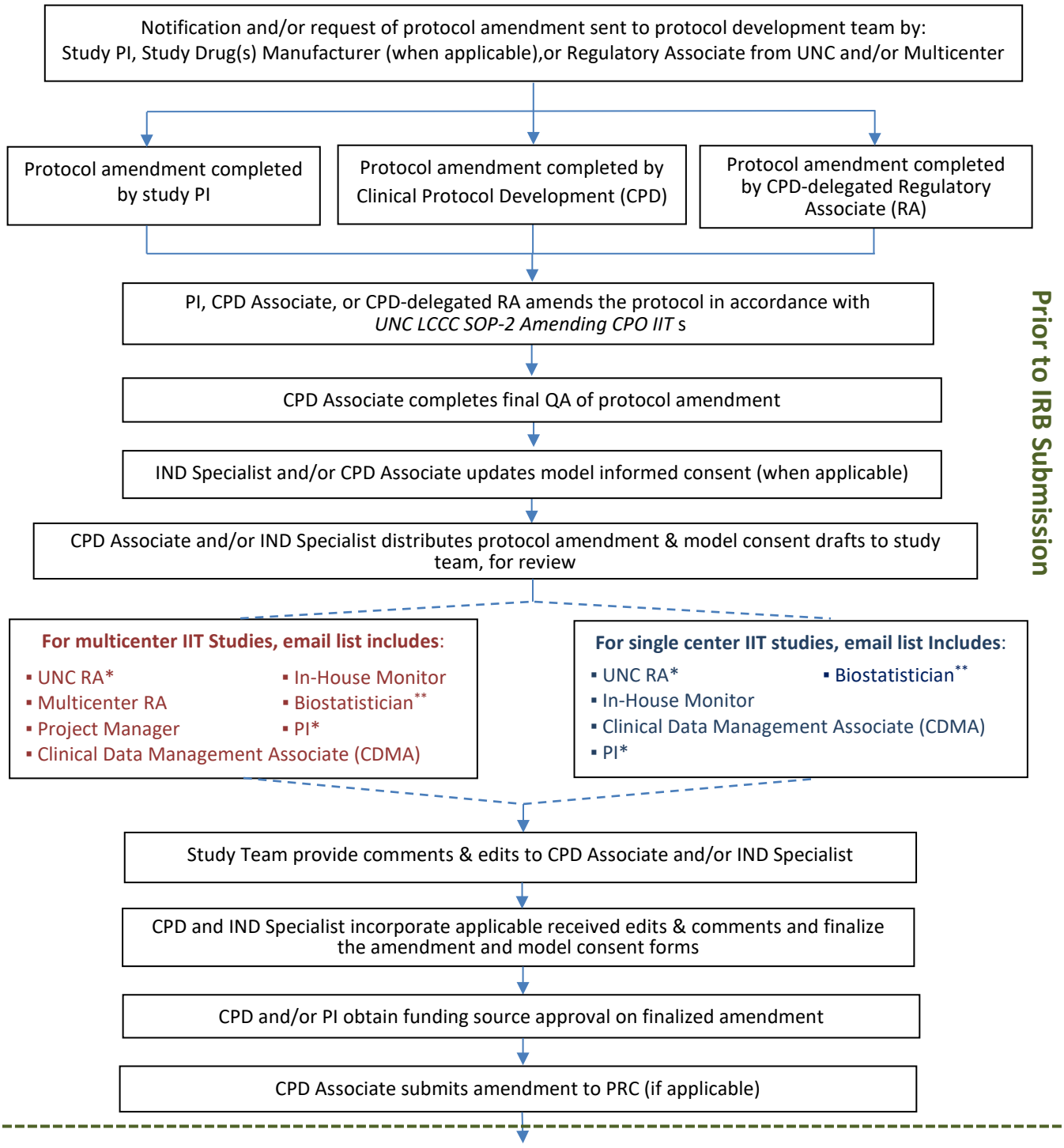
Version Number: 9 07/01/2020	Protocol Amendment-Change in Protocol WI



* Review not required when document prepared by this person

** When required for an amendment

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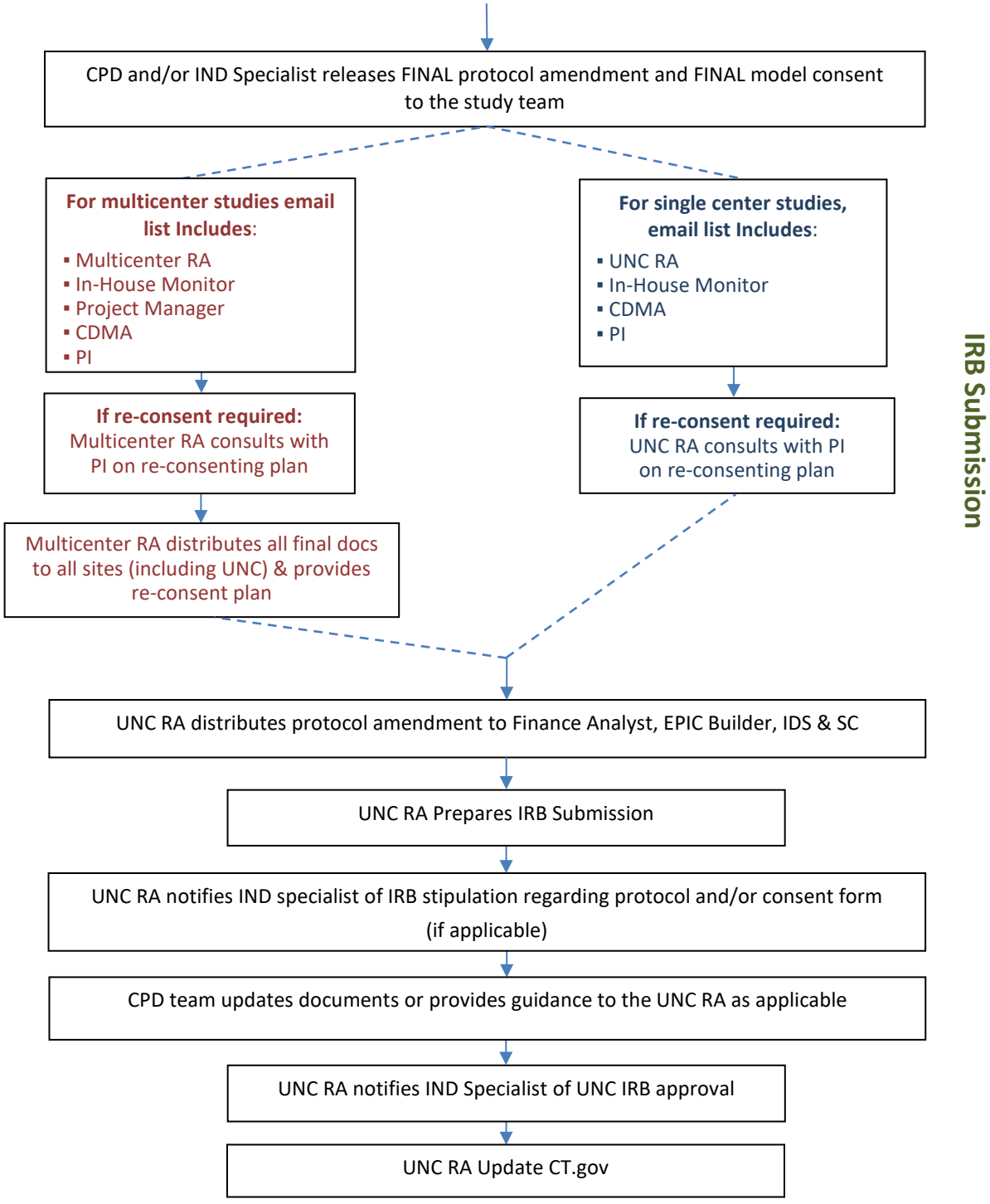

