Version Number: 1	Drafting and Amending of Investigator's Brochures (IB)
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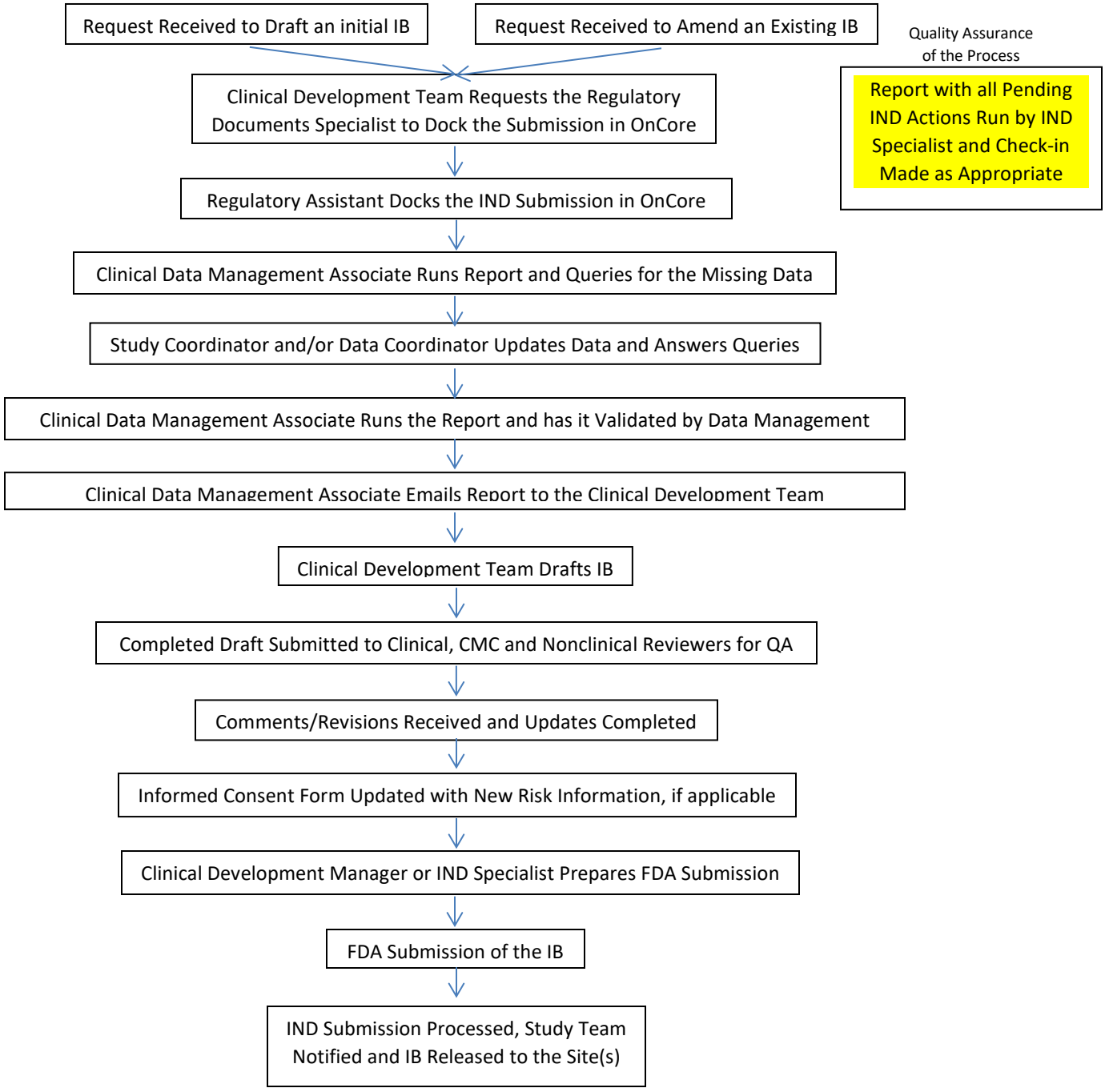

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Contents

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I. Request for an Initial or Updated IB Received

A. Request Received to Draft an Initial IND

The request for the drafting of an initial IND typically comes at the point where an investigational product is being used in a multicenter trial for the first time OR when an investigational product is being used within more than 1 clinical protocol.

