ethnic minority groups must be included in all NIH-funded clinical research studies unless there is a compelling rationale for exclusion

- Additional reporting and analysis requirements for NIH-defined phase 3 clinical trials

- Individuals of **all ages** must be included in NIH human subjects research unless there are scientific or ethical reasons not to do so

Policy Notices: NOT-OD-18-014 and
Policy Notice: NOT-OD-18-116

Subaward/Pilot Project Requirements

- **All applicable NIH policies and regulations apply to subawards and pilot projects (e.g., for research involving human subjects, regulations at 45 CFR 46 and NIH Certificate of Confidentiality Policy may apply)**

Obtain IRB approval before involving participants in nonexempt human subjects research activities.

- Note: Single IRB requirements may apply

Prior NIH IC approval may be needed, if research activity was not described in grant application.

- Note: prior approval requests must be submitted at least 30 days before proposed activity occurs

Recipient institution will submit progress reports that include relevant information on pilot projects, subawardee activities

Post Award Human Subject Activities

Submit reportable events to the IRB, NIH, and others

Unanticipated problems involving risks to subjects or others

Serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the IRB

Suspension or termination of IRB approval

Reporting adverse events

Research Performance Progress Reports (RPPR)

Annual, Final, and Interim

Request prior NIH approval for changes to human subject research activities

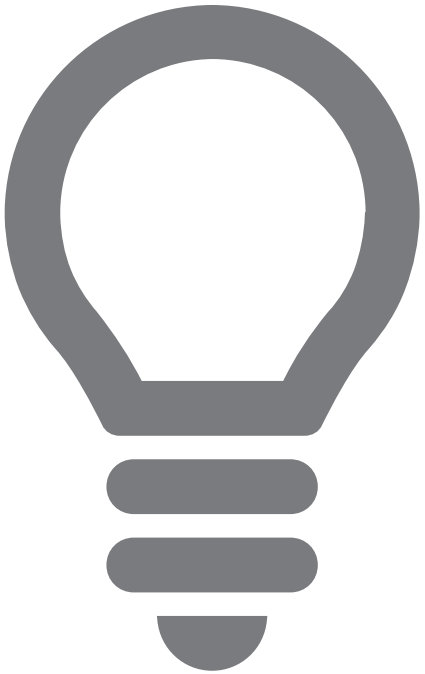
Prior Approval for Changes in Human Subjects

Situations That May Require Prior Approval:

- Results in an overall increase in risk level for subjects
- Human subjects added to project with no human subjects
- Exempt to non-exempt human subjects research
- “No Clinical Trial” to “Includes a Clinical Trial”
- Adding a performance site to a single-site study

- See NOT-OD-15-128 and NOT-OD-15-129 (delayed onset), both published on July 30, 2015

Resources: Human Subjects Protections



See flyer with QR code, Human Subjects, Clinical Trials and Inclusion Resources One-Pager

and

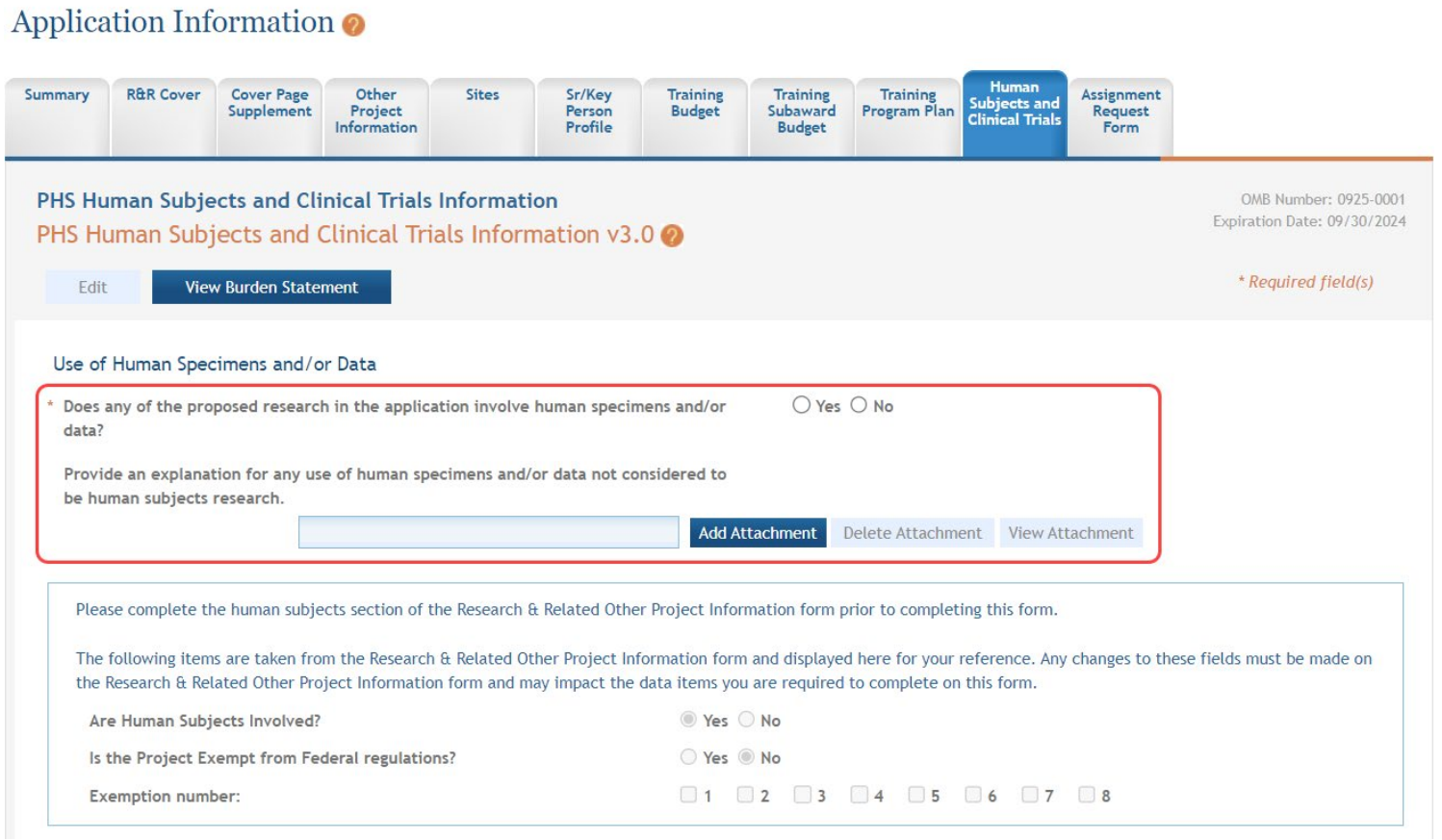
Human Subjects Research websites

Human Subjects System (HSS) Troubleshooting

Dawn Corbett, MPH
NIH Inclusion Policy Officer
Office of Extramural Research
National Institutes of Health

What is HSS/ASSIST?