Remember to use the IND flow sheet

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I. REQUESTING A PROTOCOL AMENDMENT

A protocol amendment can be requested by a member of the study team, whether at UNC or a multicenter site. These individuals include the study Principal Investigator (PI), the study Medical Monitor, Biostatistician, Regulatory Associate, or Study Coordinator. A protocol amendment can also be requested by the manufacturer of the investigative product (IP), if applicable.

The PI and/or Medical Monitor, in consultation with Clinical Protocol Development (CPD) team, will screen the amendment request to determine if there is a need for the amendment.

The following types of changes are sufficient to drive an amendment:

- Change in IP dose (including addition of a new dose level which is higher or lower), change in frequency of dosing, and change in duration of treatment
- Addition or deletion of an IP for protocol directed treatment
- Increase in the number of subjects to be enrolled
- Study design changes such as:
    - Addition or deletion of a study arm
    - Addition or deletion of a control group
    - Change in study objective
    - Addition of study objective
    - Change in study assessment (safety, statistical)
- Change in eligibility criteria
- Addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of a side effect or adverse event
- Dropping a test intended to monitor safety
- Significant patient management changes such as:
    - Revision of dose modification criteria
    - Additional vehicles for monitoring toxicity such as a diary (e.g. nausea/vomiting diary)

***Note**: An IB update does not always trigger a protocol amendment. Refer to* Appendix A: What to do When You Receive an Updated IB *for further information on how to proceed with IB updates.*

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Safety Concerns:

Immediately notify the IND Specialist if there are any safety concerns on the trial or any action letters received from the IP manufacturer (if applicable). This may result in a protocol amendment and/or IND safety report.

If the amendment request is in regard to a safety concern, the request should be screened immediately. An action letter or safety letter may be necessary if the need is urgent. Please refer to *SOP-5 (Part A) Action Letters*.

Please note: A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided that the UNC IRB (or IRB of oversight) is notified within 5 business days of making the change.

II. WHO WRITES A PROTOCOL AMENDMENT

A protocol amendment can be prepared by the following Clinical Protocol Office (CPO) personnel:

- Study PI and/or Medical Monitor
- Clinical Protocol Development (CPD) Team
- UNC Regulatory Associate (RA), when delegated by PD management

Protocol amendment prepared by PI

If a protocol amendment is prepared by the study PI, and this information is shared with the regulatory associate (and/or study coordinator), they are responsible for notifying the Clinical Development Manager and IND specialist, via email.

The notification should be sent to LCCC_IND@unc.edu. The notification should provide a brief description of the upcoming amendment (see below email example). Please refer to the IND report flow sheet to help you proceed with the amendment.

Protocol amendment prepared by CPD associate

The PI can request the CPD team to prepare the amendment. The Clinical Development Manager will delegate preparation of a draft amendment to a member of the CPD team.

Protocol amendment prepared by CPD designated regulatory associate

The Clinical Development Manager may ask the UNC RA to draft the amendment.

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The Clinical Development Manager will notify the PI, UNC RA, IND Specialist, and Regulatory Manager of this assignment for the impending amendment with a brief description of the reason for the update.

Example of a request for an amendment by regulatory associate and/or study coordinator

Hello Kaitlin,

Dr. Clack would like to update the eligibility criteria for LCCC 1514 and is requesting your assistance in finishing this. The new criteria will allow for inclusion of patients who were treated previously with PD-inhibitor. She discussed this in pod and was asking for a contact with protocol development for assistance. Please let us know if you are able to help.

Best Regards

****

Example of a request for an amendment by PI

Hi Kaitlin,

We want to put together an amendment for LCCC 1736, to add two additional cohorts. After reviewing the toxicity data with the drug maker, we have decided to reduce the MTD of ulixertinib to 450mg BID and continue to dose escalate the palbociclib. Can you and your team help in preparing an amendment draft and I will have my admin assistant schedule a meeting so we can discuss the details.