It is our standard process to:

- Start drafting an IB if an IP is used in more than 1 protocol
- Finalize an IB prior to making a study multicenter

These request should be made to the Clinical Development Manager or should be made by the Clinical Development Manager.

The Medical Monitor with the aid of the Clinical Development Manager determines:

- The necessity of an initial IB
- The timeline for finalization of the IB

B. Request Received to Amend an Existing IB

An IB may be amended due to a developing safety profile OR is amended on an annual basis.

The Clinical Development Manager ensures that IBs are amended about every 12 months per GCP recommendations.

This is ensured by putting a recurring calendar reminder invite on the LCCC_IND calendar, to remind the Clinical Development Manager that it is time for the annual IB update.

Helpful Hint: It is nice to match the timing of IB updates with IND annual reports as a result of the annual reports containing much of the same data as is included in an IB.

Expedited Updates

Updates may occur more frequently than annually due to new safety information requiring distribution to investigators. Typically, IND safety reports include this information, but there may be occasions where an IB update may additionally be helpful. Additionally, the DSMC may request an IB update.

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II. Clinical Development Team Requests the Regulatory Documents Specialist to Dock the Submission in OnCore

The member of the Clinical Development Team delegated the responsibility of drafting the new or amended IB completes the following:

The email should include the following:

- In reference to the FDA submission:
  - Protocol #
  - Request to dock a FDA action
  - Action Type: Information Amendment
  - Brief description of the submission
    - Serial Submission #
    - Information Amendment- Clinical
    - IB Submission (with the version date of the IB, if available)

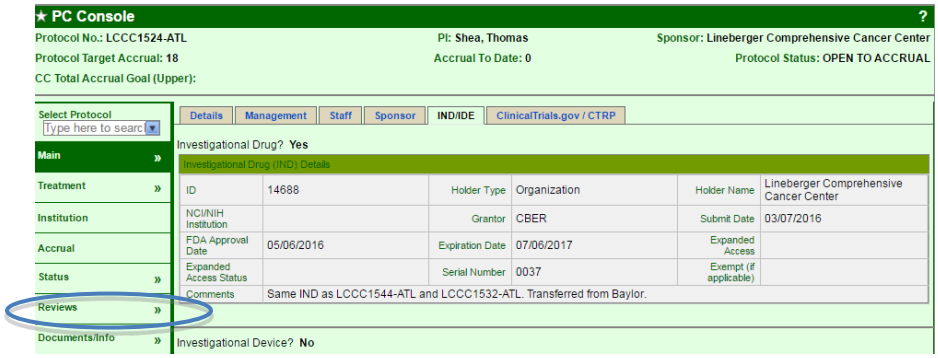
III. Regulatory Assistant Docks the IND Submission in OnCore

The Regulatory Assistant Docks the Submission using the Below Instructions.

Please Note: *If there is more than 1 protocol under an IND then this action should be docked under all protocols, not just the one being updated. These instructions can be sent in one or multiple emails.*

Regulatory Documents Specialist (or in his/her absence the Disease Group Regulatory Assistant) Completes the Following:

- Enters the Submission into Oncore- Other External Committee Actions
  - Click on Reviews



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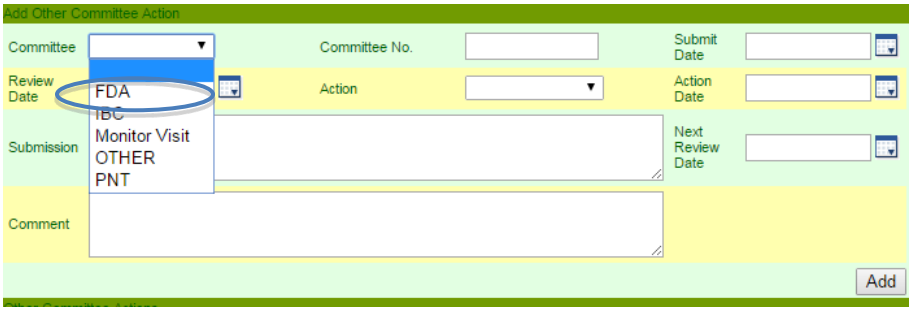
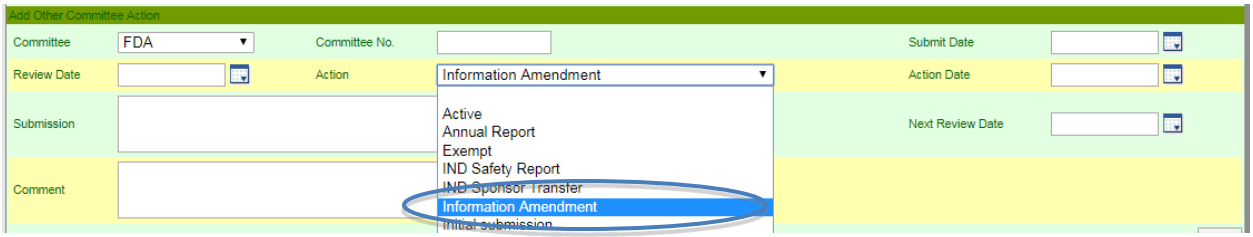
- Click on Other External Committee Actions

