Tips for Submitting an Amendment Application in iStar for Ceded Studies

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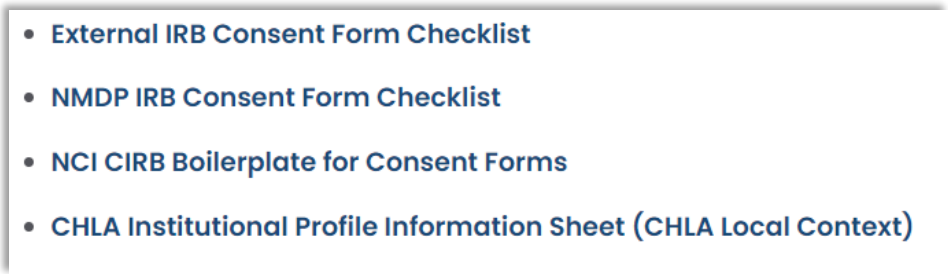
HUMAN SUBJECTS PROTECTION PROGRAM

Objectives

- To understand when an Amendment application in iStar is required for a ceded study.
- To understand the IRB of Record's Approval letter.
- To understand how to prepare an Amendment application in iStar.

Glossary

- **Ceded Study:** A research study that is deferred to an external IRB for review and oversight.
  - Ceded submissions are NOT reviewed by CHLA IRB and do not receive CHLA IRB approval.
  - Ceded submissions are reviewed by CHLA HSPP Reliance Administrators for study-specific local considerations/ local context requirements and receive *clearance*.
- Local Considerations (aka Local Context Requirements): Requirements of any applicable state or local laws, regulations, institutional policies, standards or other local factors, including local ancillary reviews, relevant to an instance of research.



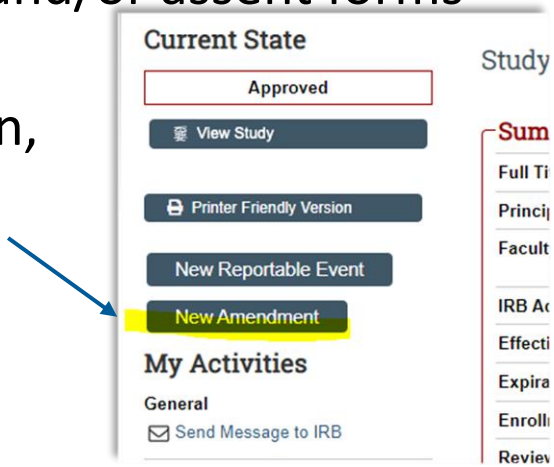
Glossary (cont.)

- **External IRB:** Any IRB that is *not* our local CHLA IRB, such as Advarra IRB, WCG IRB, etc.
- **Reviewing IRB:** The IRB serving as the IRB of Record for all participating sites in a multisite research study. A Reviewing IRB can be a central, commercial, institutional, or independent IRB.
  - Interchangeable terms: the IRB of Record, Central IRB, sIRB, or single IRB
- **Relying IRB:** The IRB that is relying on the review of another IRB, to serve as the IRB of Record for a multisite research study.

Why do I need to submit AM application in iStar for a ceded study?

- The Amendment (AM) application is necessary to maintain the initial ceded application current. Reliance Administrators review the AM application to:
  - ensure *continued* compliance with CHLA local context requirements (e.g., ancillary reviews, HS and GCP certification, etc.)
  - ensure *continued* compliance with CHLA-required language in the IRB approved CHLA-specific consent and/or assent forms

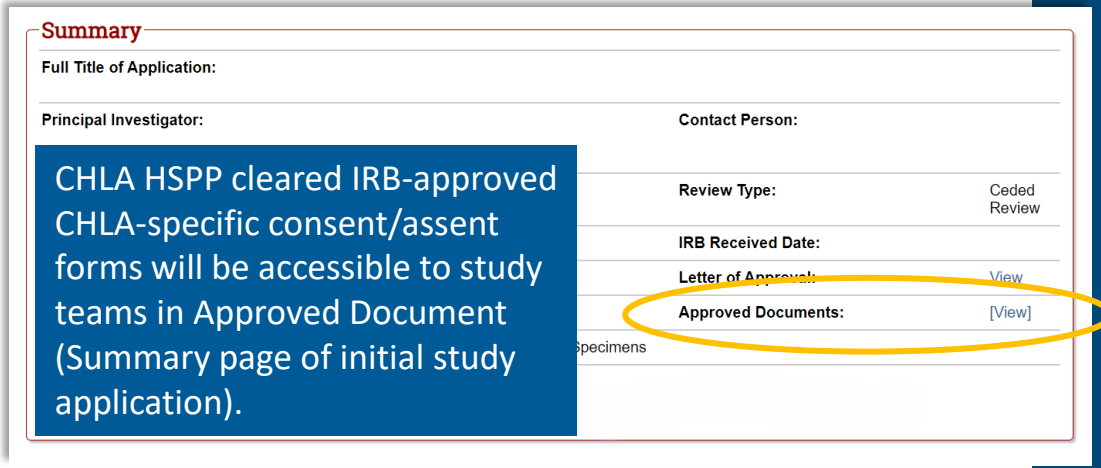
- After clearance of the initial ceded application, click on “New Amendment” to create an AM application.



When do I need to submit AM application in iStar for a ceded study?

The AM application in iStar is necessary to obtain ***CHLA HSPP clearance to use CHLA-specific IRB-approved documents, such as:***

- consent forms
- assent forms
- recruitment materials
- subject-facing documents, etc.



An AM application must be submitted in iStar the ***first time*** CHLA-specific documents are approved by the IRB of Record *(first approval)**.

**Except for studies reviewed by WCG IRB and NCI IRB, a draft version of CHLA-specific consent/assent forms were cleared in the initial ceded study application.*

Do I need to submit an AM Application in iStar every time the IRB issues an Approval Letter?

***For the life of the study,* an AM application is required in iStar:**

- When the ***IRB of Record approves***:
  - ***changes*** to the study protocol by approving an updated protocol
  - ***changes*** to CHLA-specific consent and assents forms
  - ***changes*** to CHLA-specific recruitment materials
  - ***changes*** to CHLA-specific subject-facing documents
  - Non-substantial ***changes*** to the protocol/study procedures by approving a protocol clarification memo, IB, etc.
- When the IRB of Record issues an Approval Letter for a **change in the Enrollment Study Status** (or if a memo is issued by the CRSO/sponsor)

Do I need to submit an AM Application in iStar every time the IRB issues an Approval Letter (cont.)?

For the life of the study, when the IRB of record issues the Continuing Review (CR) approval, if applicable to the study, an AM application in iStar is required.

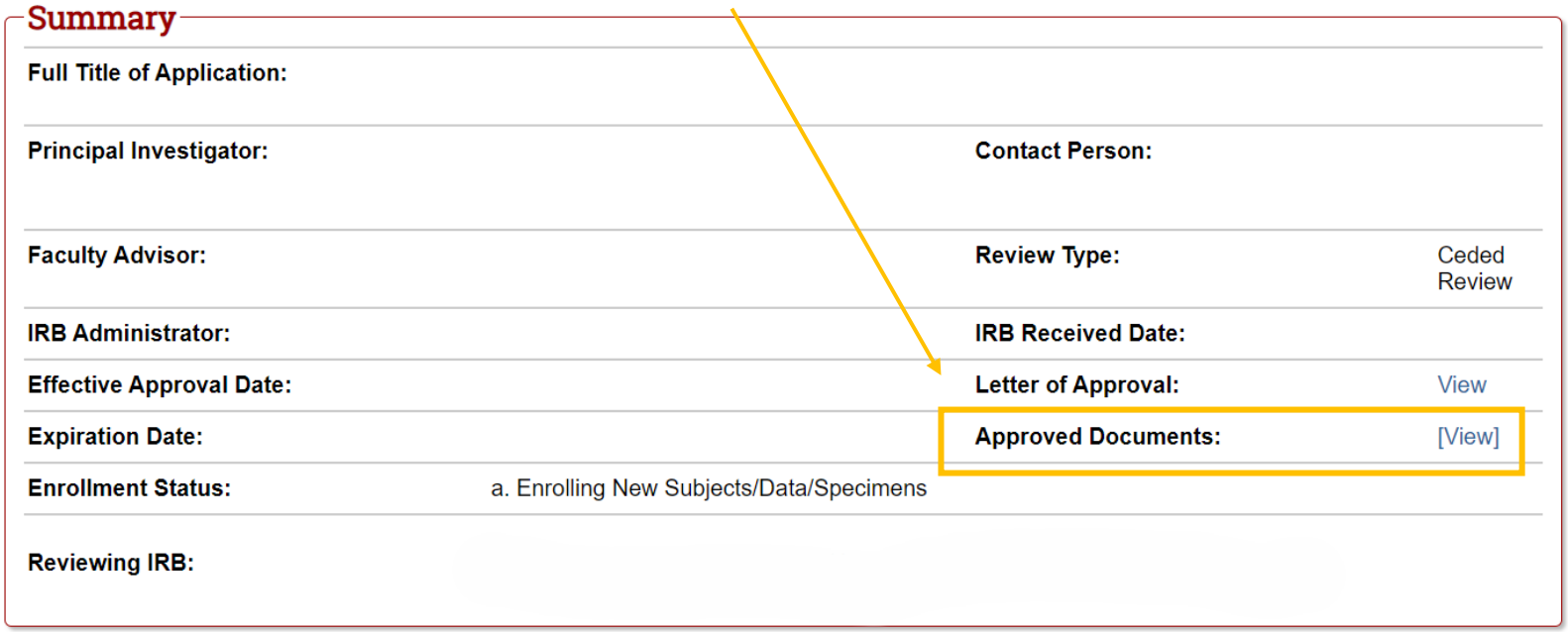
- When the IRB of Record issues consent/assent forms stamped with the updated approval and expiration date, upload them in item 24.7 of the AM application. Reliance Administrators will clear them for use. Cleared IRB-approved CHLA-specific consent/assent forms will be accessible to study teams in Approved Document (Summary page of initial study application).