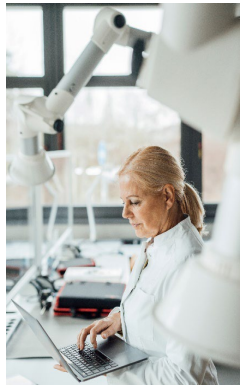
- Application Submission System & Interface for Submission Tracking (ASSIST)
  - Online system to prepare grant applications and forms
- Human Subjects System (HSS)
  - Uses ASSIST interface to allow NIH grant recipients and contract vendors to submit and update study data on human subjects



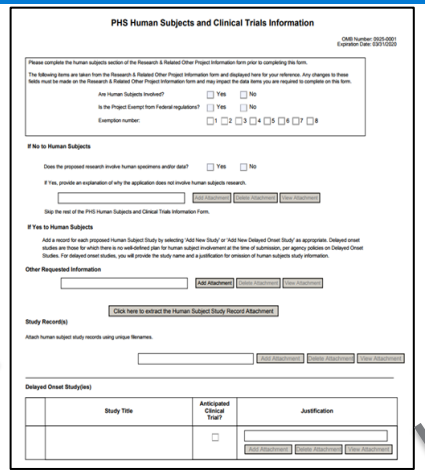
Who Uses HSS/ASSIST?

	Principal Investigator	Signing Official (SO)
View study records	X	X
Receive notifications		X
Edit fields	X	X
Initiate study record submission	X	X
Submit study record	X (if delegated by SO)	X

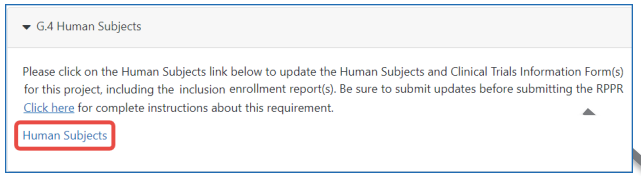
When is HSS/ASSIST Used?