- Click Update

- Select FDA as the committee



- Select IND Action- Information Amendment



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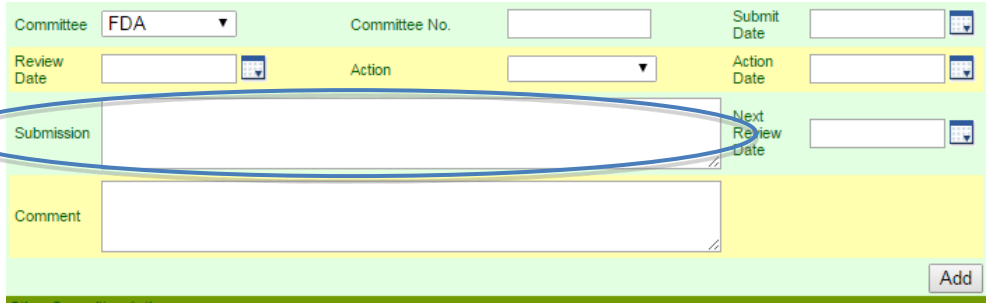
- Enter the brief description of the IND submission in the Submission box
  - This description should be written as follows: "Serial Submission XXXX- Information Amendment- Clinical"



- Enters the description of the submission: "Included: Investigator's Brochure dated MM/DD/YYYY"

IV. Clinical Data Management Associate Runs Report and Queries for the Missing Data

Example of the queries that they issue:

Data resources, June 2016							
OnCore Demographic					ss_001v21 form		
SeqNum	Hospital	Status	FU Death Date	Off Study Date	Survival Status	Death Date	Cause of Death
101	UNC-CH	EXPIRED	3/27/2013	2/17/2013		.	
102	UNC-CH	EXPIRED	7/17/2015	7/17/2015		.	

Data resources: AdverseEvent2V21 form							
SeqNum	Hospital	Toxicity	Cycle of Onset	Grade	Onset Date	Attribution	Serious
101	UNC-CH	Back Pain	.	1	12/12/2015	Unrelated	No
104	UNC-CH	Dyspnea	.	1	7/1/2013	Probable	No

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V. Study Coordinator and/or Data Coordinator Updates Data and Answers Queries

The Study Coordinator has 2 weeks to address the queries. The Clinical Data Management Associate provides a deadline for query resolution.

The Multicenter Project Manager aids in querying the multicenter sites. The multicenter sites update the data and address the queries.

VI. Clinical Data Management Associate Runs IB Report and has it Validated by Data Management

The CDMA runs the IB report within 1 month of the request for the updated data. Prior to distribution, two members of the data management team will review and validate the report for accuracy.

The completed report is distributed to the member of the Clinical Trial Development Team requesting the report.

The report will contain the following tables:

- Incidence of all AEs regardless of attribution
- Incidence of ≥Grade 3 AEs regardless of attribution
- Incidence of all AEs related to the investigational product
- Incidence of ≥Grade 3 AEs related to the investigational product
- All SAEs

If the investigational product is used across more than 1 protocol, then the report will included data for each study alone and the combined incidence across all protocols.

There are 2 formats of tables that will be in the report, as presented below.