Thanks in advance,

III. WRITING A PROTOCOL AMENDMENT DRAFT

The process of a preparing an amendment differs per the person writing the amendment. In the following sections, we describe how the process works per the person preparing the draft. Please also refer to Appendix B: How to Write a Protocol Amendment for tips on the amendment content, required administrative changes and formatting. Protocol version numbering should follow the policy statement **Protocol Version Numbering.**

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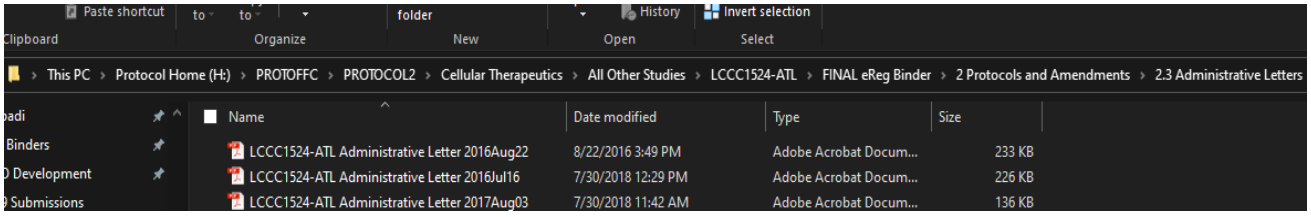
Protocol amendment written by PI

- The PI will be the main author of the amendment
- The PI will prepare the amendment in accordance with ***UNC LCCC SOP-2 Amending CPO IIT***
- PI will use the **Track Changes** function in Microsoft Word when preparing the amendment
- PI will use the protocol amendment coversheet (DT-54-Amendment Coversheet) to list all changes made in the protocol.
- PI will incorporate all changes required in the amendment and include any documents and attachments.
- PI will communicate any amendment related issues with the Clinical Development Manager.
- Clinical Development Manager will designate a CPD team member to work with the PI on completing the amendment.
- PI will email the final draft to the designated CPD team member/associate
- CPD will review and add any additional changes in the draft.
    - CPD Associate will use the **Protocol QA Check List (**Appendix C: QA Check List of a Protocol Amendment**)** to review the draft
- CPD Associate will identify any administrative letters approved since last amendment was prepared.

Note. Administrative letters can be found on the H drive, the eREG folder (# 2.3) for each study.



- CPD Associate will incorporate the information from administrative letters into the new amendment
- CPD Associate will update, review and complete the protocol amendment
- Another member of the CPD team will review the model consent form and determine if an update is required
- The designated member of the CPD team will update the model consent form per the new amendment
- CPD Associate who wrote the amendment will distribute the study amendment and model consent **DRAFTS** for team review

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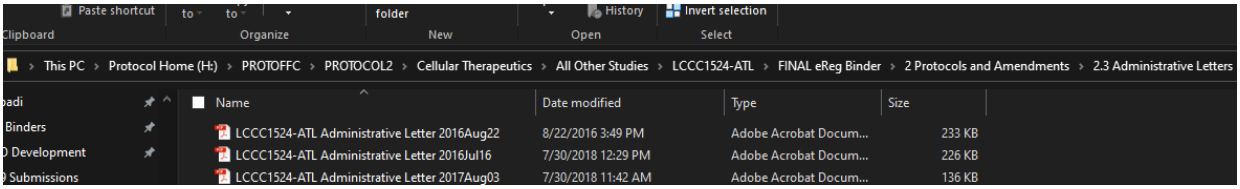
Protocol amendment written by CPD Associate

- The study PI will request assistance from the CPD team to prepare the amendment
- PI contacts Clinical Development Manager with information about the required changes
- Clinical Development Manager assess feasibility of an amendment based on PI request
- Clinical Development Manager delegates a CPD Associate in preparing the amendment
- CPD Associate will prepare the amendment in accordance with ***UNC LCCC SOP-2 Amending CPO IIT***. See Appendix B: How to Write a Protocol Amendment for instructions on how to start a protocol amendment.
- CPD Associate will use the **Track Changes** function in Microsoft Word when preparing the amendment
- CPD Associate will use the protocol amendment coversheet (DT-54-Amendment Coversheet) to list all changes made in the protocol.
- CPD Associate will incorporate all changes required in the amendment and use **Protocol QA Check List (**Appendix C: QA Check List of a Protocol Amendment**)** to ensure all necessary changes are included in the amendment
- CPD Associate will communicate any amendment related issues with the PI
- CPD Associate will identify any administrative letters approved since last amendment was prepared

Note. Administrative letters can be found on the H drive, the eREG folder (# 2.3) for each study.



- CPD Associate will incorporate the information from administrative letters into the new amendment
- CPD Associate will update, review and complete the protocol amendment
- Another member of the CPD team will review the model consent form and determine if an update is required
- The designated member of the CPD team will update the model consent form per the new amendment
- CPD Associate who wrote the amendment will distribute the study amendment and model consent **DRAFTS,** for team review

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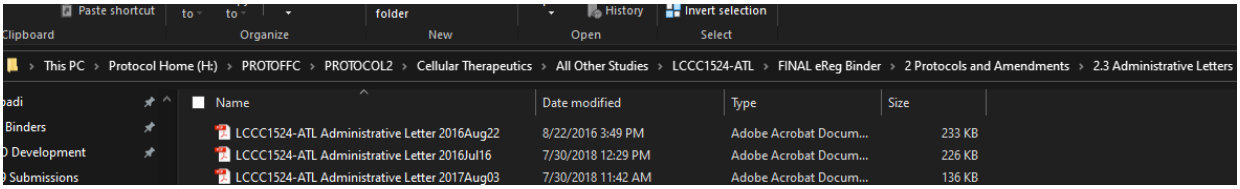
Protocol amendment written by CPD designated regulatory associate

- Clinical Development Manager will discuss a protocol amendment with the PI and other study team members.
- Depending on the nature of the change requests (administrative, editorial, scientific), Clinical Development manager will request the amendment be prepared by the study Regulatory Associate.
- Clinical Development Manager notifies the Regulatory Associate, CPD Associate, IND Specialist, PI, and Regulatory Manager, about the protocol amendment.
- Regulatory Associate will prepare the amendment in accordance with ***UNC LCCC SOP-2 Amending CPO IIT*** . See Appendix B: How to Write a Protocol Amendment for instruction on how to start a protocol amendment
- Regulatory Associate will use the **Track Changes** function in Microsoft Word when preparing the amendment
- Regulatory Associate will use the protocol amendment coversheet (DT-54-Amendment Coversheet) to list all changes made in the protocol.
- Regulatory Associate will incorporate all changes required in the amendment.
- Regulatory Associate will communicate any amendment related issues, via email, with the study PI, CD Associate, and IND Specialist (all must be copied on the email)
- Regulatory Associate will email the final draft to Clinical Development Manager and CPD Associate
- CPD Associate will identify any administrative letters approved since last amendment was prepared

Note. Administrative letters can be found on the H drive, the eREG folder (# 2.3) for each study.