NCI CIRB CR Approval

- ***For the life of the study,*** when NCI CIRB issues the CR approval, please upload in item D1.2 a zip file with all documents in the CR event.
- Reliance Administrators will stamp current IRB-approved CHLA-specific consent and/or assent forms with the new approval and expiration dates.
- Cleared IRB-approved CHLA-specific consent/assent forms will be accessible to study teams in Approved Document (Summary page of initial study application).

Where can I find cleared IRB-approved consent and assent forms?

Current **IRB-approved CHLA-specific consent and assent forms** cleared by Reliance Administrators will be accessible to study teams for use in the initial ceded application Summary page:



Amendments Initiated by CHLA

An AM application in iStar is required for the following *before* submitting to the IRB of Record:	
Change in the CHLA Principal Investigator (PI)	After CHLA HSPP clearance, the IRB of Record's approval will be obtained and submitted in iStar in a separate AM application, along with revised IRB-approved CHLA-specific Consent/Assent Form(s).
Change or addition of CHLA Co-Investigators (Co-I)	For these amendments, contact the IRB of Record to find out if IRB approval is required.
Change or addition of CHLA study personnel who will obtain consent	
CHLA-specific recruitment material(s) or subject-facing documents	After CHLA HSPP clearance, the IRB of Record's approval will be obtained and submitted in iStar in a separate AM application, with the IRB-approved document.

Amendments: PI, Co-I, personnel obtaining consent

- Reliance Administrators will verify human research training requirements are completed for changes in study personnel
- When applicable, Reliance Administrators will verify that revised consent form contains financial conflict of interest language, as suggested by CMP.

IRB of Record Approval Letter

Terms IRBs use to refer to the IRB Approval Letter:

IRB of Record	Approval Letter
WCG IRB	Certificate of Action
Advarra IRB	Approval Notice
UCSF IRB	Outcome Letter
NMDP IRB	Notice of Action
JCHR IRB	Decision Letter
Sterling IRB	Approval Notification
BRANY IRB	MASTER File Approval Notice
City of Hope IRB	Notification of ___ Approval

Understanding the IRB Approval Letter

The IRB of Record Approval letter *may* contain pertinent information for the AM application in iStar, such as:

- List of IRB approved documents
- IRB approval and expiration date, when applicable
- Re-consent instructions, when applicable
- Regulatory determinations
- PI Responsibilities, etc.

Example: Advarra IRB

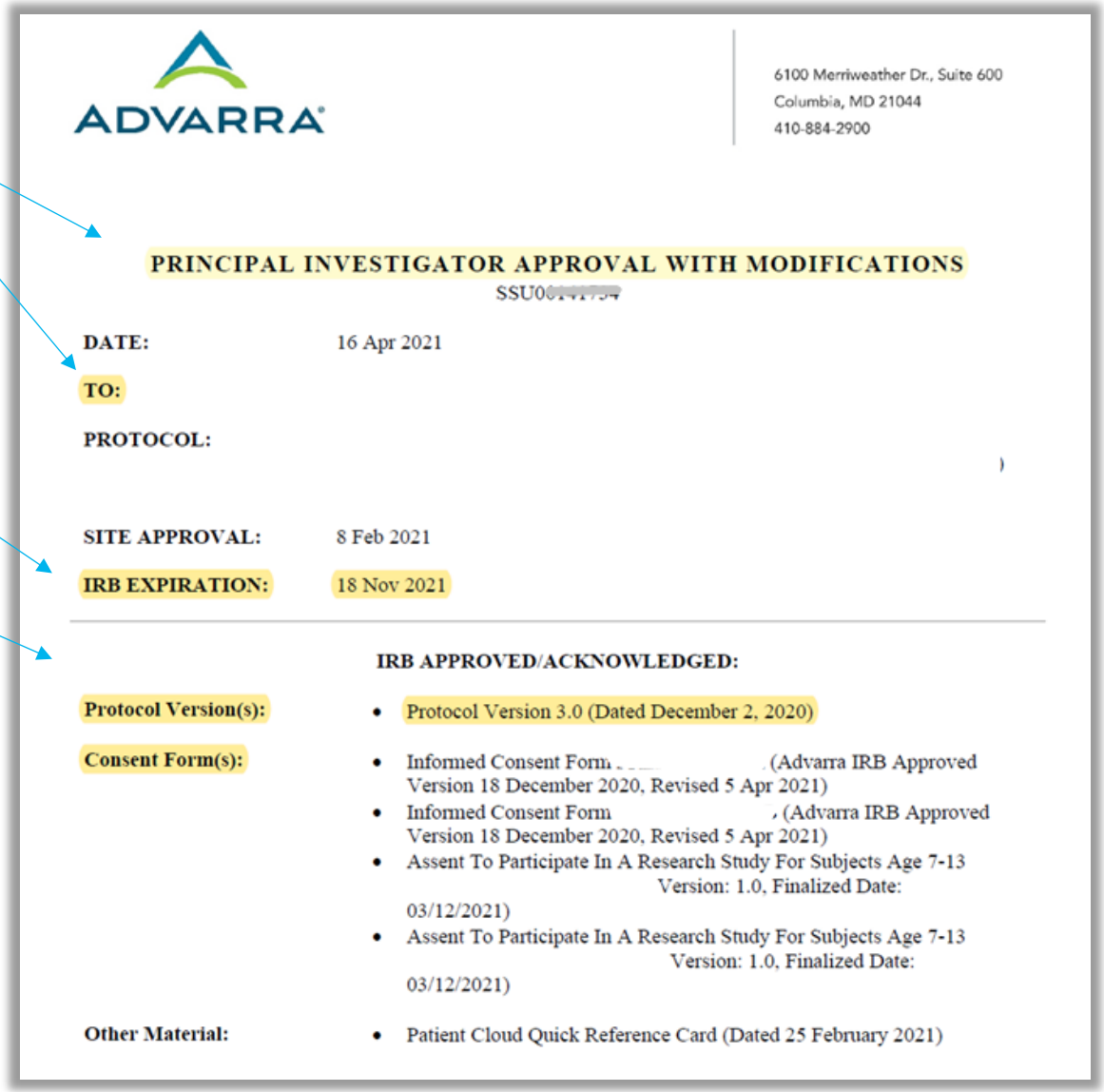
This letter is approving the PI of the site (along with modifications to the research).

Tells us when the IRB approval expires.

Specifies the approved documents.

Documents that will be submitted in AM application in iStar:

- ***protocol***
- ***Consent and assent form***



ADVARRA

6100 Merriweather Dr., Suite 600
Columbia, MD 21044
410-884-2900

PRINCIPAL INVESTIGATOR APPROVAL WITH MODIFICATIONS

SSU0[redacted]

DATE: 16 Apr 2021

TO:

PROTOCOL:

SITE APPROVAL: 8 Feb 2021

IRB EXPIRATION: 18 Nov 2021

IRB APPROVED/ACKNOWLEDGED:

Protocol Version(s):
- Protocol Version 3.0 (Dated December 2, 2020)

Consent Form(s):
- Informed Consent Form [redacted] (Advarra IRB Approved Version 18 December 2020, Revised 5 Apr 2021)
- Informed Consent Form [redacted] (Advarra IRB Approved Version 18 December 2020, Revised 5 Apr 2021)
- Assent To Participate In A Research Study For Subjects Age 7-13 Version: 1.0, Finalized Date: 03/12/2021)
- Assent To Participate In A Research Study For Subjects Age 7-13 Version: 1.0, Finalized Date: 03/12/2021)

Other Material:
- Patient Cloud Quick Reference Card (Dated 25 February 2021)