Toxicity Category	Toxicity	Combined Count (%) N=36	LCCCXXXX Count (%) N=8	LCCCXXXX Count (%) N=28
Investigations	Activated Partial Thromboplastin Time Prolonged	1 (2.78%)	0(0)	1 (3.57%)
	Alanine Aminotransferase Increased	7 (19.44%)	2 (25.00%)	5 (17.86%)
Metabolism And Nutrition Disorders	Acidosis	1 (2.78%)	0(0)	1 (3.57%)

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				Toxicity Grade				
Toxicity	Count (%) N=36	LCCCXXXX Count (%) N=8	LCCCXXXX Count (%) N=28	1	2	3	4	5
Abdominal Pain	3 (8.33%)	1 (12.50%)	2 (7.14%)	2	.	1	.	.
Acidosis	1 (2.78%)	0(0)	1 (3.57%)	.	.	.	1	.

An example of the SAE table:

Study	Pt #	Toxicity	Tox. Category	Grade	Trt. Type	Start Date	Attribution	DLT	SAE
LCCCXXXX	##	Acidosis	Metabolism And Nutrition Disorders	4	ATL CAR.CD30	08/12/2018	Unlikely	No	Life-threatening
		Acute Kidney Injury	Renal And Urinary Disorders	4	ATL CAR.CD30	08/03/2018	Possible	Yes	Life-threatening

VII. Clinical Data Management Associate Emails Report to the Clinical Development Team

The Clinical Data Management Associate emails the finalized report to the member of the Clinical Development team requesting the report and copies the LCCC_IND@unc.edu email account.

VIII. Clinical Development Team Drafts IB

A member of the Clinical Development Team, typically the Clinical Development Manager, drafts the new or updated Investigator's Brochure.

Several key things to remember:

- Use the LCCC IB Template
  - This template is in eCTD format, so updates should be made in accordance with eCTD formatting requirements.
- Draft changes to the protocol using the Track changes function in Microsoft Word
- Incorporate any IND Safety Reports submitted to FDA since the last IB update
- For amendment to the initial IB, be sure to include a summary of changes

IX. Completed Draft Submitted to Clinical, CMC and Nonclinical Reviewers for QA

The completed draft of the IB is sent to the following individuals for quality assurance:

- Nonclinical reviewer (typically the individual who completed the preclinical animal experiments and is completing any correlative analysis associated with the clinical trial)

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- Clinical reviewer (the Medical Monitor or an individual that he/she delegates to review the IB on his/her behalf)
- CMC Reviewer (typically the GMP Director)

Sections of the IB should be marked to help direct the reviewer's QA efforts.

X. Comments/Revisions Received and Updates Completed

The delegated member of the Clinical Development Team who is in charge of drafting/amending the IB makes changes as appropriate to the document.

XI. Informed Consent Form Updated with New Risk Information, if applicable

The Clinical Development Team consult with the Medical Monitor to determine if the consent form(s) for the applicable study(ies) require updates to capture new or developing risk information.

The consent form(s) are updated per standard office practice.

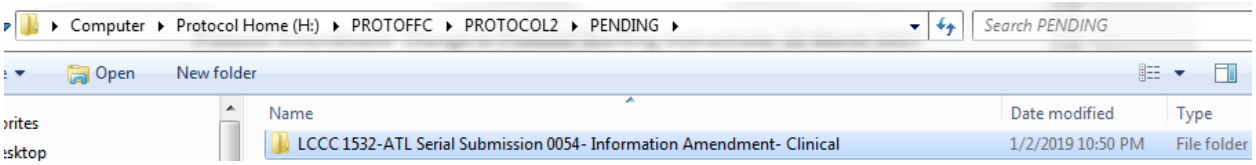
XII. Clinical Development Manager or IND Specialist Prepares FDA Submission

Either the Clinical Development Manager (if the author of the IB) or the IND Specialist (if delegated by the Clinical Development Manager) may complete the FDA submission.

The Clinical Development Manager or IND Specialist sets up a folder within the "Pending" folder on the H drive.

The folder should be titled: Serial Submission XXXX Information Amendment- Clinical. Remember the Serial Submission # is sequential and is based upon the # of the previous submission(s).

Example:



You can find the previous serial submission # used in OnCore.