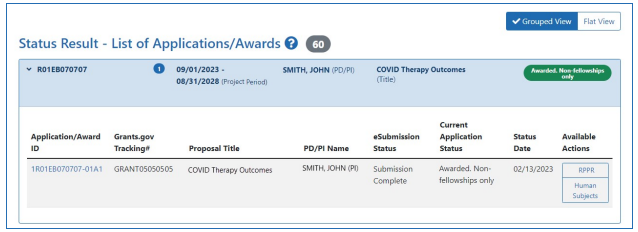
Grant application



Progress Reports



Direct updates via eRA Commons



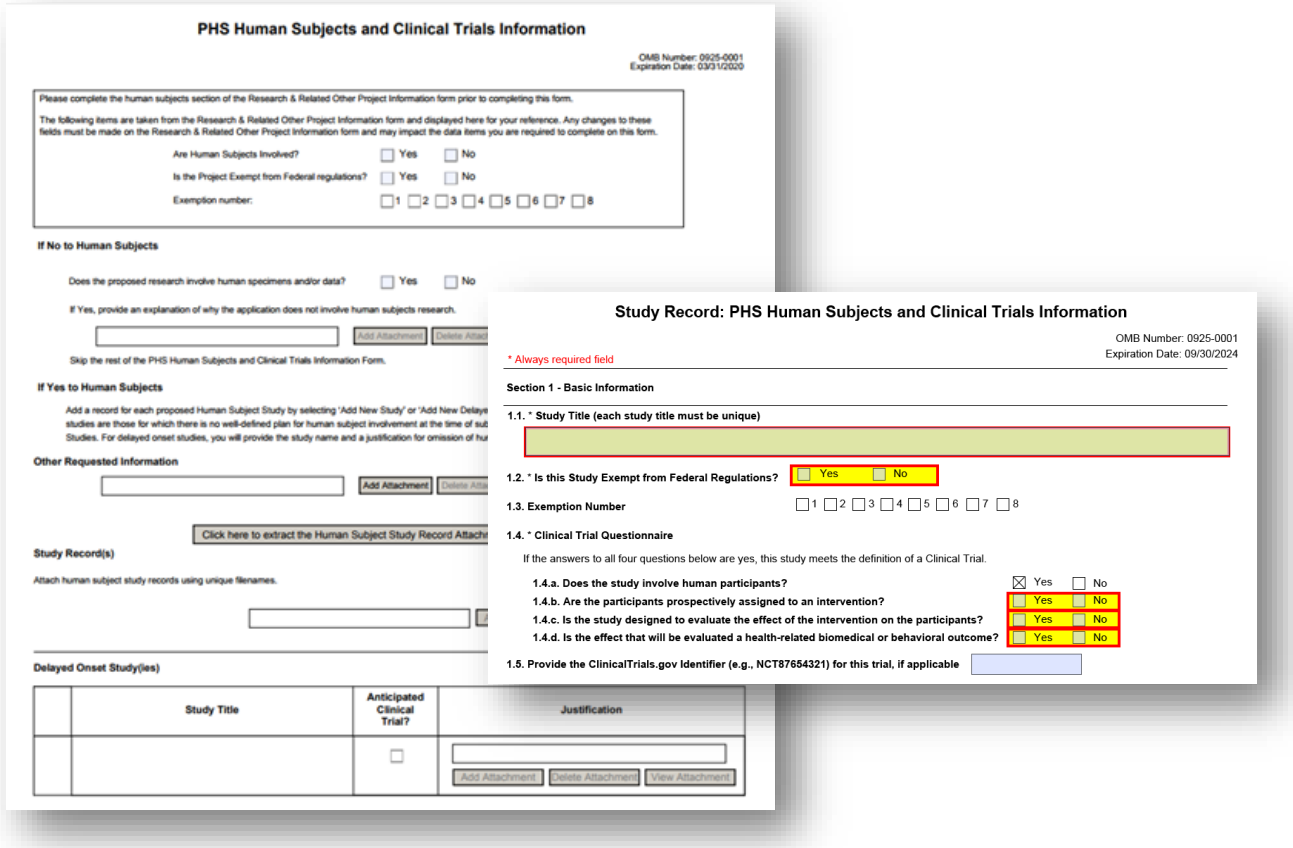
Responsible Party

ClinicalTrials.gov

HSS
Human Subjects System

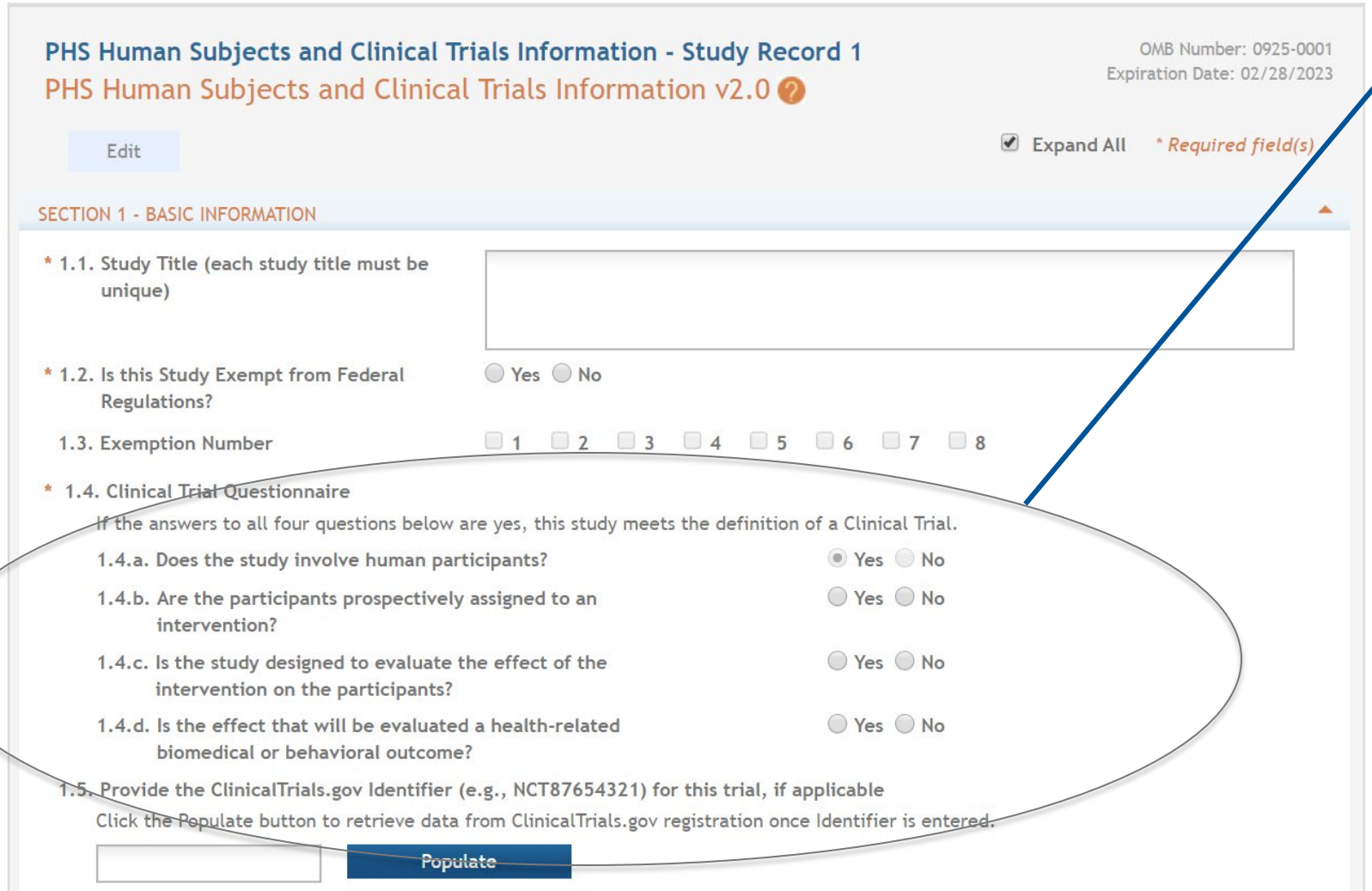
What Information is Entered in HSS/ASSIST?

1. Basic Information
2. Study Population Characteristics
3. Protection and Monitoring Plans
4. Protocol Synopsis (**CT only**)
5. Other Clinical Trial-related Attachments (**CT only**)
6. Clinical Trial Milestones (**post-submission CT only**)



See the **Application Guide** for detailed instructions

Section 1: Basic Information


PHS Human Subjects and Clinical Trials Information - Study Record 1

PHS Human Subjects and Clinical Trials Information v2.0

OMB Number: 0925-0001
Expiration Date: 02/28/2023

Edit

Expand All * Required field(s)

SECTION 1 - BASIC INFORMATION

* 1.1. Study Title (each study title must be unique)

* 1.2. Is this Study Exempt from Federal Regulations? Yes No

1.3. Exemption Number 1 2 3 4 5 6 7 8

* 1.4. Clinical Trial Questionnaire

If the answers to all four questions below are yes, this study meets the definition of a Clinical Trial.

1.4.a. Does the study involve human participants? Yes No

1.4.b. Are the participants prospectively assigned to an intervention? Yes No

1.4.c. Is the study designed to evaluate the effect of the intervention on the participants? Yes No

1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome? Yes No

1.5. Provide the ClinicalTrials.gov Identifier (e.g., NCT87654321) for this trial, if applicable

Click the Populate button to retrieve data from ClinicalTrials.gov registration once Identifier is entered.