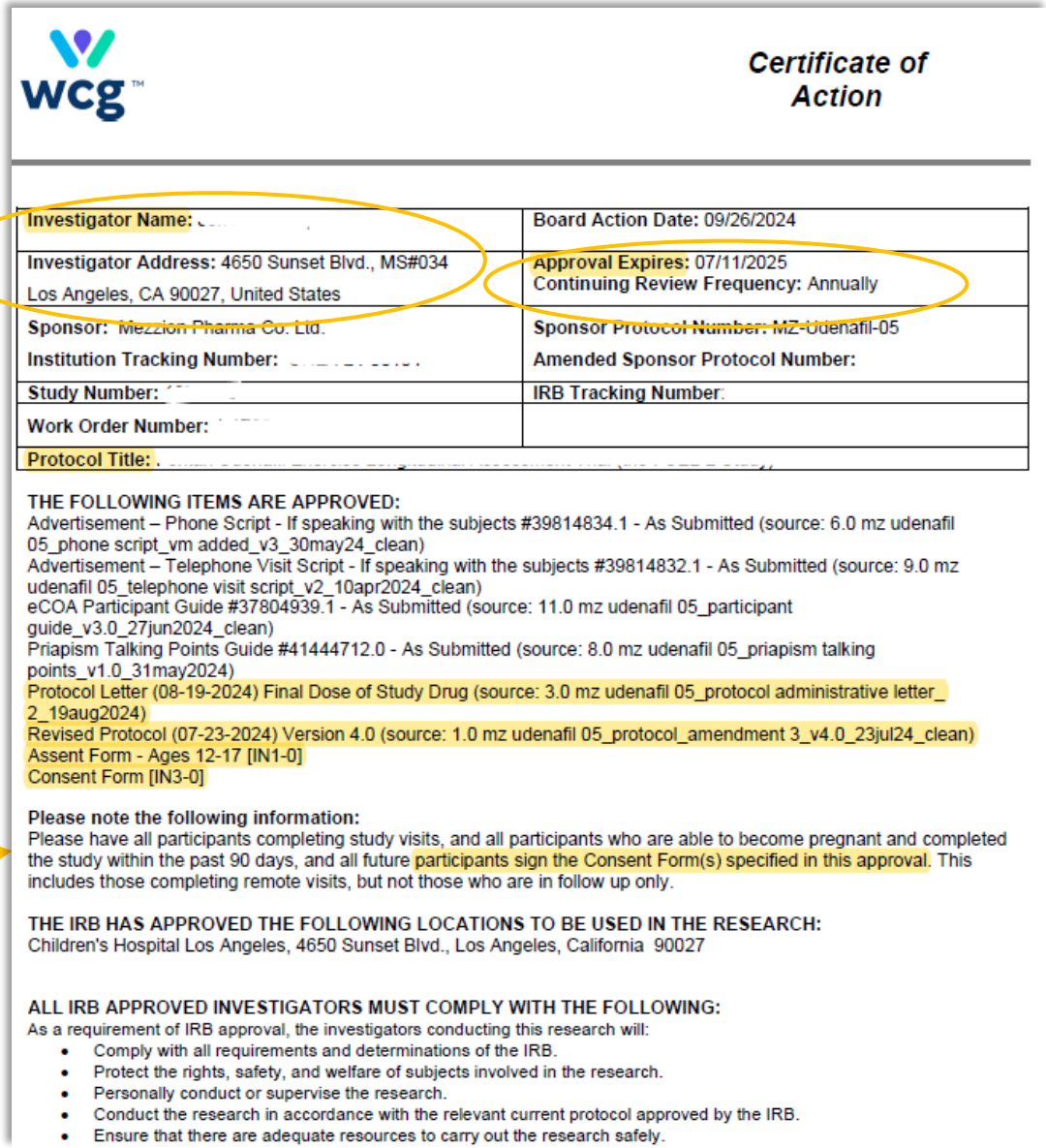
Example: WCG IRB

Specifies approved documents:

Documents that will be submitted in AM application in iStar:

- ***Protocol letter***
- ***Protocol***
- ***Consent and assent form***

Special notes



wcg™

Certificate of Action

Investigator Name:	**Board Action Date:** 09/26/2024
Investigator Address: 4650 Sunset Blvd., MS#034 Los Angeles, CA 90027, United States	**Approval Expires:** 07/11/2025 **Continuing Review Frequency:** Annually
Sponsor: Mezzion Pharma Co. Ltd. **Institution Tracking Number:**	**Sponsor Protocol Number:** MZ-Udenafil-05 **Amended Sponsor Protocol Number:**
Study Number:	**IRB Tracking Number:**
Work Order Number:	
Protocol Title:	

THE FOLLOWING ITEMS ARE APPROVED:
Advertisement – Phone Script - If speaking with the subjects #39814834.1 - As Submitted (source: 6.0 mz udenafil 05_phone script_vm added_v3_30may24_clean)
Advertisement – Telephone Visit Script - If speaking with the subjects #39814832.1 - As Submitted (source: 9.0 mz udenafil 05_telephone visit script_v2_10apr2024_clean)
eCOA Participant Guide #37804939.1 - As Submitted (source: 11.0 mz udenafil 05_participant guide_v3.0_27jun2024_clean)
Priapism Talking Points Guide #41444712.0 - As Submitted (source: 8.0 mz udenafil 05_priapism talking points_v1.0_31may2024)
Protocol Letter (08-19-2024) Final Dose of Study Drug (source: 3.0 mz udenafil 05_protocol administrative letter_2_19aug2024)
Revised Protocol (07-23-2024) Version 4.0 (source: 1.0 mz udenafil 05_protocol_amendment 3_v4.0_23jul24_clean)
Assent Form - Ages 12-17 [IN1-0]
Consent Form [IN3-0]

Please note the following information:
Please have all participants completing study visits, and all participants who are able to become pregnant and completed the study within the past 90 days, and all future participants sign the Consent Form(s) specified in this approval. This includes those completing remote visits, but not those who are in follow up only.

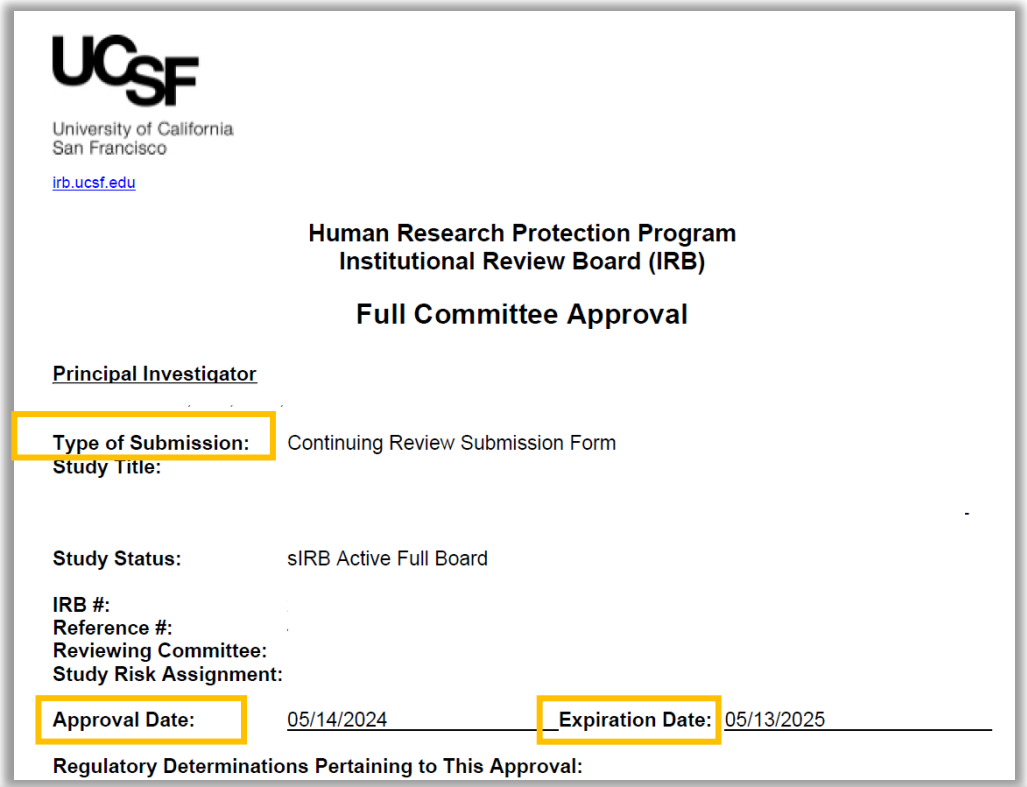
THE IRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:
Children's Hospital Los Angeles, 4650 Sunset Blvd., Los Angeles, California 90027

ALL IRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:
As a requirement of IRB approval, the investigators conducting this research will:

- Comply with all requirements and determinations of the IRB.
- Protect the rights, safety, and welfare of subjects involved in the research.
- Personally conduct or supervise the research.
- Conduct the research in accordance with the relevant current protocol approved by the IRB.
- Ensure that there are adequate resources to carry out the research safely.

Example: UCSF IRB

- Approval letter can be lengthy. In this example, page 4 contains four of the 15 IRB approved CHLA-specific Consent Forms.
- Some IRBs will stamp consent and assent forms with new approval and expiration dates at CR.
- Some approval letter contains minimal information.