- CPD Associate will incorporate the information from administrative letters into the new amendment
- A member of the CPD team will review the model consent form and determine if an update is required. Typically, amendments delegated to the regulatory team will not require model consent form updates
- CPD Associate and/or IND Specialist will update the model consent form per the new amendment

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- IND Specialist and/or CPD Associate will distribute the study amendment and model consent **DRAFTs,** for team review (if applicable). Minor changes performed by the Regulatory Associate may not require full team review such as updating the protocol PI.

IV. REQUESTING TEAM REVIEW OF AMENDMENT AND CONSENT DRAFT

The amendment and consent **drafts** are to be reviewed for quality assurance by the study team.

For a Multicenter IIT Study:

- The **amendment draft** is sent for review to the: Multicenter Regulatory Associate; UNC Regulatory Associate; Project Manager; Study Coordinator; Clinical Data Management Associate; In-house Monitor; Biostatistician (when applicable); PI (when applicable)

- The **model consent form draft** is sent for review to the: Multicenter Regulatory Associate; UNC Regulatory Associate; Project Manager; PI (when applicable)

For Single Center IIT Study:

- The **amendment draft** is sent for review to the: UNC regulatory Associate; Clinical Data Management Associate; In-house Monitor; Biostatistician (when applicable); PI (when applicable)

- The **model consent form draft** is sent for review to the: UNC Regulatory Associate; PI (when applicable)

Reviewers are provided a deadline to submit their edits and comments (typically 7 days, including non-business days). Reviewers must do their best effort in reviewing the updated documents.

Example of an email request for review of protocol amendment draft for a multicenter IIT study:

Study Title: LCCC1904-ATL: Phase II Study of The Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Relapsed/Refractory CD3+ Peripheral T Cell Lymphoma

Dear study team,

Included is a draft of Protocol Amendment # 2 for LCCC 1904-ATL. Please review and submit your comments/edits by Thursday, June 20.

Thank you,

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Example of an email request for review of a model consent draft for single center IIT study:

Good afternoon,

Included is a tracked copy of the updated consent form for LCCC 1820. Note the changes were triggered by a newly released IB which included change in risk language for Parsaclisib. Additionally, the eligibility criteria were updated per protocol amendment 1, to allow for enrollment of men and women diagnosed with breast cancer (previously limited to women only). Please review the document and submit your comments/edits by June 27.

Thank you,

V. TEAM REVIEW OF THE PROTOCOL AMENDMENT AND MODEL CONSENT DRAFTS

Protocol Amendment and Model Consent **drafts** are reviewed by the study team.

The following points should be considered when reviewing a **protocol amendment draft** :

- Bring up any issues that have been going on in the study so that they can be addressed with this amendment
- Make sure that the protocol is clear, easy to follow, and unambiguous

For both the protocol and the model consent:

Editorial/stylistic edits and comments should be limited to areas of the protocol and consent that have been changed. Other substantive edits/comments are encouraged.

Note: Any edits & comments after the set review period may be incorporated in the ongoing amendment as a result of the amendment being finalized/released. The new findings will be submitted in the next protocol amendment, or via an administrative letter (if applicable)

Note: The Amendment QA List for protocols **(**Appendix C: QA Check List of a Protocol Amendment**)** and consent forms (Appendix D: QA Checklist for a Model Consent Form) should be used to check all sections were updated accordingly.

- **Reviewers** submit amendment **edits & comments** in Track Changes to CPD Associate within specified review period. Any edits received after the date may be incorporated to the amendment as the protocol amendment may be finalized and released prior to receipt

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- **Reviewers** submit consent **edits & comment** in Track Changes to the member of the CPD team delegated with the ICF update and must include any CAPAs agreed upon by the IRB during this review period.

VI. FINALIZATION OF THE PROTOCOL AMENDMENT

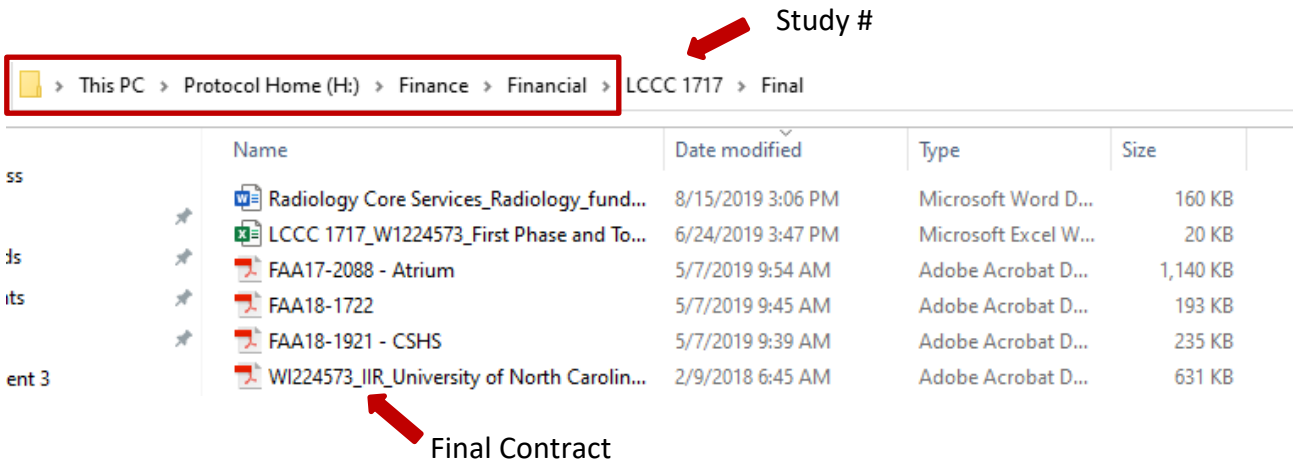
The CPD Associate incorporates applicable edits & comments and finalizes the amendment. The amendment is provided to the PI for final approval and sign-off.