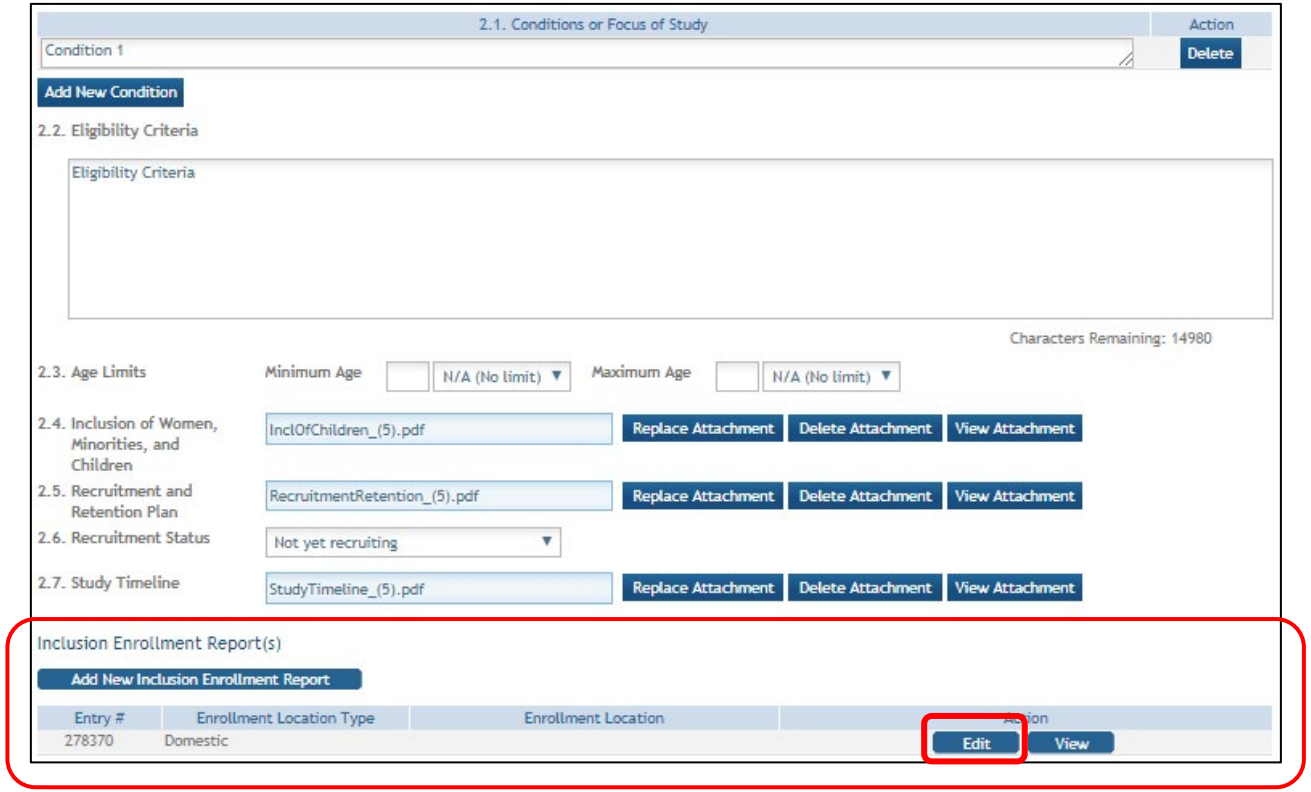
Populate

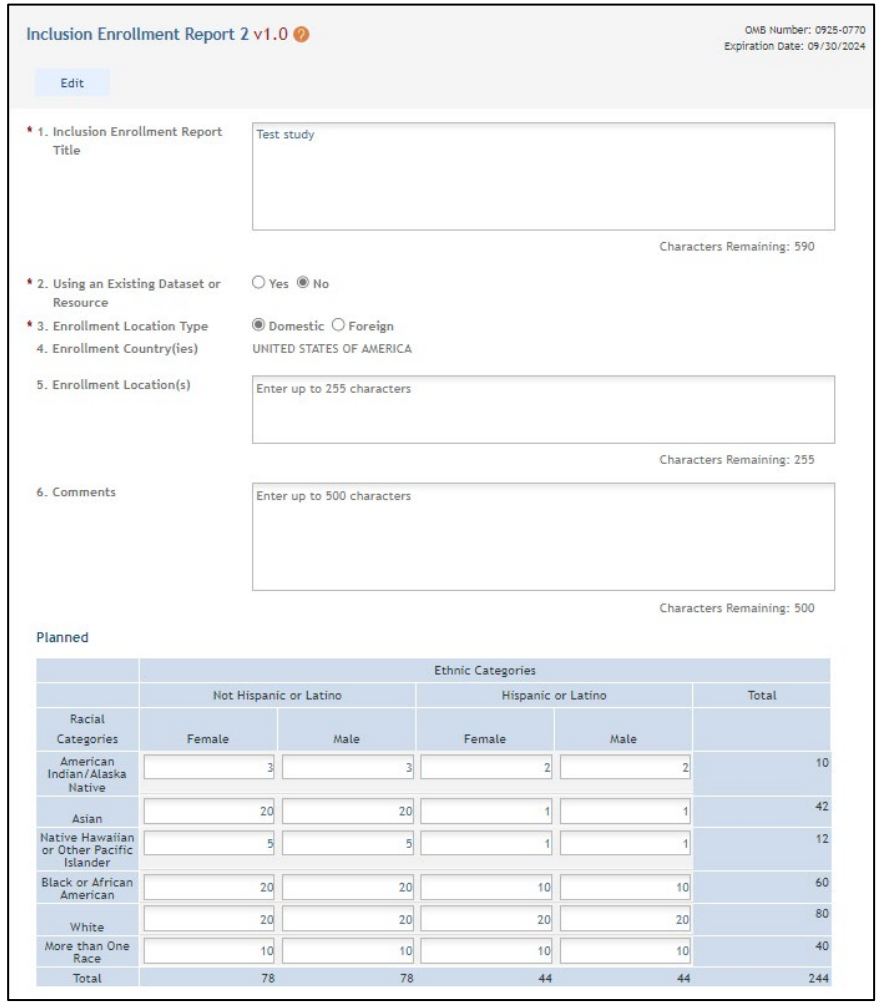
For trials, select "Yes" to all 4 questions

Answer drives validations for:

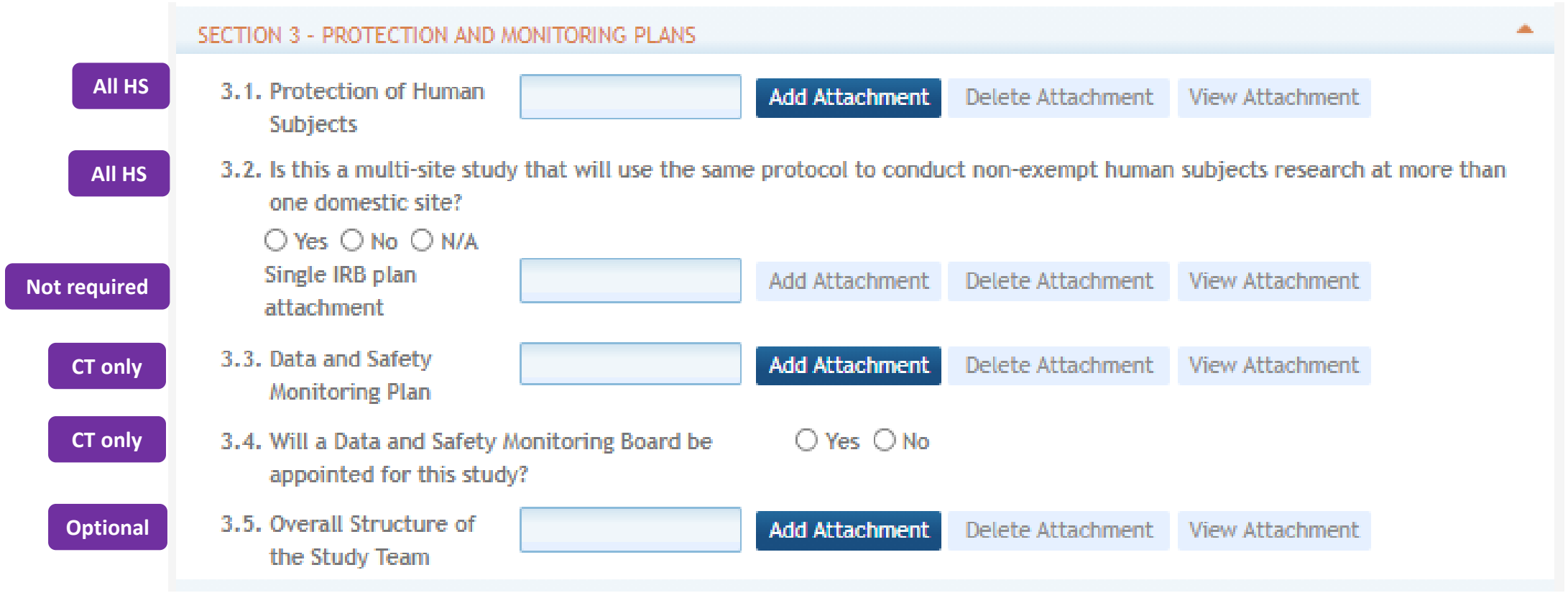
- NOFOs to which the application may be submitted
  - ✓Clinical Trial Required
  - ✓Clinical Trial Not Allowed
  - ✓Clinical Trial Optional
- Required/accessible sections of the form:
  - NCT
  - Data and Safety Monitoring Plan
  - Sections 4, 5, & 6