UCSF

University of California
San Francisco

irb.ucsf.edu

Human Research Protection Program
Institutional Review Board (IRB)

Full Committee Approval

Principal Investigator

Type of Submission: Continuing Review Submission Form
Study Title:

Study Status: sIRB Active Full Board

IRB #:
Reference #:
Reviewing Committee:
Study Risk Assignment:

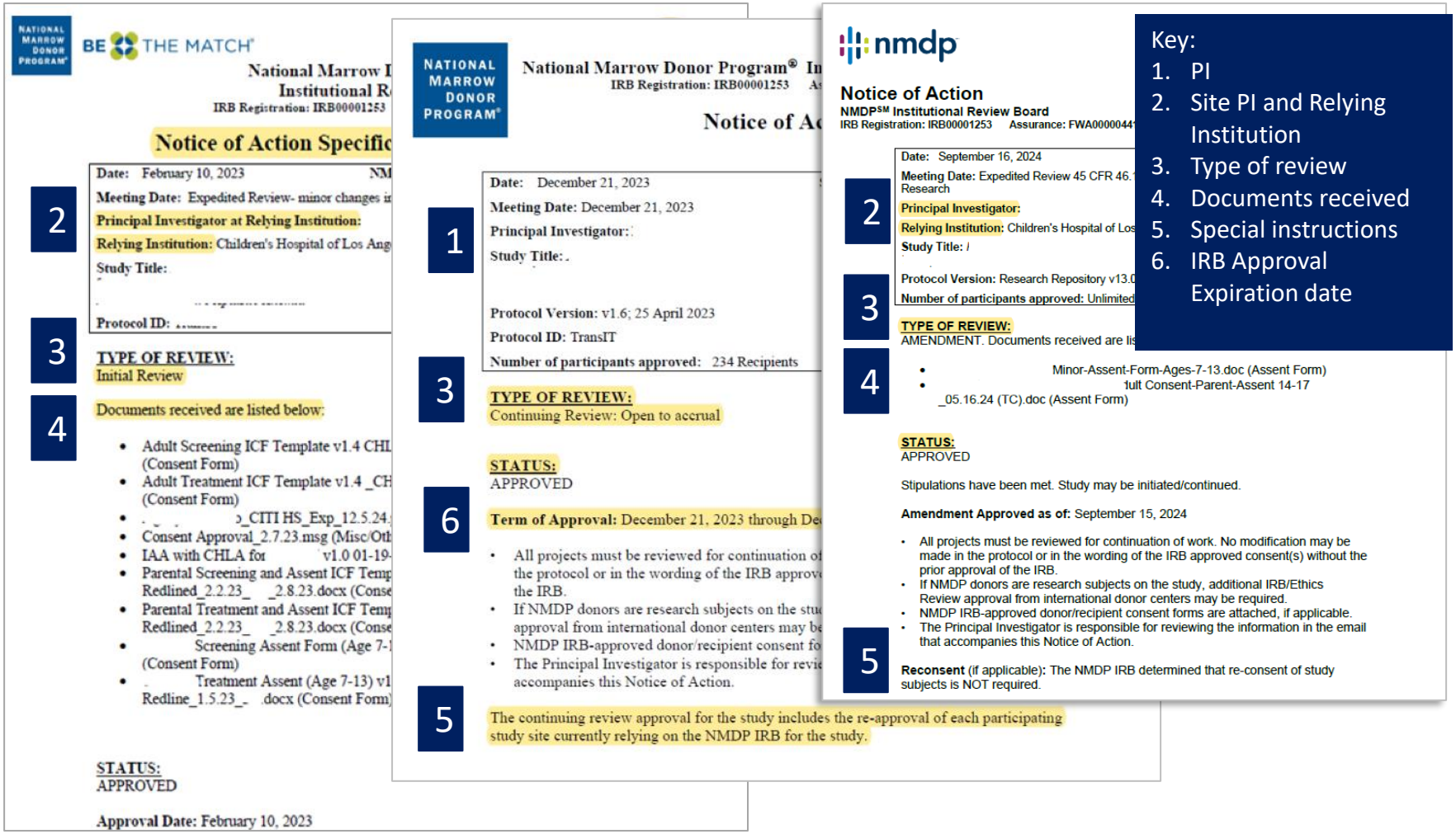
Approval Date: 05/14/2024 **Expiration Date:** 05/13/2025

Regulatory Determinations Pertaining to This Approval:

	HMH_PNOC022 CC 200821_Tx_ ICF_Cohort 4 MP_30Jan2024	Version 1.1	01/30/2024	Approved
	~~HMH_PNOC022 CC 200821_Tx_ ICF_Cohort 4 AA_30Jan2024~~	~~Version 1.1~~	~~01/30/2024~~	~~Approved~~
	CHLA PNOC022 CC 200821_ ICF_Cohort_5 MP_30Jan2024.	Version 1.1	01/30/2024	Approved
	CHLA_PNOC022 CC 200821_ ICF_Cohort_5 AA_30Jan2024	Version 1.1	01/30/2024	Approved
	CHLA_PNOC022 CC 200821_Tx_ ICF_Cohort 4 MP_30Jan2024	Version 1.1	01/30/2024	Approved
	CHLA _PNOC022 CC 200821_Tx_ ICF_Cohort 4 AA_30Jan2024	Version 1.1	01/30/2024	Approved
	WUSTL_PNOC022 CC 200821_ ICF_Cohort_5 MP_30Jan2024	Version 1.1	01/30/2024	Approved
	WUSTL_PNOC022 CC 200821_ ICF_Cohort_5 AA_30Jan2024	Version 1.1	01/30/2024	Approved
	WUSTL_PNOC022 CC 200821_Tx_ ICF_Cohort 4 MP_30Jan2024	Version 1.1	01/30/2024	Approved
	WUSTL_PNOC022 CC 200821_Tx_ ICF_Cohort 4 AA_30Jan2024	Version 1.1	01/30/2024	Approved
	UCSD-RCHSD_PNOC022 CC 200821_ ICF_Cohort_5 MP_30Jan202	Version 1.1	01/30/2024	Approved