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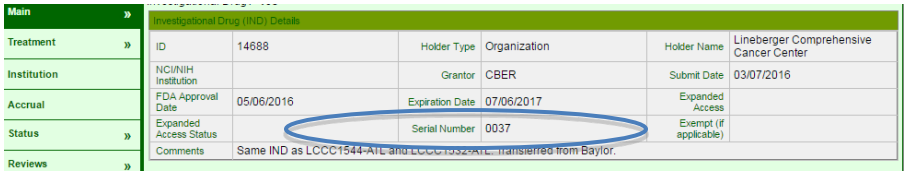
- Remember that you need to increase sequentially by 1 for the current serial submission #. So, for the below example the serial submission # for the protocol amendment would be 0038.

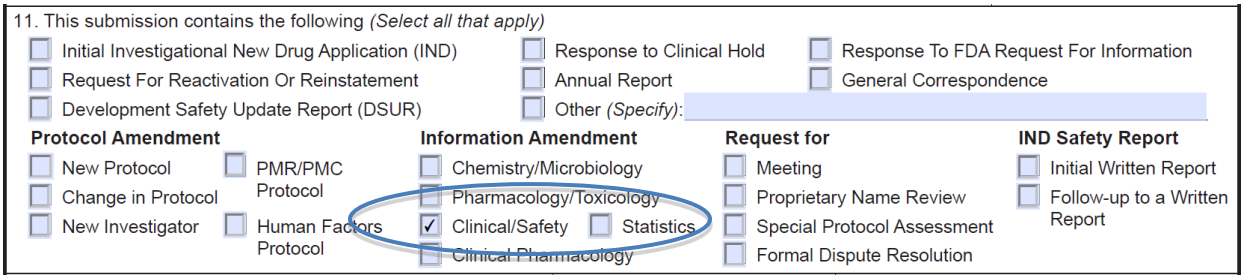


The Clinical Development Manager or IND Specialist prepares Form FDA 1571.

The Form FDA 1571 will be downloaded directly from FDA's website to guarantee the most recent version is used.

As with any time you fill out a Form FDA 1571, don't forget to update the date of submission (box 2) and the serial submission number (box 10).

- In section 11 of the 1571, where you indicate what the serial submission contains (what type of serial submission it is), indicate that it is an Information Amendment- Clinical/Safety



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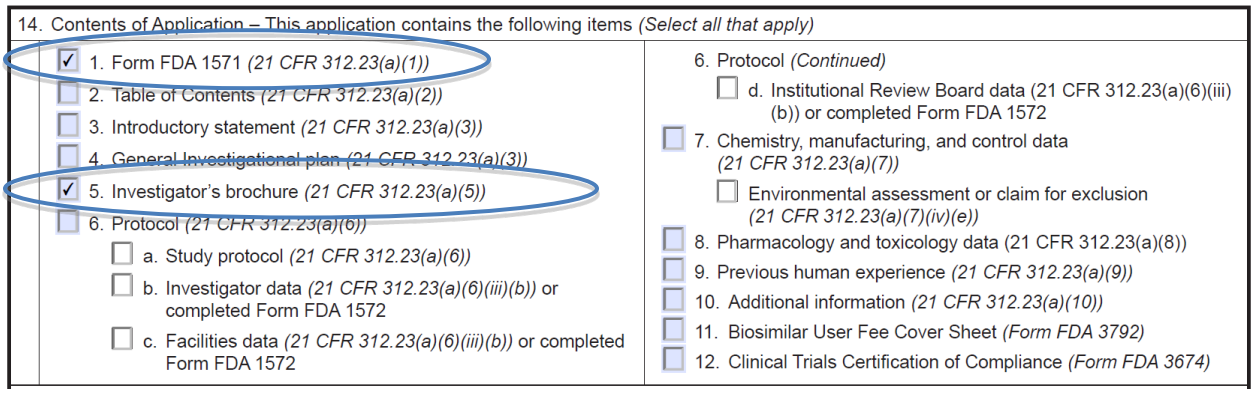
- In section 13 of the 1571, where you indicate what documents are included check:
  - Form FDA 1571
  - Investigator's Brochure


14. Contents of Application – This application contains the following items *(Select all that apply)*

- ☑ 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
- ☐ 2. Table of Contents *(21 CFR 312.23(a)(2))*
- ☐ 3. Introductory statement *(21 CFR 312.23(a)(3))*
- ☐ 4. General investigational plan *(21 CFR 312.23(a)(3))*
- ☑ 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
- ☐ 6. Protocol *(21 CFR 312.23(a)(6))*
  - ☐ a. Study protocol *(21 CFR 312.23(a)(6))*
  - ☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
  - ☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
- 6. Protocol *(Continued)*
  - ☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
  - ☐ Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
- ☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- ☐ 9. Previous human experience *(21 CFR 312.23(a)(9))*
- ☐ 10. Additional information *(21 CFR 312.23(a)(10))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

The Clinical Development Manager or IND Specialist will prepare the Cover Letter to FDA.