If the protocol involves an update to the statistics, then the protocol is sent to the study's biostatistician (as listed on the protocol cover page) for review/sign off. The biostatistician sign-off sheet can be found on the PRC website: https://unclineberger.org/protocolreview/forms/

VII. FUNDING SOURCE REVIEW/APPROVAL OF THE PROTOCOL

The CPD Associate submits amendment to funding source(s), to obtain their approval. This submission may occur via email or via a required portal depending on the funding source.

- For the contractual obligations for review, the CPD Associate should review the contract, which can be found in a study-specific folder in the finance folders:



- CPD Associate can find the list of Medical Science Liaisons (MSLs) who can either accept the submission via email or direct the CPD Associate on how to submit the protocol for review here: **R:\LCCC_CPO Development\Administrative\MSL Contact List**
    - *Please Note:* This list should be updated by the CPD Associate if a new contact is discovered during the amendment review process.

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- If there is a portal to submit through many funding sources only allow access to one individual at LCCC. If the funding source limits access to the portal, the CPD Associate requests the following individual to submit through the portal on their behalf:
    - For multicenter trials: Multicenter project manager
    - For single center: Study coordinator

VIII. PROTOCOL REVIEW COMMITTEE REVIEW (IF REQUIRED)

CPD Associate submits amendment to PRC, if required. The following types of amendments require PRC review:

- Adding a new drug to patient treatment or adding another treatment (e.g. radiation, surgery)
    - Does not include an additional infusion of the same drug
    - May include a new route of administration
- Changing the primary objective of the study
- Adding or subtracting an element from the study that changes the statistics

If clarification is needed as to whether an amendment requires PRC review, the CPD Associate may send the finalized amendment to the PRC Coordinator for a determination of review status.

The CPD Associate submits the amendment to the PRC through ePRMS. See Appendix D: Instructions for Submitting Protocol Amendments to the PRC for details.

- If a protocol amendment requires PRC review, CPD Associate will incorporate any requested changes by the PRC reviewers. As the protocol has been previously approved by the funding source, the protocol version's number should be updated to reflect post initial approval editing has been performed. The numbering should be updated in accordance with the **Protocol Version Numbering** policy.

IX. FINALIZATION OF THE CONSENT FORM

CPD team member delegated with the model consent form update incorporates applicable edits & comments that result from required protocol updates from the funding source and/or PRC. The model consent form is finalized.

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X. RELEASING PROTOCOL AMENDMENT AND MODEL CONSENT

A **FINAL** copy of an amendment and model consent form is **released b**y a member of the Clinical Protocol Development team.

- If it is a protocol amendment only (no ICF updates), the CPD Associate who wrote and/or finalized the amendment will release the final documents
- If the informed consent form has been updated, the CPD Associate who updated the ICF will release the final documents.

For a Multicenter IIT Study:

- A **FINAL** copy of the amendment is **released** to: Multicenter Regulatory Associate; Project Manager; Clinical Data Management Associate (CDMA); In-house Monitor; PI
- A **FINAL** copy of the model consent form is **released** to: Multicenter Regulatory Associate; and Project Manager
- Multicenter Regulatory Associate will distribute the **FINAL** amendment and/or model consent forms to all participating sites (including UNC)
    - Note: This release will occur after a re-consent plan has been determined if the consent form has been updated (refer to section XI, below).

For a Single Center IIT Study:

- A **FINAL** copy of the amendment is **released** to the following individuals: UNC Regulatory Associate; CDMA ; In-house Monitor; PI
- A **FINAL** copy of the model consent form is **released** to the following individuals: UNC Regulatory Associate

Example notification of release of new amendment for a multicenter IIT study:

Study Name: LCCC 1725, A Phase II Study of Durvalumab (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk Head and Neck Squamous Cell Carcinoma

Dear study team,

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Attached find Amendment #2 (dated October 27, 2019) for the above-mentioned study. Changes include updates to eligibility criteria, and clarification on radiation therapy dose and frequency. The Adult Informed Model Consent was also updated to accommodate changes in the amendment.
Attached are:

- LCCC 1725 Protocol Amendment #2 v2.0 (dated 10/27/2019) FINAL, tracked and clean copies
- LCCC 1725 Adult Model Consent (v 10/27/2019) FINAL, tracked and clean copies
- LCCC 1725 Specimen Consent (v 10/27/2019)FINAL, tracked and clean copies

Please distribute the documents to all participating sites. Let me know if you have any questions.

Best,

****

Example notification of release of new amendment for single center IIT study:

Study Name: LCCC 1725, Phase Ib/II Study Of IV Nivolumab And Intrapleural Talmogene Laherparepvec For Patients With Malignant Pleural Effusion

Dear study team,

Attached find protocol amendment # 4 for LCCC 1626. The adult consents were also updated to accommodate changes in the treatment and updates in nivolumab risks, per the recently released IB. Attached are:

- LCCC 1626 Protocol Amendment #4 v2.0 (dated 06/25/19) FINAL, clean and tracked copies
- LCCC 1626 Adult Model Consent (v o6/25/19) FINAL, clean and tracked copies
- LCCC 1626 Specimen Consent (v 06/25/19) FINAL, clean and tracked copies

Regulatory: Please notify me via email of the following: date of submission to IRB, any IRB stipulations for the protocol/consent, and finally, the date of IRB approval.

Best,

XI. RE-CONSENTING PLAN

A protocol amendment and a consent update often require re-consenting subjects already participating in the study. The decision to re-consent subjects and the re-consenting plan is determined by the study PI. Protocol changes that might require re-consenting:

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- Change in treatment (including changes in schedule of treatments, doses of investigative drug, frequency of treatments)
- Change in risks associated with the study drug and procedure
- Change in Drug manufacture
- Change in eligibility criteria

For Multicenter IIT Study:

Multicenter Regulatory Associate will consult with the study PI and prepare a re-consenting plan. The finalized re-consenting plan is distributed by Multicenter Regulatory Associate to all participating sites (including UNC). This plan can be submitted along with the protocol amendment and/or updated consent forms, to all participating sites (described previously in section X)

For a Single Center IIT Study:

UNC Regulatory Associate will consult with the study PI and prepare a re-consenting plan.