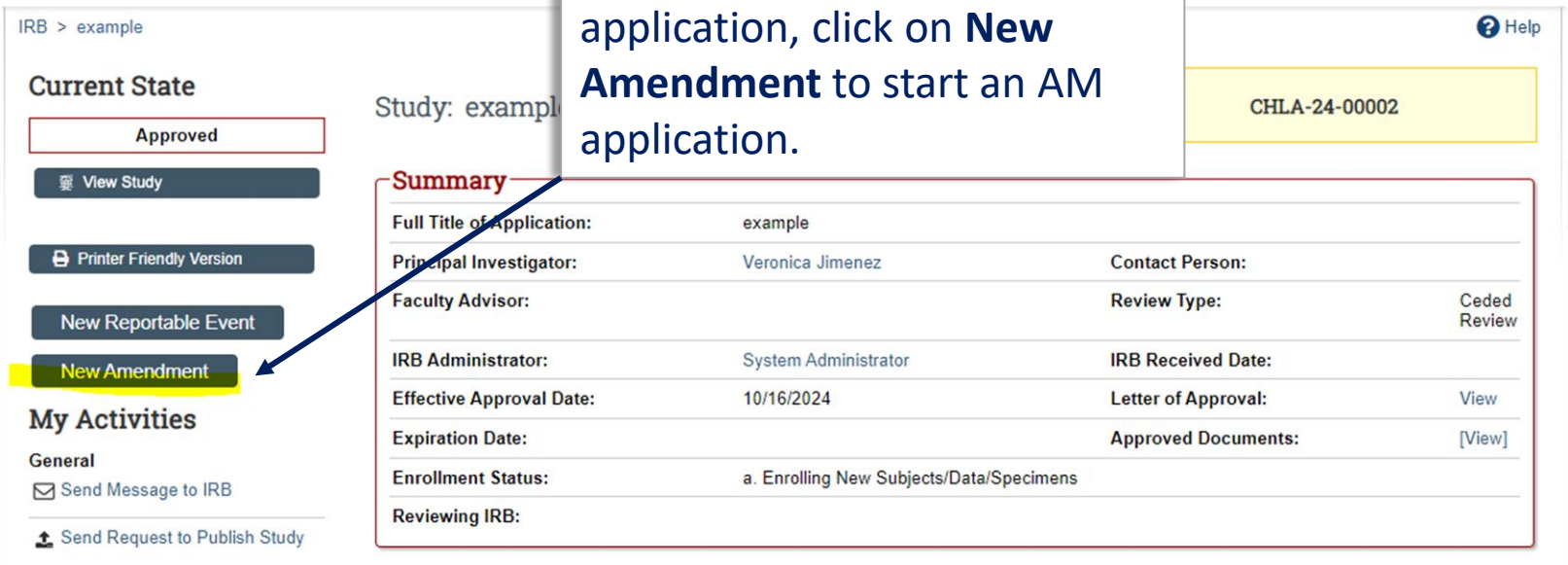
Children's Hospital LOS ANGELES

Example: NMDP IRB

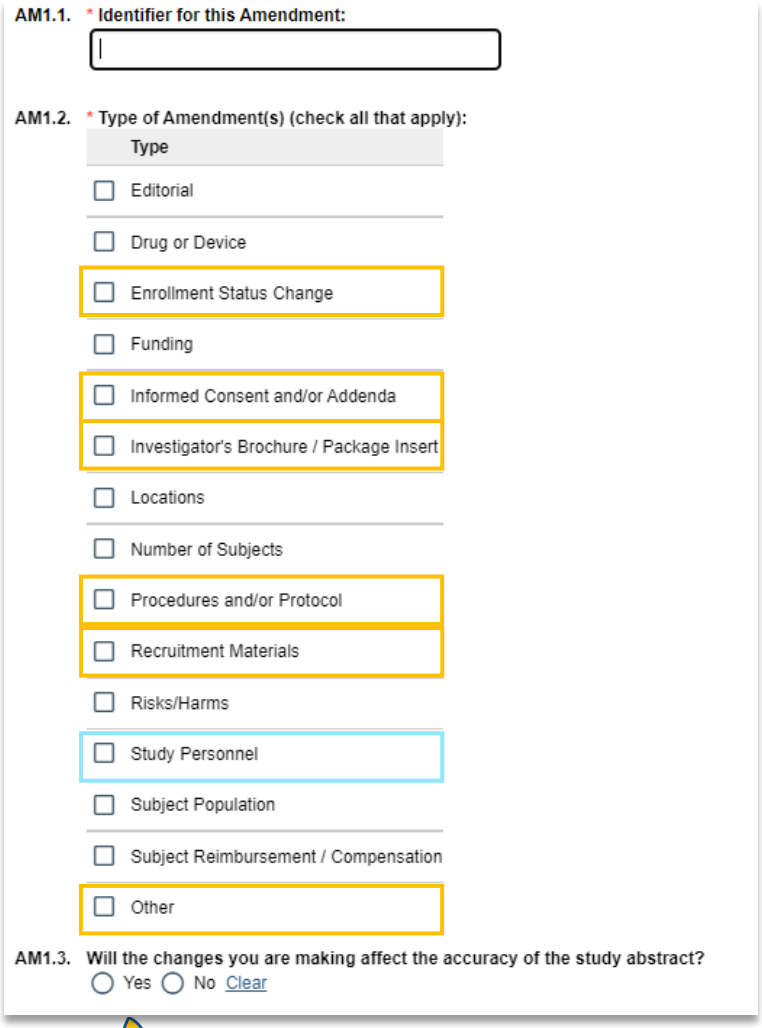


Creating an AM application in iStar

From the initial study application, click on **New Amendment** to start an AM application.



Type of Amendment



AM1.1. * Identifier for this Amendment:

AM1.2. * Type of Amendment(s) (check all that apply):

Type
☐ Editorial
☐ Drug or Device
☐ Enrollment Status Change
☐ Funding
☐ Informed Consent and/or Addenda
☐ Investigator's Brochure / Package Insert
☐ Locations
☐ Number of Subjects
☐ Procedures and/or Protocol
☐ Recruitment Materials
☐ Risks/Harms
☐ Study Personnel
☐ Subject Population
☐ Subject Reimbursement / Compensation
☐ Other

AM1.3. Will the changes you are making affect the accuracy of the study abstract?
○ Yes ○ No Clear

- Common type of amendments for ceded applications.
- The response to item AM1.2 usually depends on the IRB Approval letter.
- Change in study personnel is typically initiated by CHLA.

IRB Approval Letter determines response to AM1.2

AM1.2. * Type of Amendment(s) (check all that apply):

Type
☐ Editorial
☐ Drug or Device
☐ Enrollment Status Change
☐ Funding
☐ Informed Consent and/or Addenda
☐ Investigator's Brochure / Package Insert
☐ Locations
☐ Number of Subjects
☐ Procedures and/or Protocol

IRB APPROVED:

Example #1

- Protocol (Version 5.0, Dated 15 Apr 2024)
- Informed Consent and Assent Form (Ages 14-17) (Advarra IRB Approved Version 18 Jun 2024)
- Assent Form (Ages 7-13) (Advarra IRB Approved Version 25 Jun 2024)

AM1.2. * Type of Amendment(s) (check all that apply):

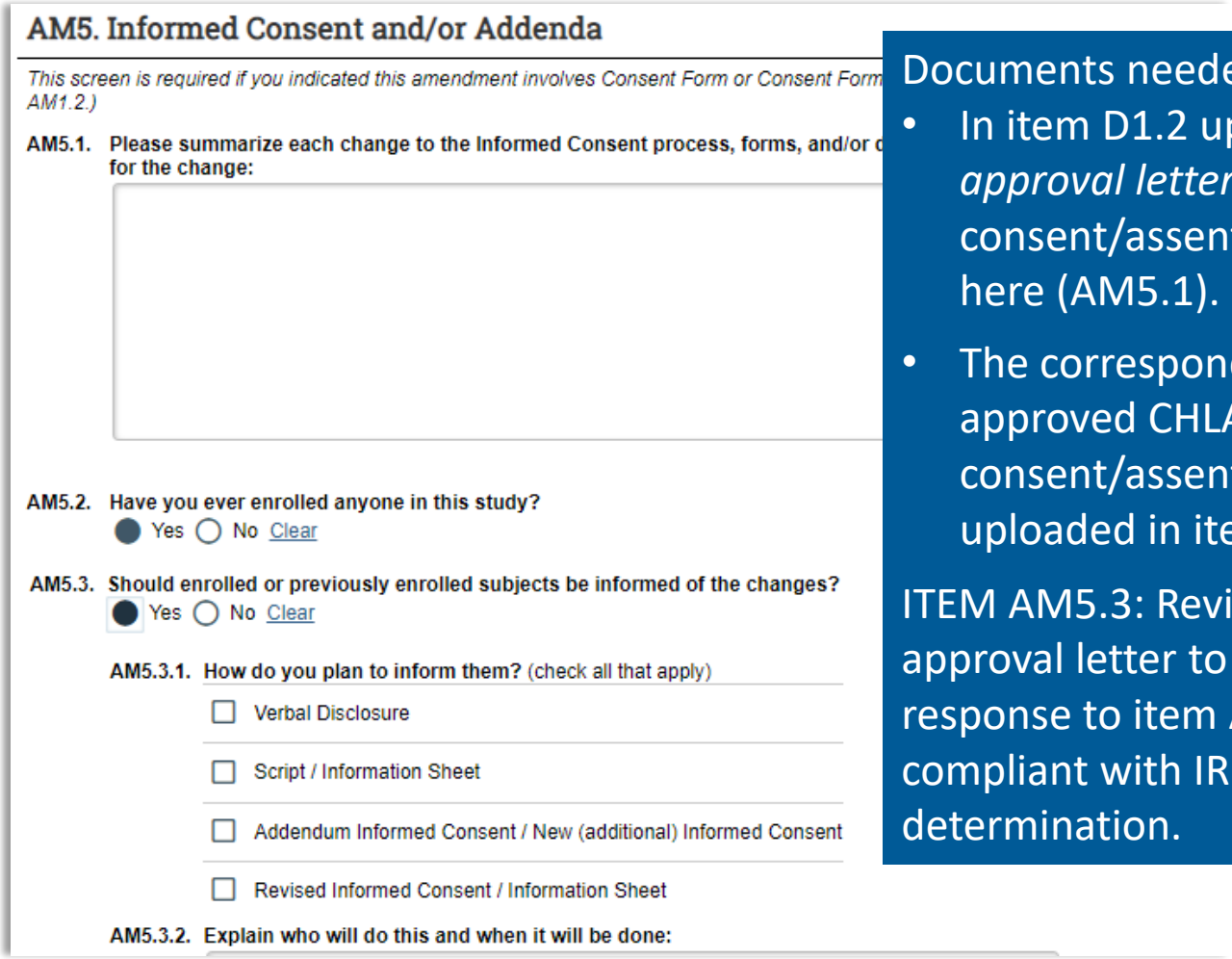
Type
☐ Editorial
☐ Drug or Device
☐ Enrollment Status Change
☐ Funding
☐ Informed Consent and/or Addenda
☐ Investigator's Brochure / Package Insert

IRB APPROVED:

Example #2

- Investigator's Brochure for [redacted] (I [redacted] 1120) (Version 21, Dated 05 Apr 2024)
- Main Informed Consent and Assent Form Ages 14-17 (Advarra IRB Approved Version 29 Jul 2024)

AM5. Informed Consent and/or Addenda



AM5. Informed Consent and/or Addenda

This screen is required if you indicated this amendment involves Consent Form or Consent Form
AM1.2.)

AM5.1. **Please summarize each change to the Informed Consent process, forms, and/or d**
for the change:

AM5.2. **Have you ever enrolled anyone in this study?**
● Yes ○ No Clear

AM5.3. **Should enrolled or previously enrolled subjects be informed of the changes?**
● Yes ○ No Clear

AM5.3.1. **How do you plan to inform them?** (check all that apply)

- ☐ Verbal Disclosure
- ☐ Script / Information Sheet
- ☐ Addendum Informed Consent / New (additional) Informed Consent
- ☐ Revised Informed Consent / Information Sheet

AM5.3.2. **Explain who will do this and when it will be done:**

Documents needed:

- In item D1.2 upload the *IRB approval letter* for the approved consent/assent forms described here (AM5.1).
- The corresponding IRB-approved CHLA-specific consent/assent forms will be uploaded in item 24.7.