The Clinical Development Manager or IND Specialist uses the Updated IB Cover Letter template to prepare the FDA Cover Letter.

Example:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

IND 14688 **Information Amendment- Clinical Investigator's Brochure Update** **Serial 0056**

Dear Ms. Glen:

Please note that the following individuals may act on behalf of the above referenced IND: J. Kaitlin Morrison, PhD, Jonathan Serody, MD, and Shaw Scott. The contact information for these individual is included at the end of this cover letter.

The purpose of this serial submission is to provide FDA with an updated Investigator's Brochure for ATLCAR.CD30 cells. This investigator's brochure update includes the following major changes:

- Updates on two ongoing clinical trials:
  - LCCC 1524-ATL: Phase 1 Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

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  - LCCC 1532-ATL: Phase Ib/II Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Relapsed/Refractory CD30 Hodgkin's Lymphoma and CD30+ Non-Hodgkin's Lymphoma
- Updated information to reflect the approval of Kymriah™ for relapsed or refractory diffuse large B-cell lymphoma

The submission contains the following documents:

- FDA form 1571
- ATLCAR.CD30 Investigator's Brochure (dated 12/11/2018)

The following individuals may also act on behalf of this IND:

XIII. FDA Submission of the IB

The submission could occur within 10 days of the IB and ICF (if applicable) being finalized.

Formatting requirements:

- All regulatory submissions should be three hole punched on the left side of the page
- The left margin should be at least ¾ of an inch to assure text is not obscured in the fastened area
- US standard paper size (8 ½ by 11 inches) is preferred. However, it may occasionally be necessary to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions. These pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refold without damage when the volume is shelved

Documents that must be collected to compile the submission:

1. **Form FDA 1571:** The Clinical Development Manager or IND Specialist will correct the date on the FDA Form 1571 to reflect the submission date and will acquire the IND PI's signature on this form.
2. **Cover Letter:** The Clinical Development Manager or IND Specialist will correct the date on the IND Cover Letter to reflect the submission date and will acquire the IND PI's signature on the cover letter.
3. **Investigator's Brochure**
4. **Informed Consent Form (if applicable)**
5. **Informed Consent Form Tracked Changed (if applicable)**

Version Number: 1	Drafting and Amending of Investigator's Brochures (IB)
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The documents should be arranged in the following order:

1. Cover Letter
2. Form FDA 1571
3. Investigator's Brochure
4. Informed Consent Form (if applicable)
5. Informed Consent Form Tracked Changed (if applicable)

Please note: All sections should be marked by tabs.

The submission should be bound in the following way (this part typically completed by CPO Administrative Assistant):

Once the documents are arranged in the proper order, make 3 copies of the packet.

Recommendation: The copier has a setting that will allow you to copy and 3-hole punch at the same time; this will save you some time.

Hole punch the original packet and bind it in a gray ACCO binder. Please note that the binder clip clasps in the inside of the binder, not the outside.

There should be 4 total copies of the IND submission bound in the following colors:

- Gray- Original copy with wet-ink signatures for FDA
- Red- First reviewer copy for FDA
- Color of your choice besides gray or red- 2nd reviewer copy for FDA
- Black- File copy. This stays in LCCC files and is filed under "IND Submissions"

ACCO binders with the protocol amendment and/or IND transfer should be labeled in the following way:

INDXXXX
Name of investigational product(s)
LCCCXXXX
Information Amendment- Clinical
Copy X of 3 OR File Copy

An Electronic PDF copy of the entire submission should be made and saved to the "Pending" folder in the H drive. Please make sure that the PDF is made using the signed documents.

- Note: you only need to scan documents that were signed the rest of the documents may just be combined using Adobe Acrobat Pro.