XII. DISTRIBUTION OF PROTOCOL AMENDMENT TO CROSS FUNCTIONAL TEAMS AT UNC

At UNC, Regulatory Associate will receive a copy of the **FINAL** protocol amendment and/or model consent, regardless of the type of the study (i.e. multicenter or single center). UNC Regulatory Associate will distribute a final copy of the protocol amendment to various (internal) cross-functional teams per normal office processes in order for them to prepare for the amendment approval and enactment.

Note: Internal distributions once the amendment is received from Clinical Protocol Development should mirror distribution for an externally received amendment. Recipients should include: Beacon, IDS, Finance, Tissue Procurement, CTSU lab, etc.

XIII. IRB AND IBC (IF APPLICABLE) SUBMISSION

UNC Regulatory Associate and (if applicable) the site regulatory team will submit the new protocol amendment and/or model consent form to the IRB of oversight for approval.

UNC Regulatory Associate will complete the following steps:

- Notify Regulatory Documents Specialist and/or Regulatory Assistant for docking of the IRB submission in OnCore (not to be confused with the previous IND docking).

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- Prepare modification application in IRBIS, following the CPO office and IRB standard procedures
- Prepares the UNC site specific ICF based upon the model consent form
- If the modification submission is scheduled for full board IRB review, the UNC Regulatory Associate should notify the IND Specialist of the full board meeting date.

UNC and/or Multicenter Regulatory Associate completes the following:

- Informs CPD team if the IRB issues any stipulations regarding the amendment and CPD team will work with the UNC or Multicenter Regulatory Associate to address any protocol related issues.
    - ***Note***: If changes are made to the protocol in response to IRB stipulations and the study is a single center study, the version # of the protocol should be updated in accordance with the **Version Numbering Policy.** If the study is multicenter, any IRB mandated changes must be addressed in a formal amendment since the protocol has been released to multiple clinical trial sites for review/approval.
- Informs CPD team if the IRB issues any major stipulations requiring substantial changes to the consent form. CPD team will work with the UNC or Multicenter Regulatory Associate to approve any associated major changes.

Note: *If the study involves human gene transfer experiments and falls under the purview of the Institutional Biosafety Committee (IBC) the following types of amendments must be submitted to the IBC for review*:

- Protocol amendments that involve changes to the recombinant or synthetic nucleic acids that will be administered to human subjects, including vector, genes of interest, dose, etc.
- Protocol amendments that involves changes to the handling of the recombinant or synthetic nucleic acids by UNC employees, including waste disposal, personal protective equipment changes etc.

XIV. PROCESSING OF IRB APPROVAL

The UNC Regulatory Associate will email the study team per typical regulatory team processes to inform of IRB approval of the submitted protocol amendment. The IND Specialist **MUST** also be copied on this correspondence. Additionally, applicable additional LCCC Sponsor team members should be included on this correspondence including the Project manager, Multicenter Regulatory Associate, In-house Monitor, and Clinical Data Management Associate.

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***Note**: This email should also clearly indicate the re-consenting plan as detailed in SOP-21 Informed Consent.*

XV. UPDATING CT.GOV

Changes to clinicaltrial.gov **MUST** be completed within 30 days of receiving the new protocol amendment. Please refer to Work Instructions 47 for additional details.

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APPENDIX A: WHAT TO DO WHEN YOU RECEIVE AN UPDATED IB

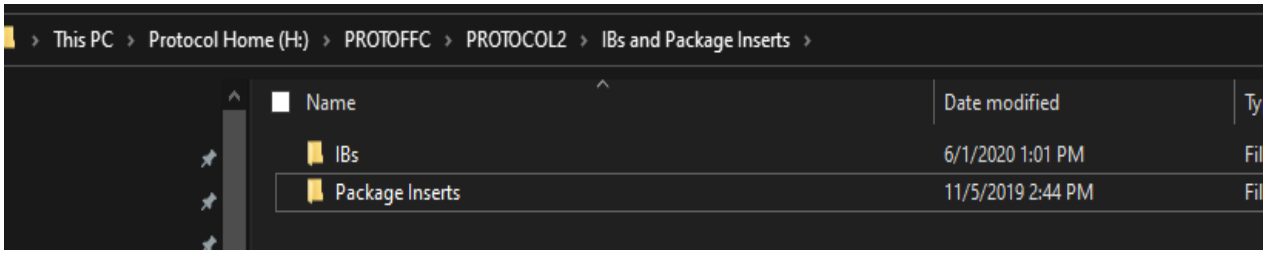
An Investigator Brochure (IB) includes guidance for PIs on monitoring drug induced toxicity and adverse events, and often this is information is included in a protocol. An update in the Investigator Brochure for an investigative drug (IP) can sometimes require a protocol amendment. Additionally, IBs include cumulative adverse events expected for an IP and this information is included in the informed consent document. Any updates in an IB must be reviewed carefully to determine how it may affect the protocol and consent form.

An updated IB can be sent from a funding source/drug manufacturer to any of the following Clinical Protocol Office (CPO) personnel:

Principal Investigator	IND Specialist
Regulatory Associate	Clinical Development Manager
Regulatory Assistant	Project Manager
Study Coordinator	Regulatory Manager

As soon an any of the above mentioned personnel receives a copy of an updated IB, they must notify regulatory associates via the regulatory list serve email (regulatory_associates@listserv.med.unc.edu), and include copies of the received IB documents.

The CPO regulatory team (i.e. Regulatory Managers, Associates, Assistants), as well as CPD team must save a copy of the received IB documents in the H drive-> IB and PI folder (H:\PROTOFFC\PROTOCOL2\IBs and Package Inserts). This will allow access to all regulatory personnel to the new documents.



CPD team will inform the Regulatory Associate if the changes in the new IB will impact the protocol and/or the consent form.

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CPD Team will work with the PI to address any changes in the guidances for monitoring drug induced toxicities and adverse events. If the PI determines the protocol must be updated to accommodate the changes, an amendment draft will be started as described in sections 1-7 of this working instruction.