Section 2: Study Population Characteristics

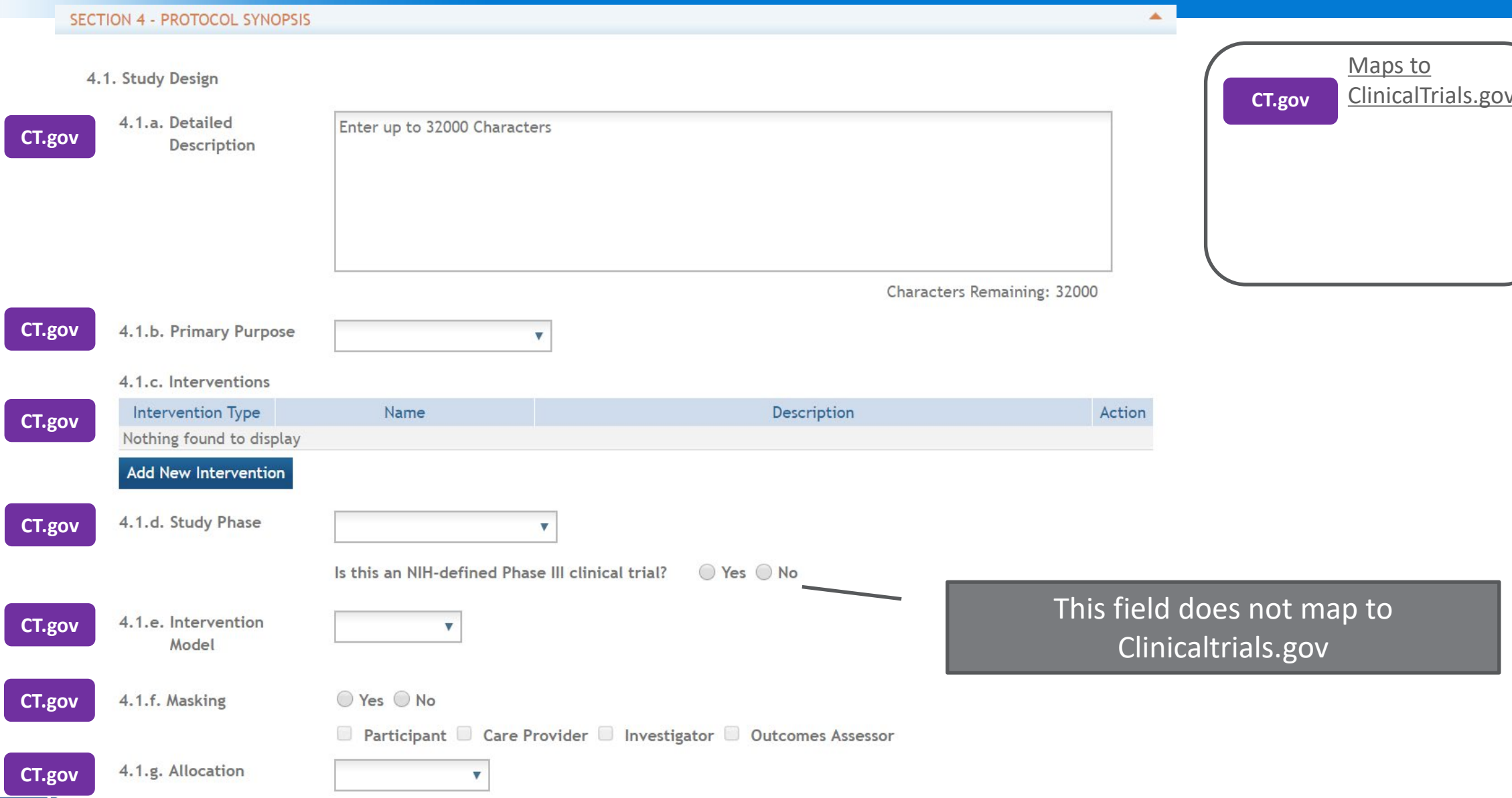




Section 3: Protection and Monitoring Plans



Section 4: Protocol Synopsis



CT.gov Maps to ClinicalTrials.gov

This field does not map to Clinicaltrials.gov

What's Updated in the Progress Report?

For all study types

Section 2

- Inclusion enrollment
- Recruitment status

If applicable:

- Convert delayed onset study
- Additional information requested by NIH program officer

For clinical trials

Section 1

- NCT (Clinicaltrials.gov ID)

Section 6

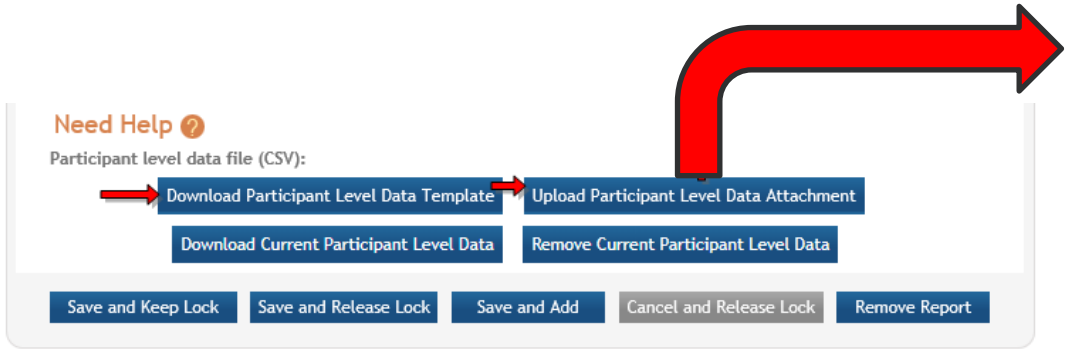
- Clinical trial milestones
  - Enrollment of First Participant Date
  - Study Completion Date
  - 25% Enrollment Date, etc.