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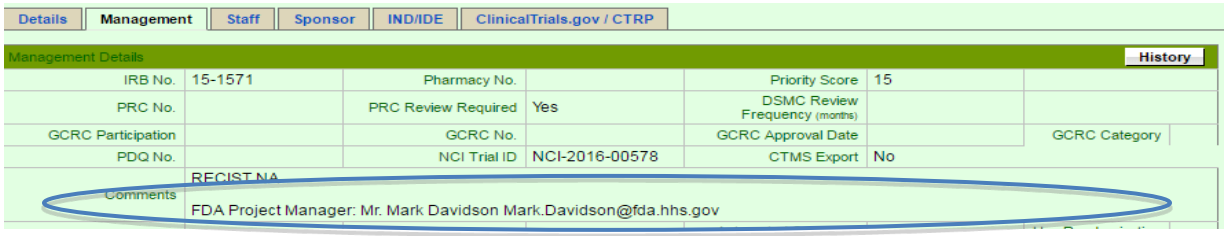
The IND submission should be shipped via FedEx to the FDA Central Document Room:

CDER

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
ATTN: [Insert Name of Project Manager- listed in the Management Screen in OnCore]

Project Manager:



CBER

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
Building 71, Room G112
Silver Spring, MD 20993-0002

Please note: for CBER submissions staff names should NOT be placed on the document packaging or envelope address.

Please note: Never ship more than one submission together. Each FDA shipment should be boxed and shipped separately!

The *SIGNED* FedEx receipt should be saved on the H drive and printed once FDA receives the submission. The printed copy should be included in the bound black file copy of the FDA submission.

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XIV. IND Submission Processed, Study Team Notified and IB Released to the Sites

Clinical Development Manager or IND Specialist Distributes the Completed IB and Updated ICF (if applicable) to the study's Regulatory Associate. If the study is multicenter, the completed documents are distributed to the Multicenter Regulatory Associate for distribution to all sites including UNC.

Clinical Development Manager or IND Specialist Completes the Following:

- Cleans up the H Drive folder. The Folder should include:
  - The Electronic (PDF) copy of the serial submission
  - Any IB, ICFs, FDA Forms, etc. included in the submission
- Give the following to the Regulatory Assistant:
  - Bound, completed, file copy of the serial submission (with FedEx receipt inside)
  - Completed flow sheet
  - Paper folder

Regulatory Assistant Completes the Following:

- Updates the Serial Number to the Serial Submission Number of the protocol amendment submission

- Enters the Submission into Oncore
  - Click on Reviews

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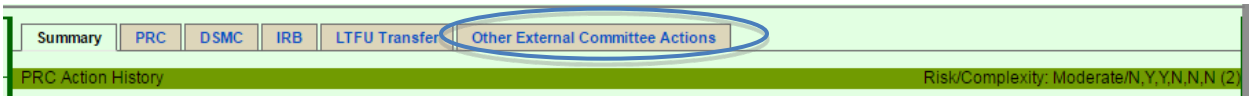
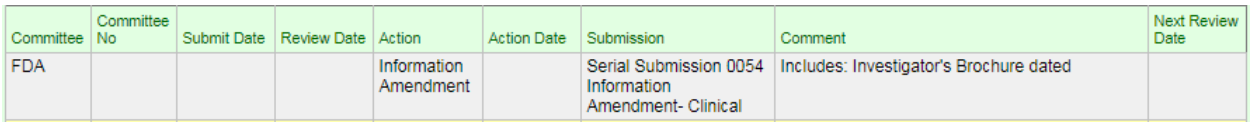
- Click on Other External Committee Actions

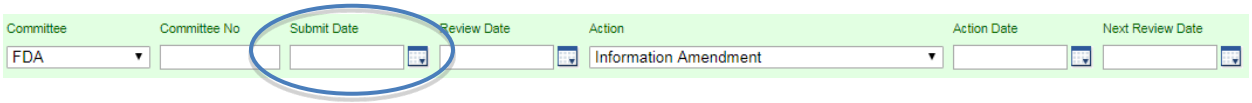


- Click Update and choose the docked serial submission

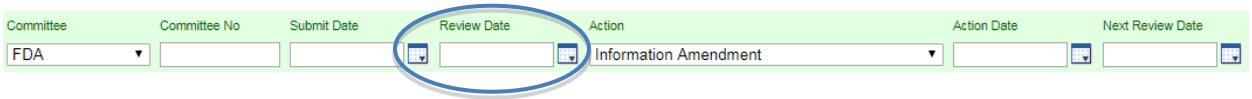


Committee	Committee No	Submit Date	Review Date	Action	Action Date	Submission	Comment	Next Review Date
FDA				Information Amendment		Serial Submission 0054 Information Amendment- Clinical	Includes: Investigator's Brochure dated	