A CPD Associate will assess updates in the risk portfolio of the IP and update the informed consent. IND Specialist will notify PI, UNC Regulatory Associate, Multicenter Regulatory Associate, and Project Manager of impending changes in the consent form.

The CPD Associate will update the Model consent as appropriate. Another CPD member and PI (when applicable) will QA and review the updated consent form.

Once the PI approves the changes in the ICF, a FINAL copy of the updated model consent is released to the study team as described in section X of this working instruction.

Example Notification from IND Specialist about an IB update:

Hi team,

Merck released a new IB (version 17) and it includes changes in the risk portfolio of pembro. I also received an updated Injury language from Merck. I am currently working on updating all affected consent forms and will release as soon as internal QA/review is completed. The new risk include Steven Johnsons Syndrom, and headache (both listed as rare).

Thanks,

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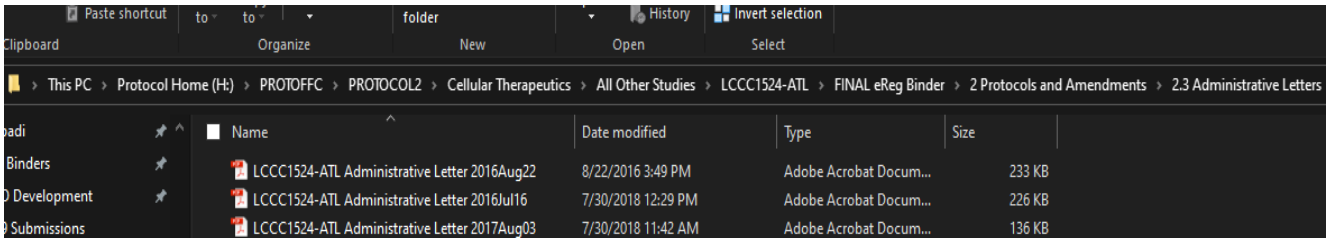
APPENDIX B: HOW TO WRITE A PROTOCOL AMENDMENT

A protocol amendment can be prepared by the study PI, or CPD and their designee (protocol development associates, IND Specialist, regulatory associate, and biostatistician).

When preparing an amendment, the author must follow the following steps:

- Identify any administrative letters approved since last amendment was prepared. Administrative letters can be found on the H drive, the eREG folder (# 2.3) for each study.



- Incorporate the information from the administrative letters into the current amendment
- Prepare protocol amendment in accordance with ***UNC LCCC-SOP-2 Amending CPO IIT***
- Use the **Track Changes** function in Microsoft Word when preparing the amendment
- Use the protocol amendment coversheet (**DT-54-Amendment Coversheet**) to list all changes made in the protocol. A copy of the DT-54 Coversheet is located in SAKAI
- The Coversheet should be inserted as the top/first page of the protocol.
- The protocol amendment should be numbered consecutively (1,2 3,…) and this number should be included to the top of the coversheet.

- Select the type of change(s) in the amendment, on the coversheet.
- Write a brief and concise summary of the rational and changes by “category” in the coversheet

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SUMMARY OF CHANGES

Protocol Amendment #___

LCCC####: Insert Title

AMENDMENT INCORPORATES:

__ Editorial, administrative changes

__ Scientific changes

__ Therapy changes

__ Eligibility Changes

Rationale for amendment: Add amendment rationale here and the major changes. This will be the information provided to FDA in the cover letter summarizing the amendment.

Editorial, administrative changes:

Sections ___ Add description of change

Section ___ Add description of change

Scientific changes:

Section ___ Add description of change

Therapy changes:

Section ___ Add description of change

Eligibility changes:

Section ___ Add description of change

THE ATTACHED VERSION DATED MONTH DD, YYYY INCORPORATES THE ABOVE REVISIONS

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Example Summary of Changes for an Amendment

Protocol Amendment #1

LCCC1904-ATL: Phase II Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Relapsed/Refractory CD30+ Peripheral T Cell Lymphoma

AMENDMENT INCORPORATES:

X Editorial, administrative changes

X Scientific changes (IRB approval)

X Therapy changes (IRB approval)

X Eligibility Changes (IRB approval)

Rationale for amendment: The primary purpose of this amendment is to make administrative changes throughout the protocol including updating the Medical Monitor to Jonathan Serody, MD. Additionally, an allowance was added for subjects with bendamustine hypersensitivity to receive cyclophosphamide in combination with fludarabine for lymphodepletion for their first infusion.

Editorial, administrative changes:

Sections 7.6, 10.3.1, 12.6, 12.9, 14	Updated to remove references to the UNC IRB.
Section 12.4	Updated to reflect the current multicenter registration process.
Section 12.9	The DSMC was updated to the DSMC Blue, which is a DSMC set up to review studies with institutional conflict of interest (COI)
Section 18.1	The medical monitor was updated from Barbara Savoldo, MD, PhD to Jonathan Serody, MD
Section 18.6	Updated to only include strong inhibitors and inducers of 1A2

Scientific changes:

Section 11.2	Clarification of subjects included in the primary efficacy analysis.

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Therapy changes:

Section 4.1.3, T&E Table Footnotes, Section 8.2	Added allowance for subjects who have hypersensitivity to bendamustine to receive lymphodepletion with cyclophosphamide and fludarabine prior to the first infusion.
Section 4.1.3, T&E Table Footnotes, Sections 8.2, 8.2.2.5 and 8.2.3.5	Clarified that the timeframe for determining if ANC has not recovered enough to receive a full dose of lymphodepletion for the second infusion is from the first day of lymphodepletion prior to the initial cellular product administration.

Eligibility changes:

Section 5.2	Exclusion for the study was updated to remove the requirement for HIV viral load testing as HIV antibody testing is sufficient.

THE ATTACHED VERSION DATED FEBRUARY 21, 2020 INCORPORATES THE ABOVE REVISIONS

Note: It is important to include not only the section of the protocol that was updated, but to also include a general idea of how it is updated. Someone who is not familiar with the protocol should be able to look at the coversheet and know what was changed and why.

Note: If the protocol amendment may affect other IIT studies/protocols and also may trigger an amendment then the person writing the amendment should notify all applicable individuals

For Example: Use of ICANS as new grading system to assess neurotoxicity in CAR T cell therapy. This will apply to all CAR T cell studies.