Editing a study record

See also *How Do I Edit Studies?* in the HSS Online Help

Inclusion Enrollment Report

	A	B	C	D	E
1	Race	Ethnicity	Sex	Age	Age Unit
2	Asian	Not Hispanic or Latino	Male	23	Years
3	White	Hispanic or Latino	Female	6	Months
4	Unknown	Unknown	Unknown	15	Days
5	More than one race	Not Hispanic or Latino	Male	30	Years
6	American Indian	Not Hispanic or Latino	Male	10	Years
7	Black	Not Hispanic or Latino	Female	15	Years
8	Hawaiian	Not Hispanic or Latino	Male		Unknown
9	Unknown	Unknown	Female		Ninety Plus



Cumulative (Actual)

	Ethnic Categories									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			Total
Racial Categories	Female	Male	Unknown /Not Reported	Female	Male	Unknown /Not Reported	Female	Male	Unknown /Not Reported	
American Indian/Alaska Native	0	0	0	0	1	0	0	0	0	1
Asian	131	189	0	0	0	0	0	0	0	320
Native Hawaiian or Other Pacific Islander	32	36	0	0	0	0	0	0	0	68
Black or African American	103	92	3	0	0	0	0	0	0	198
White	24	23	0	7	1	0	0	0	0	55
More than One Race	21	12	0	5	4	0	0	0	0	42
Unknown or Not Reported	5	3	0	1	1	0	0	0	0	10
Total	316	355	3	13	7	0	0	0	0	694

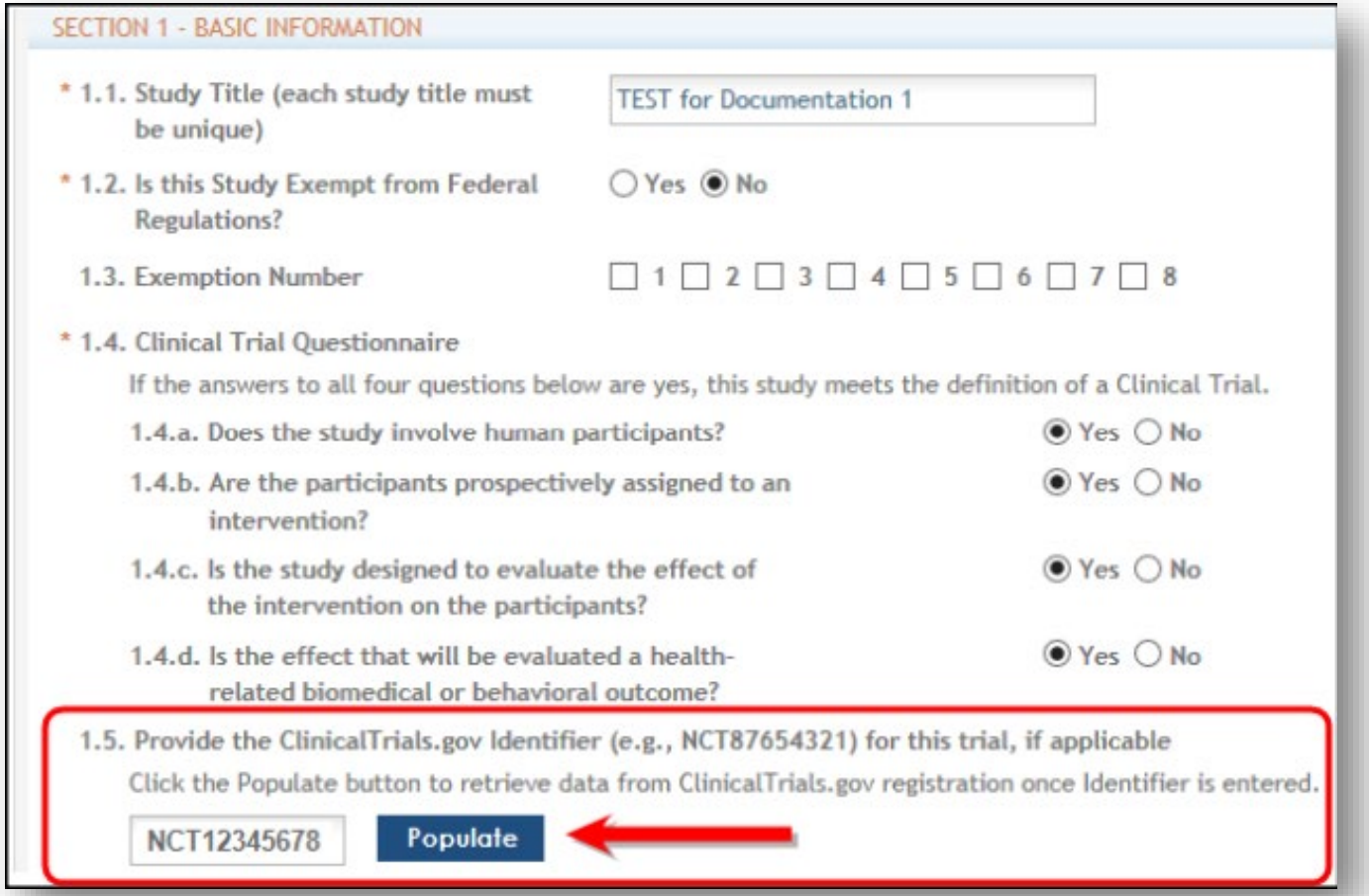
Age Enrollment Report

Age Categories	0-1	2-5	6-12	13-17	18-25	26-45	46-64	65-75	76+	Unknown/ Not Reported	Total
Total	54	53	41	20	191	102	119	95	7	12	694

Note: Less than 5 participants will not appear in any Age Enrollment Report category except within the Total.