ITEM AM5.3: Review the IRB approval letter to ensure the response to item AM5.3 is compliant with IRB of Record's determination.

AM5.1 – First Approval

- If submitting IRB approved consent and/or assent forms for the *first time*, indicate as such.

Examples:

- *"Submitting site approval and IRB-approved consent forms."*
- *"The study protocol (v4.0 which supersedes v3.4) has been updated to include an observational cohort. The English and Spanish consent form for the observational cohort has been approved and is being submitted. "*
- *"Parent/Youth Assent is being added to the study for a new arm of the study".*
- *"The sub-study consent form is being added to the study as CHLA is now participating in this arm of the study."*

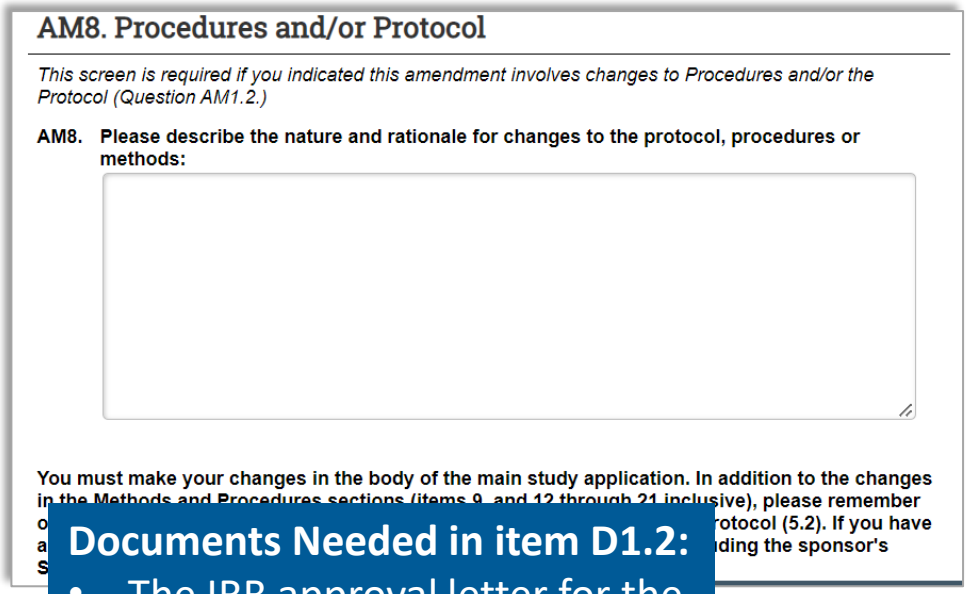
AM5.1 – Revised IRB Approved CHLA-specific Consent and/or Assent Forms

- If submitting ***current revised*** CHLA IRB-approved consent and/or assent forms:
  - Please briefly summarize the major IRB-approved changes
  - Include rationale for changes (e.g., due to protocol change, IB, etc.)
  - Do not provide a detailed description changes
  - Do not state "see summary of changes/ tracked changes document"

  These are consent forms previously cleared for use that have been revised, and revisions have approved by the IRB of record.

  Examples:
  - *"The study is being modified to remove x, y procedures. The consent form is being revised to reflect these protocol changes. Additionally, the ICF is being modified to correct for previous typos and for clarity."*
  - *"Edits were made to the parent ICF and assent form."*

AM8. Procedures and/or Protocol



AM8. Procedures and/or Protocol

This screen is required if you indicated this amendment involves changes to Procedures and/or the Protocol (Question AM1.2.)

AM8. Please describe the nature and rationale for changes to the protocol, procedures or methods:

You must make your changes in the body of the main study application. In addition to the changes in the Methods and Procedures sections (items 9, and 12 through 21 inclusive), please remember o rotocol (5.2). If you have a ding the sponsor's S

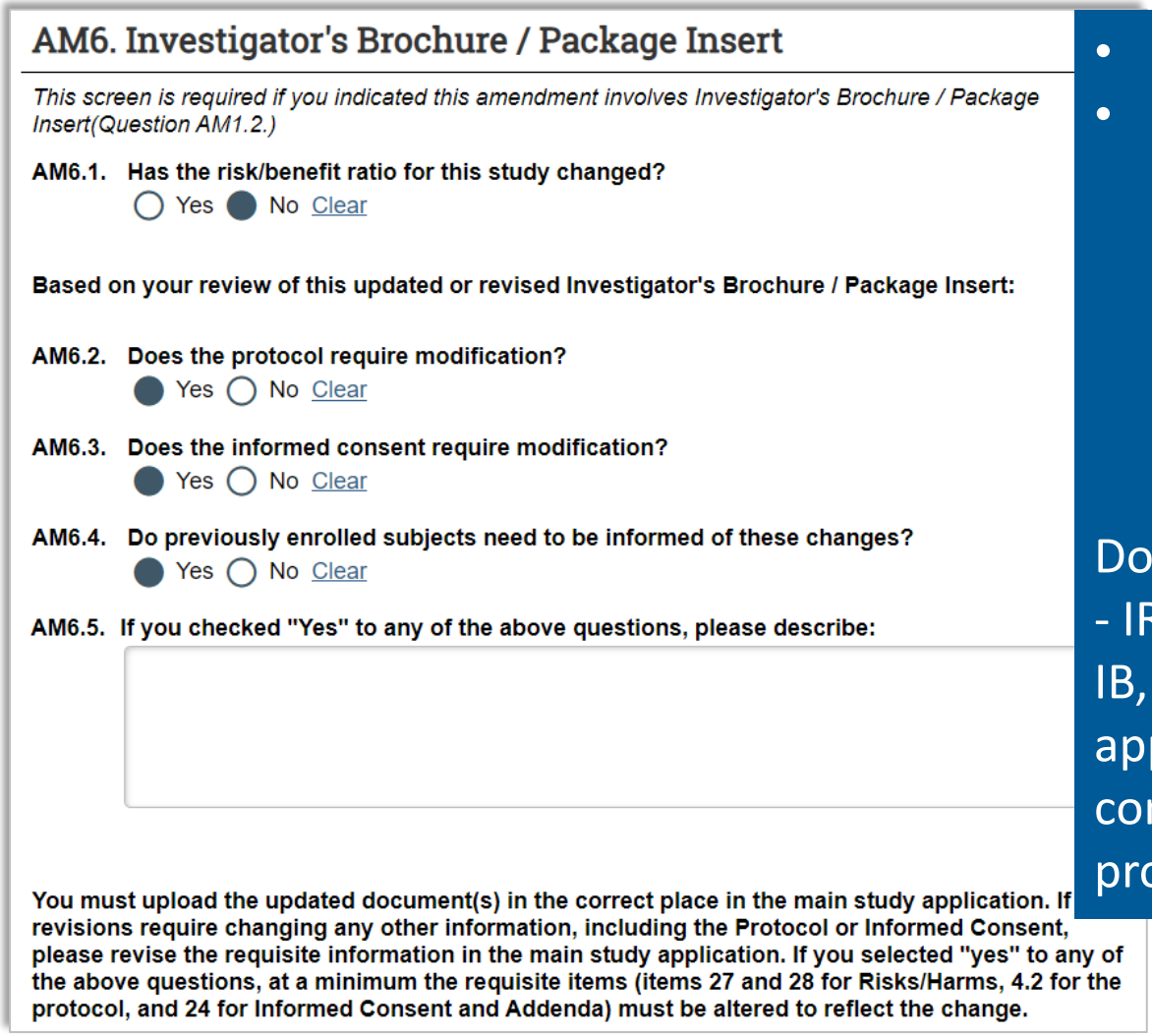
Documents Needed in item D1.2:

- The IRB approval letter for the approved protocol described here (AM8)
- The corresponding IRB approved protocol
- Protocol Summary of Change, if it's not in the protocol (or redlined copy of the protocol)

- Provide a *summary* of the major changes (i.e., added study procedures, new software/data storage location, added questionnaires, etc.)
- Include rationale for changes (e.g., due IB, etc.)
- *Do not* copy and paste from the summary of changes.
- *Do not* state "see summary of changes/redlined document/protocol/etc."

Example response: Protocol amendment v6.0 has recently been approved. The amendment includes both administrative and non-administrative changes. Notably, the exclusion for acute SARS-CoV-2 infection has been removed, while the exclusion for any active respiratory infection causing significant deterioration in respiratory function has been further codified. There is no revised ICF associated with protocol amendment v6.0.

AM6. Investigator's Brochure (IB)



AM6. Investigator's Brochure / Package Insert

This screen is required if you indicated this amendment involves Investigator's Brochure / Package Insert(Question AM1.2.)

AM6.1. Has the risk/benefit ratio for this study changed?

○ Yes ● No Clear

Based on your review of this updated or revised Investigator's Brochure / Package Insert:

AM6.2. Does the protocol require modification?

● Yes ○ No Clear

AM6.3. Does the informed consent require modification?

● Yes ○ No Clear

AM6.4. Do previously enrolled subjects need to be informed of these changes?