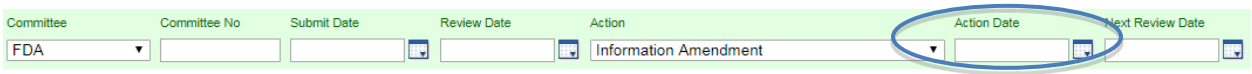
- Go to the previously docked FDA action
- Enter the submit date as the date that the IND submission was shipped- This will be written on the flowsheet



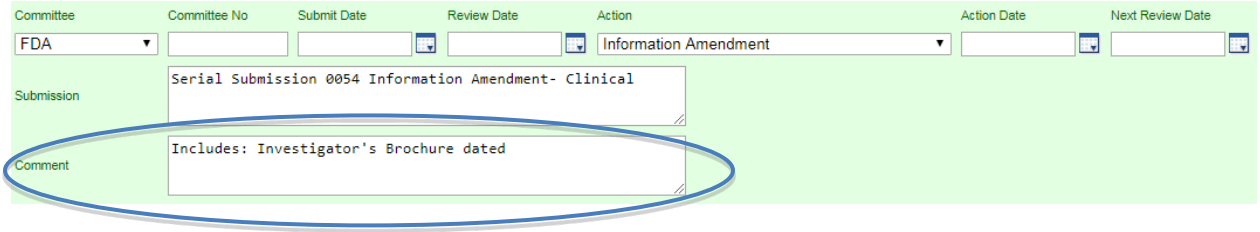
- Enter the review date as the date that the IND transfer and/or protocol amendment was received- This will be written on the flowsheet



- Enter the FDA Receipt Date as the Action Date



- Enter the documents submitted and a brief summary of the submission in the submission description box.
  - For example: Addition of Jared Weiss as a Sub-Investigator



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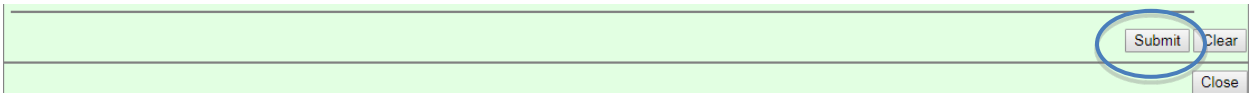
- Click Submit



- It should look something like this when complete

Committee	Committee No	Submit Date	Review Date	Action	Action Date	Submission	Comment	Next Review Date
FDA		01/01/2019	01/02/2019	Information Amendment	01/02/2019	Serial Submission 0054 Information Amendment- Clinical	Includes: Investigator's Brochure dated	

- Moves the entire "Pending" subfolder folder (as is) into the IND folder on the H Drive
- Files the paper file copy of the IND Transfer and/or Protocol Amendment in the Regulatory paper files FDA folder
- Returns the flow sheet to the Regulatory Associate for QA of values entered into OnCore

Regulatory Associate Completes the Following:

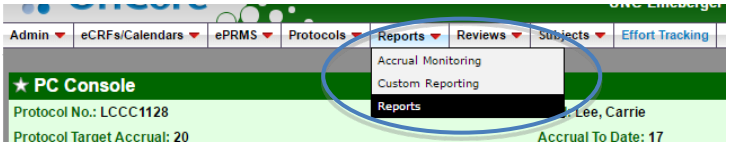
- QAs the IND Serial Submission # in OnCore
- QAs the other committee review entry

Please note: This process should be completed within 1 week of FDA receiving the submission.

XV. Report of All Pending IND Actions Run by IND Specialist and Check-in Made as Appropriate

The IND Specialist will periodically run an "Other External Committee Actions" lapse report to check on the status of any pending docked IND submissions.

- Clicks on reports and selects reports:



- Selects "External Committee Lapse Report" under Quality Assurance