Populate Feature

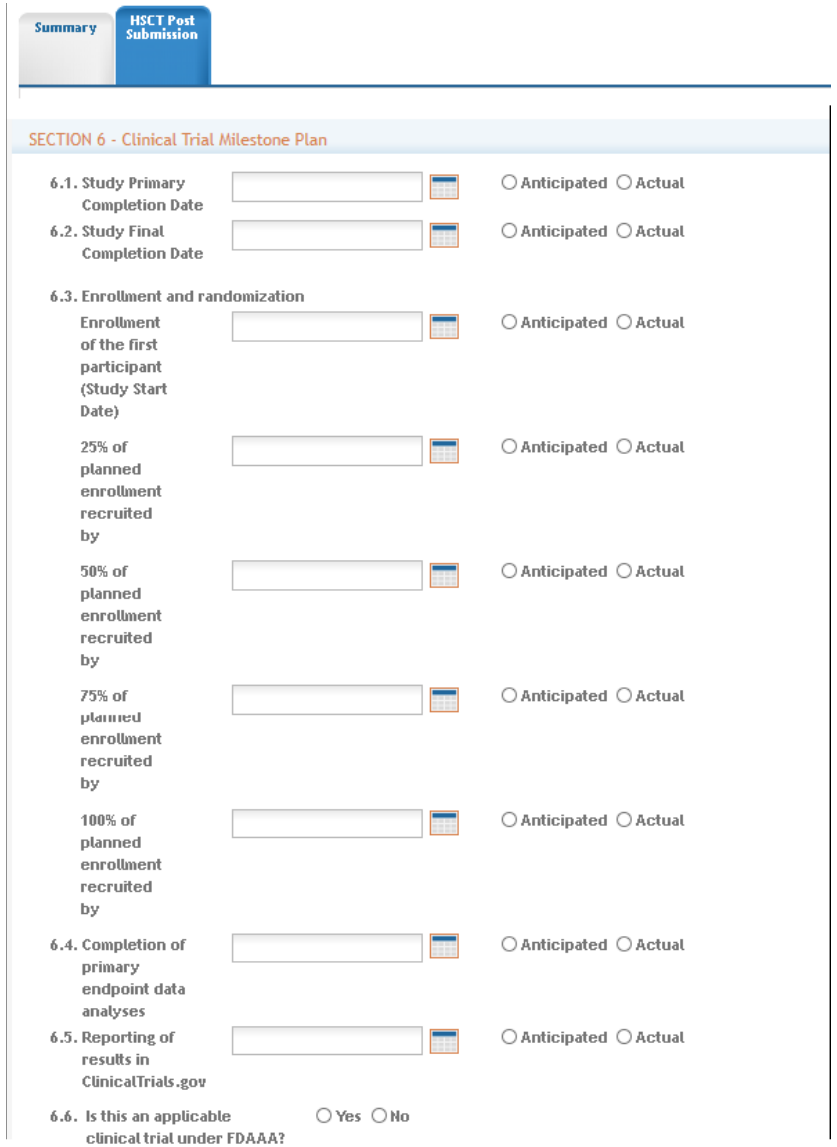
Once an NCT is entered, the Populate button can be used to update HSS fields that map to ClinicalTrials.gov



Populated Fields

HSS Fields	Clinicaltrials.gov Fields
Study Title	Brief Title
Conditions or Focus of Study	Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study
Eligibility Criteria	Eligibility Criteria
Age Limits	Age Limits
Recruitment Status	Overall Recruitment Status
Narrative Study Description	Detailed Description
Primary Purpose	Primary Purpose
Study Phase	Study Phase
Interventions	Interventions, including Intervention Type and Intervention Name(s)
Intervention Model	Interventional Study Model
Masking	Masking
Allocation	Allocation
Outcome Measures	Primary Outcome Measure Information
Study Primary Completion Date	Primary Completion Date
Study Final Completion Date	Study Completion Date
Enrollment of the first participant	Study Start Date
Reporting of results in ClinicalTrials.gov	Results First Submitted

Section 6: Update Clinical Trial Milestones



- Update dates to “actual” when milestones are met
- Enrollment of First Participant and Study Primary Completion date are locked once set to “actual”
  - Can still be refreshed directly from Clinicaltrials.gov if registered
  - NIH program officer must contact inclusion@mail.nih.gov for assistance when needed

HSS/ASSIST and Clinicaltrials.gov Match Checks

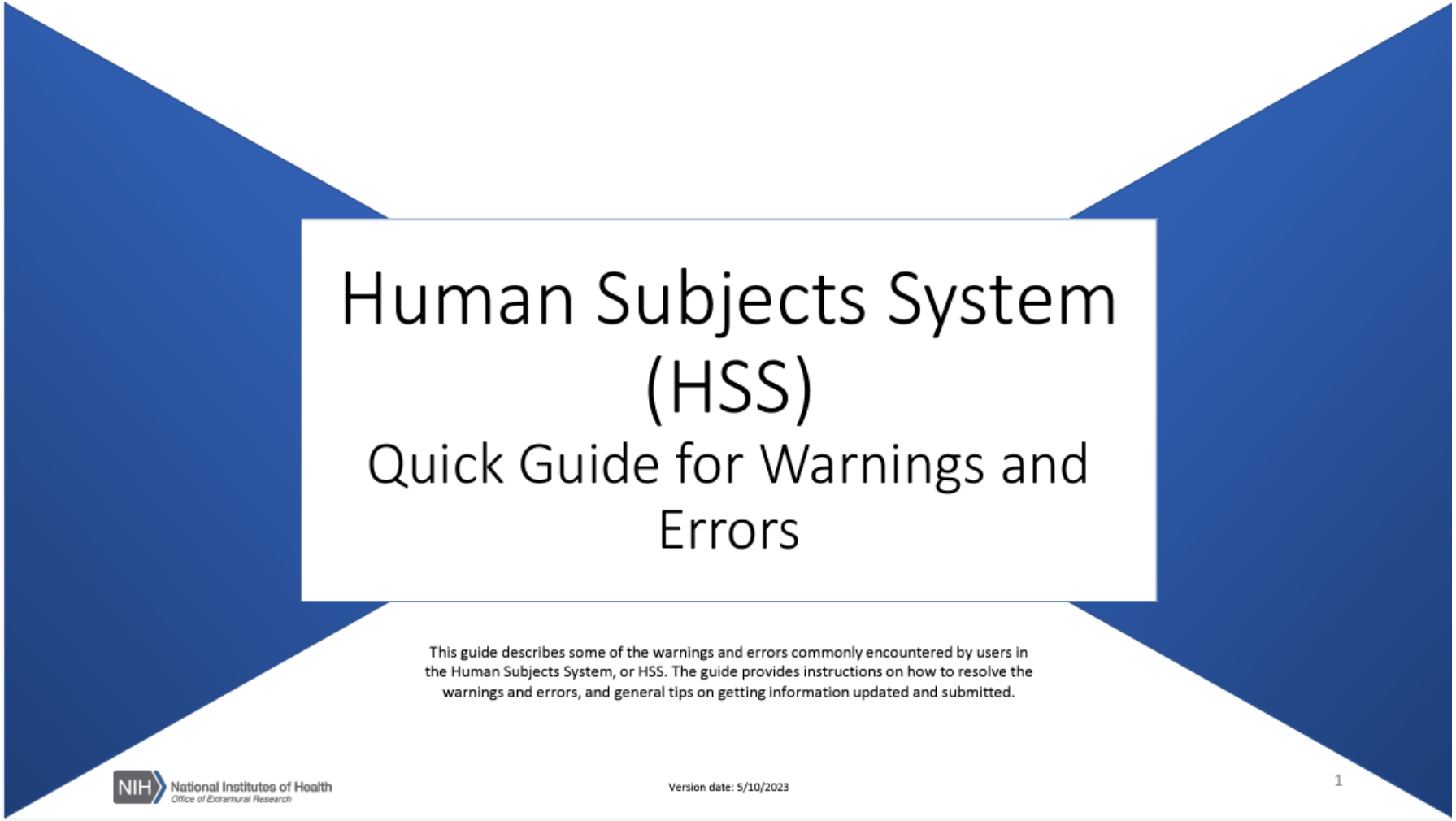
Clinicaltrials.gov Fields	HSS Fields	HSCT Form Section
Age Limits	Age Limits	Section 2
Overall Recruitment Status	Recruitment Status	Section 2
Primary Purpose	Primary Purpose	Section 4
Study Phase	Study Phase	Section 4
Masking	Masking	Section 4
Allocation	Allocation	Section 4
Primary Completion Date	Study Primary Completion Date	Section 6
Study Completion Date	Study Final Completion Date	Section 6
Study Start Date	Enrollment of the First Participant	Section 6
Results First Submitted	Reporting of Results in ClinicalTrials.gov	Section 6