● Yes ○ No Clear

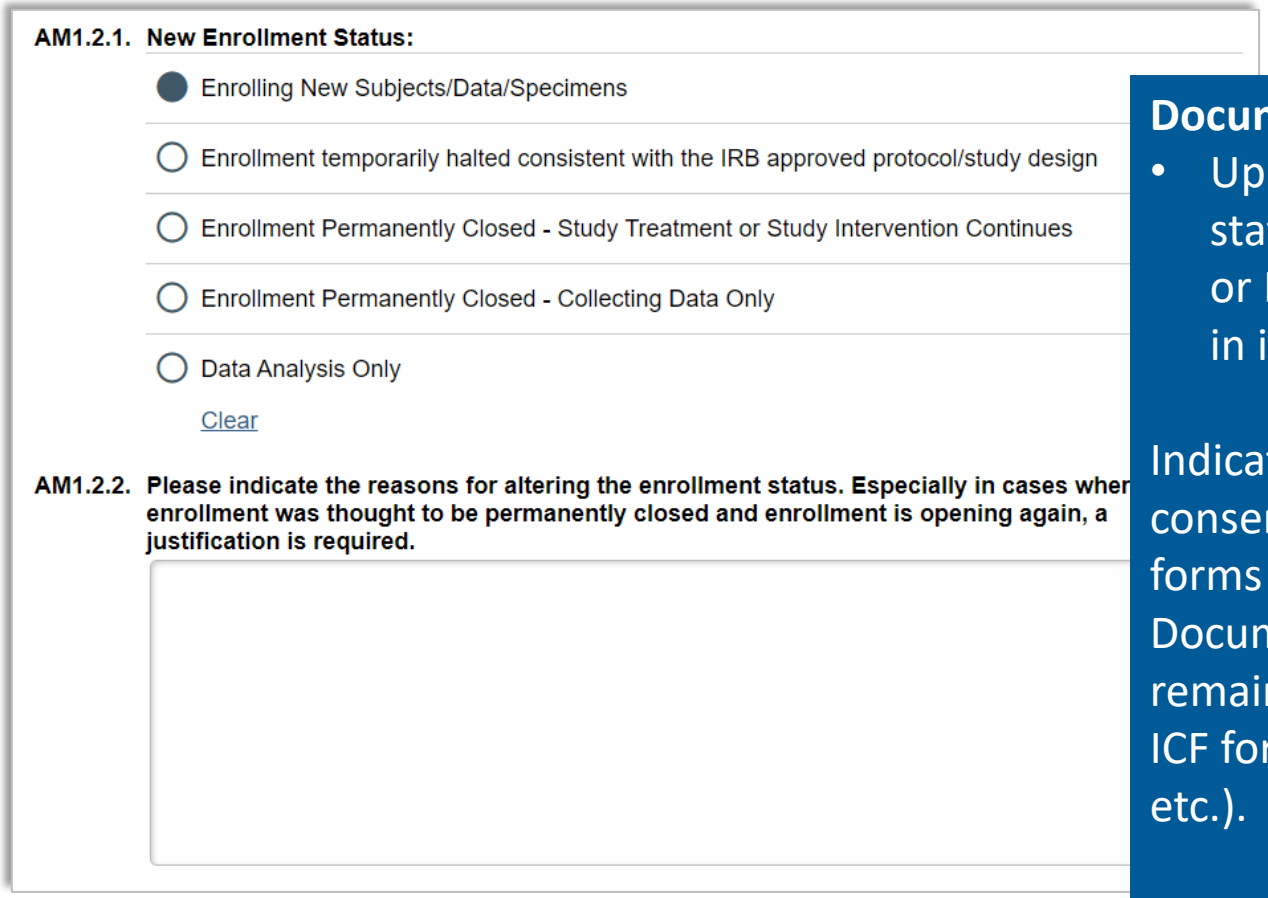
AM6.5. If you checked "Yes" to any of the above questions, please describe:

You must upload the updated document(s) in the correct place in the main study application. If revisions require changing any other information, including the Protocol or Informed Consent, please revise the requisite information in the main study application. If you selected "yes" to any of the above questions, at a minimum the requisite items (items 27 and 28 for Risks/Harms, 4.2 for the protocol, and 24 for Informed Consent and Addenda) must be altered to reflect the change.

- DO NOT submit the IB.
- Refer to the Amendment application submitted to the IRB of Record to provide applicable response to item AM6.

Documents Needed:
- IRB approval letter for IB, and if listed on IRB approval letter revised consent/assent form and protocol

AM1.2.1 New Enrollment Status

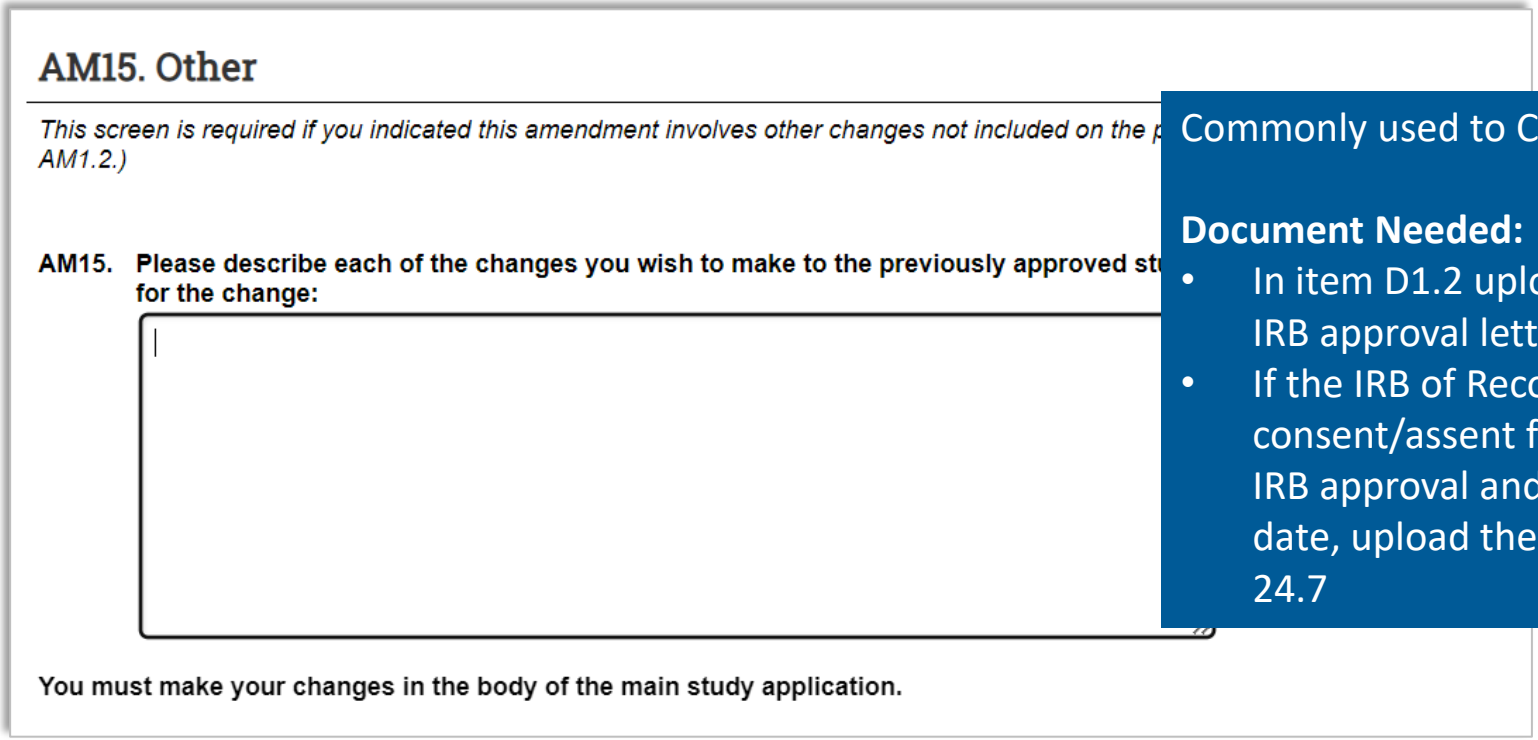


Document Needed:

- Upload the enrollment status change memo or IRB approval letter in item D1.2.

Indicate whether any consent and/or assent forms in Approved Documents should remain active (.e.g., main ICF for reconsent at AOM, etc.).

AM15. Other



Commonly used to CR approval

Document Needed:

- In item D1.2 upload the CR IRB approval letter
- If the IRB of Record stamps consent/assent forms with IRB approval and expiration date, upload them in item 24.7

Uploading Documents

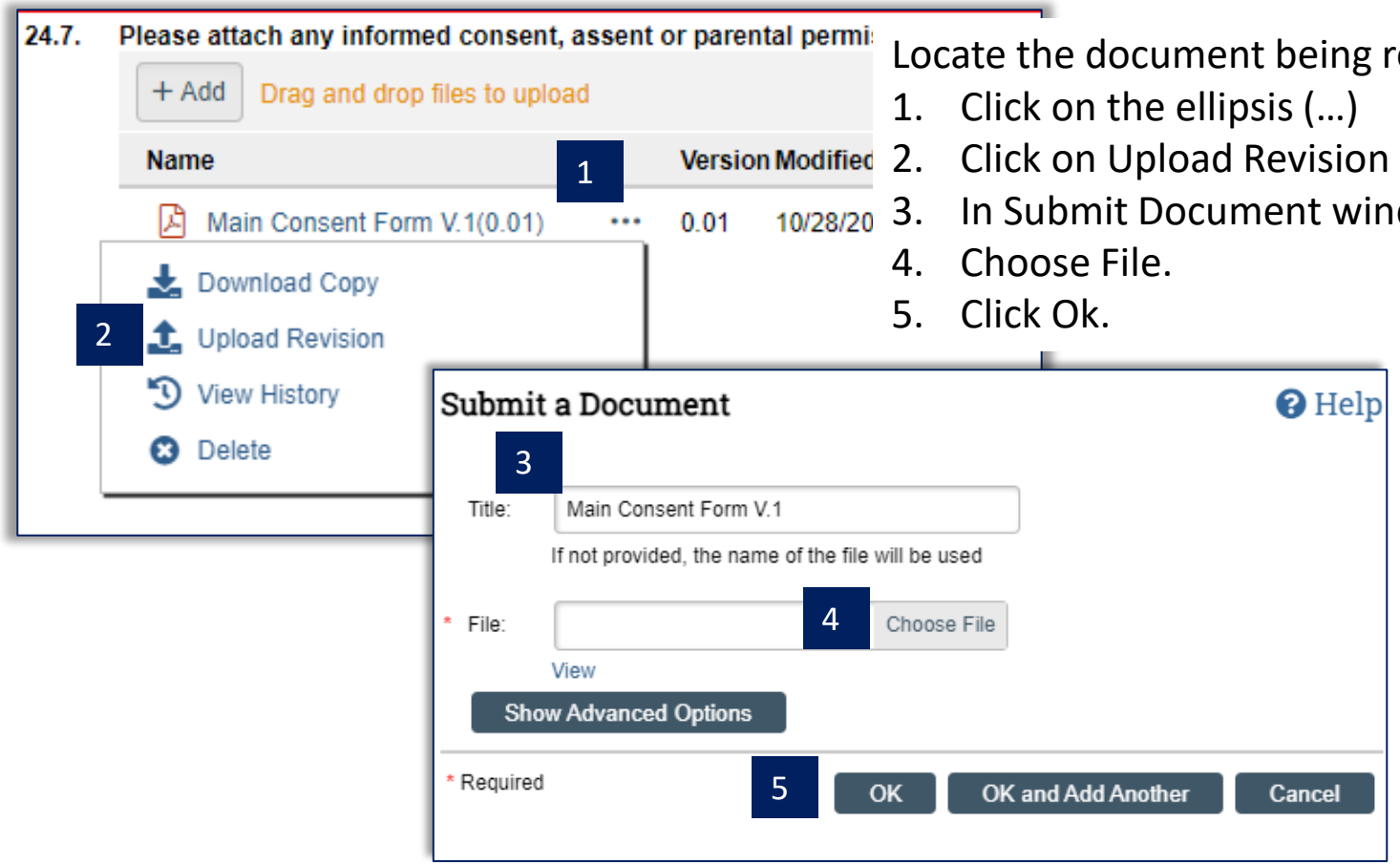
- **Item D1.2 is reserved for:**
  - Correspondences from the reviewing IRB, such as IRB approval letters, acknowledgements, memos, notifications, signed reliance documents, etc.
  - Protocols
  - Consent from templates

These are study devel documents you receive from your sponsor, reviewing IRB, lead site, etc.

- **Item 24.7 is reserved for finalized, IRB-approved CHLA-specific:**
  - consent forms
  - assent forms
  - parental permission forms
  - information sheets

Stacking Documents

When uploading revised documents in items D1.2 and 24.7, please upload them over current documents.



Locate the document being revised.

1. Click on the ellipsis (…)
2. Click on Upload Revision
3. In Submit Document window update Title
4. Choose File.
5. Click Ok.

Example of Stacked Documents

D1.2. Provide the following as they apply to the study:

- **Protocol**
- **Consent Form(s)**
- **Approval letter (if available)**
- **other documents from the reviewing IRB (e.,g. agreement)**

NOTE: When approval from the reviewing IRB is received, submit an amendment to submit the approved protocol, consent forms, and any other approved documents.

editable → editable

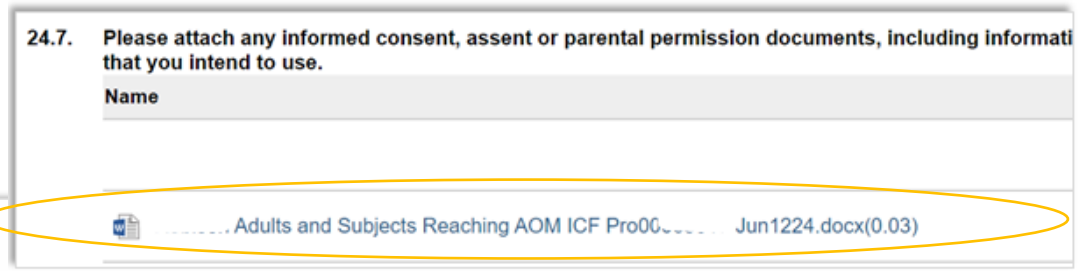
Classify the documents based on document type as you upload them.

Name		Version	Document Type	Modified Date
Advarra Approval Letters(0.04)	•••	0.04		8/22/2024 11:58 AM
Protocol v.4 with Tracked Changes(0.03)	•••	0.03		7/2/2024 11:50 AM
Continuing Review 2023(0.02)	•••	0.02		4/4/2024 5:13 PM
Advarra Approval Letter - New PI(0.11)	•••	0.11	IRB Approval	4/4/2024 5:16 PM
Protocol (0.07)	•••	0.07	Protocol	7/2/2024 11:07 AM

Stacking keeps documents organized

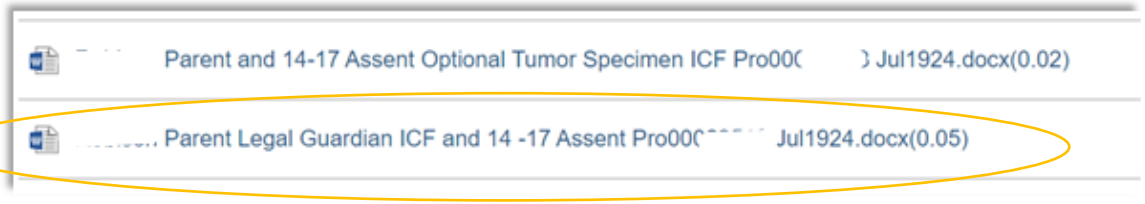
Inconsistent Naming Convention

When the file name of consent/assent forms uploaded in item 24.7 are not consistent with documents listed on the IRB approval letter, please provide naming clarification.



IRB APPROVED:

- Main Informed Consent Form (Advarra IRB Approved Version 12 Jun 2024, Revised 12 Jun 2024)



IRB APPROVED:

- Parent/Legal Guardian Main Informed Consent Form and Assent Form Ages 14-17 (Advarra IRB Approved Version 12 Jun 2024, Revised 19 Jul 2024)

Resources

https://www.chla.org/research/human-subjects-protection-program-hspp-and-institutional-review-board-irb/hspp-ceded-review-checklists-and-forms

HSPP Ceded Review Checklists and Forms

The information below is for relying on an external IRB. There is information, guidance and checklists that must be used to customize sponsor template or lead site consent forms so that they include CHLA specific language.

Ceded Review Workflow

Relying on a Central IRB

- Instructions for Making a Submission to a Central IRB for Industry Sponsored Multi-Center Clinical Trials
- Template Document: Key Information Summary Section for Consent Forms
- Template Document: Disclosure of Financial Conflicts of Interest Statement for Consent Forms
- Reference Document: Advarra IRB Getting Started Guide
- Reference Document: WCG IRB Getting Started Guide
- Reference Document: Sterling IRB SilverLink Getting Started Guide
- Presentation: New Connexus Overview for WCG IRB
- Presentation: Initial Review Submissions to WCG IRB
- Presentation: Managing Studies Approved by WCG IRB
- Advarra IRB Resources
- WCG IRB Resources
- Sterling IRB Resources

Relying on Other External IRBs

- Reliance on Another IRB for Review and Oversight
- External IRB Consent Form Checklist
- NMDP IRB Consent Form Checklist
- NCI CIRB Boilerplate for Consent Forms
- CHLA Institutional Profile Information Sheet (CHLA Local Context)

Contact Us

- IRB **Reliance** Inbox (IRBReliance@chla.usc.edu)
- Veronica Jimenez, Reliance Administrator (vjimenez@chla.usc.edu)
- Liz Stefani, Reliance Administrator (estefani@chla.usc.edu)
- Regulatory Affairs (regulatoryaffairs@chla.usc.edu)
- HSPP / CHLA IRB Inbox (hspp@chla.usc.edu)

Questions?