TIP: It's typically easiest to have separate study record for trial and non-trial activities (e.g. 1 Clinicaltrials.gov record = 1 HSS/ASSIST Study Record)

Common HSS warnings and errors

Warning or error	Have you…?
No participant-level data and falls under Inclusion Across the Lifespan Policy	...**submitted** individual-level inclusion data?
Enrollment of 1st participant is more than 21 days ago and **no NCT has been provided**	…**registered** in Clinicaltrials.gov?
Primary completion date is more than 12 months ago and **no results have been provided**	…**reported results** in Clinicaltrials.gov?
Information does not match the information in Clinicaltrials.gov	…refreshed data from Clinicaltrials.gov using the "**Populate**" feature?

TIP: Update Clinicaltrials.gov first, then use the "Populate" feature to refresh the data in HSS/ASSIST



Human Subjects System (HSS)

Quick Guide for Warnings and Errors

This guide describes some of the warnings and errors commonly encountered by users in the Human Subjects System, or HSS. The guide provides instructions on how to resolve the warnings and errors, and general tips on getting information updated and submitted.

NIH National Institutes of Health
Office of Extramural Research

Version date: 5/10/2023

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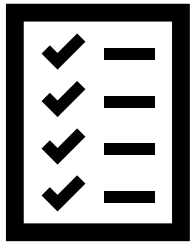
https://www.era.nih.gov/files/HSS-error-and-warning-PI-and-SO-quick-guide.pdf

Submission



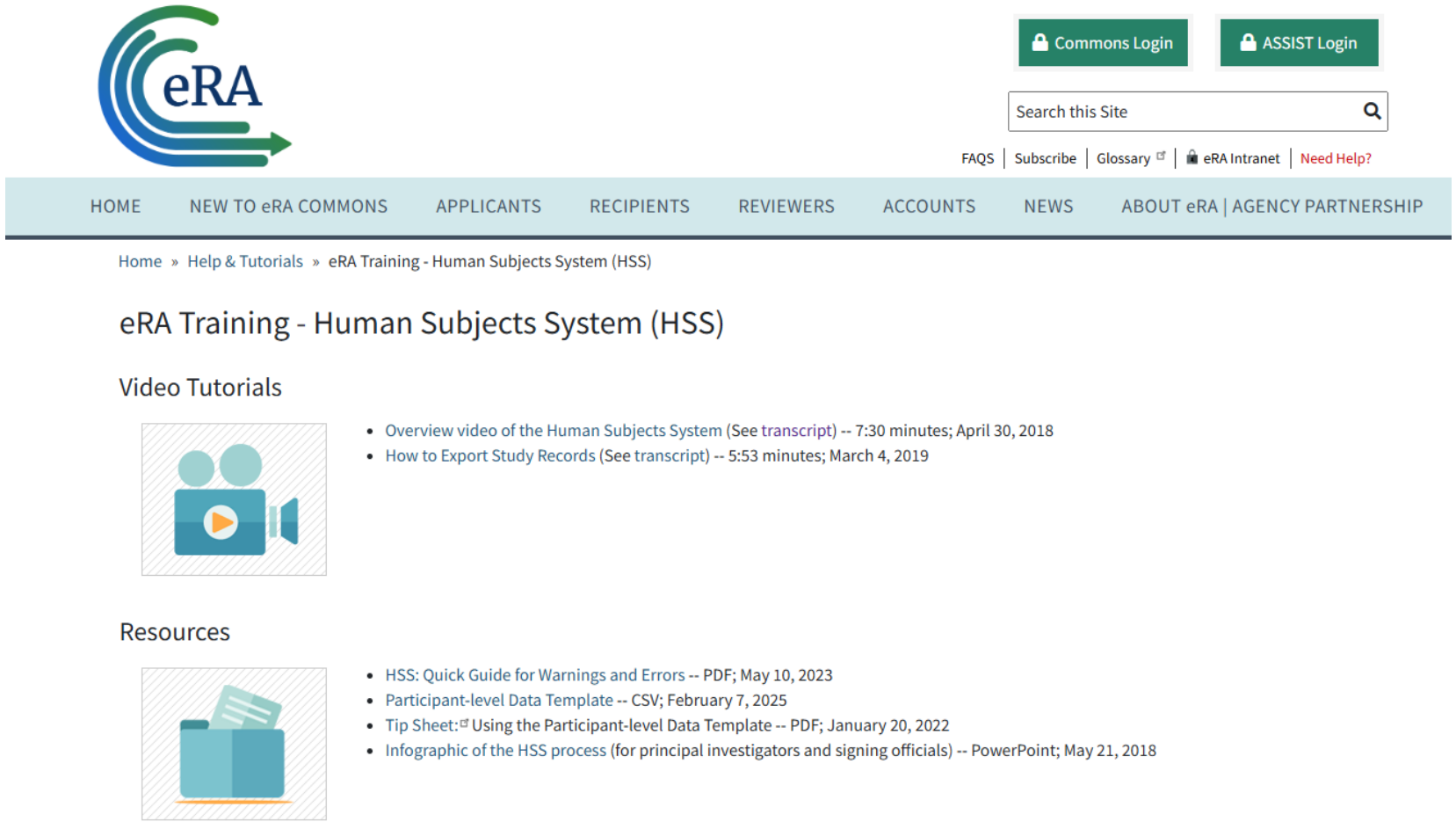
Before submitting:

- Resolve all warnings and errors
  - "Validate" feature can be used to check prior to submission
  - Read the warnings and errors in the RPPR Module and in HSS: they often mention what the problem is
- Make sure you have submitted updated cumulative individual-level participant data if you have enrolled participants
- Change status from *Work in Progress* to *Ready for Submission*

Warnings and errors remain for NIH staff and may delay award!

Submit HSS data **prior to** submitting RPPR

HSS Training Page



https://www.era.nih.gov/help-tutorials/era-training-hss.htm