- The CPD Associate preparing and/or reviewing the draft protocol, will inform **all** of the CPD Team of the finding. The CPD team will organize a strategy on how to update related amendments, with the approval of the study PI.

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Each protocol update has a date associated with it. The date is located at least in the following locations in the protocol:

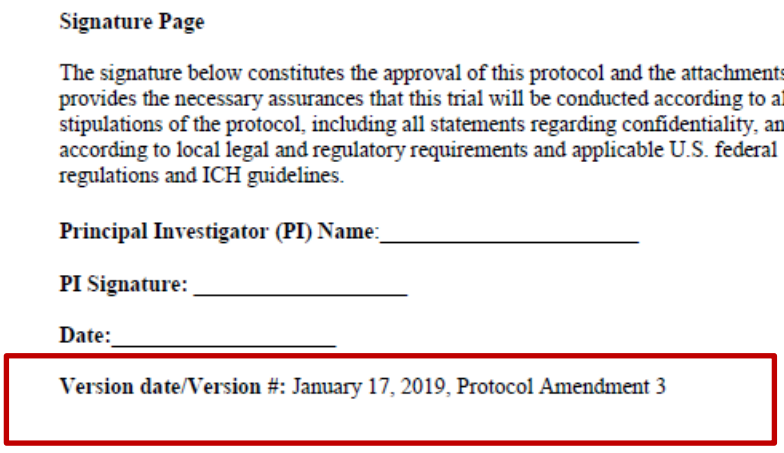
- Protocol amendment coversheet, bottom end
- Protocol introductory page
- Protocol header, on every protocol page
  - Note: If there is a section break the date in the header will not always automatically update in other sections of the document. After every section update the header date, as needed.
- Protocol signature page

One may use Control-F (find function) to find the date locations in the protocol and update it accordingly. The new date will reflect the date the protocol amendment draft is prepared.

Example of locations of protocol version date

- ***Header of all protocol pages***

- ***Signature page of a protocol***



Version Number: 9 07/01/2020	Protocol Amendment-Change in Protocol WI

APPENDIX C: QA CHECK LIST FOR A PROTOCOL AMENDMENT

Use the following checklist to complete QA of a protocol amendment draft

Complete	Task
QA to address early in the amendment process	
	Have there been any sections of the protocol that have been confusing to the study team? Have they been addressed?
	Have all administrative letters been incorporated?
	Have all requested changes been incorporated?
	If a new study objective has been added is there the need for a new endpoint? Has a new endpoint been added?
	If there is an IB update, has the risk information in the protocol, dose modification information, dosing information, premedications, etc. been updated accordingly?
	If any single subject exceptions have been approved, has protocol been evaluated to see if the protocol can be updated to allow that type of subject in the future?
	Is there any new template language from the funding sponsor that needs to be incorporated?
QA to address after the initial changes to the protocol are made	
	Are changes to sample size reflected throughout the protocol?
	Are changes to eligibility reflected throughout the protocol?
	If a new study group is being engaged has that been updated in the study synopsis?
	If a new study group is being engaged has that been updated in the inclusion/exclusion criteria?
	Has the accrual duration been updated as necessary? For example, if the study says it will accrue for 24 months and we are at month 36, then the accrual duration in the protocol should be adjusted accordingly.
	Do the footnotes and the time and events table match?
	Do the study assessment section and time and events table match?
	If the timeframe during which a study assessment should occur has been updated in the eligibility criteria has it also been updated in the time and events table and the study assessments section?
	If additional investigational products or study arms have been added to the protocol, has the protocol been updated with rationale to support those additions?
	Is all of the updated text easy to read and follow?
	Statistician sign-off?
QA to finalized protocol	
	Has the previous list of Co-investigators been removed?
	Has a coversheet with a summary of changes been added to the front of the protocol?

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	Do the summary of changes are the changes in the protocol match?
	Has the date of the protocol been updated on the protocol cover page?
	Has the date of the protocol been updated on the protocol signature page?
	Has the date of the protocol been updated in the protocol header?
	Has the table of contents been updated?

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APPENDIX D: QA CHECKLIST FOR A MODEL CONSENT FORM

The following check list can be used when reviewing a model consent draft

QA Of Model Consent Draft	
	Have all changes in the protocol been incorporated into the consent?
	If the time and events table of the protocol has been updated, has the "what will happen if you take part in the study" section been updated?
	If the eligibility criteria of the protocol have been updated, was there any changes in the "Are there any reasons you should not be in this study" section?
	If the study duration has increased (follow-up or treatment) has the "How long will your part in this study last" section been updated?
	If the study accrual has been updated has the "how many people will take part in this study" section been updated?
	If a new study group or study drug is being added, has the "what is the purpose of this study" section been updated accordingly?
	If a new study assessment has been added, were risks related to the assessment (if applicable) updated in the consent?
	Has the date on the ICF, and header (if included) been updated?
	Is the most recent version of the IB and/or package insert OR sponsor model risk language being used for the consent form risk profile?

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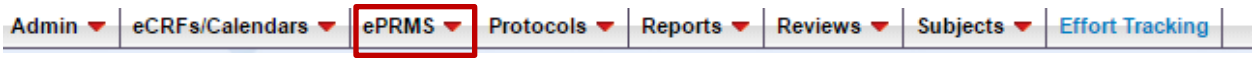
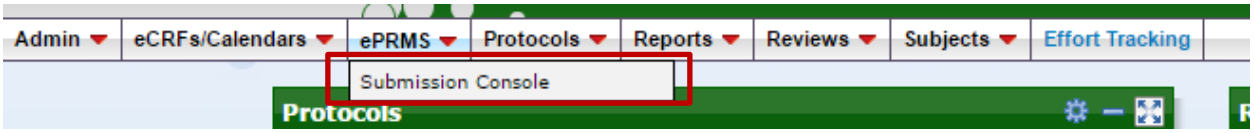
APPENDIX E: INSTRUCTIONS FOR SUBMITTING PROTOCOL AMENDMENTS TO THE PRC

Amendments requiring PRC review should be submitted via the ePRMS Submissions Console by the Regulatory Associate using the "Change Review" option.

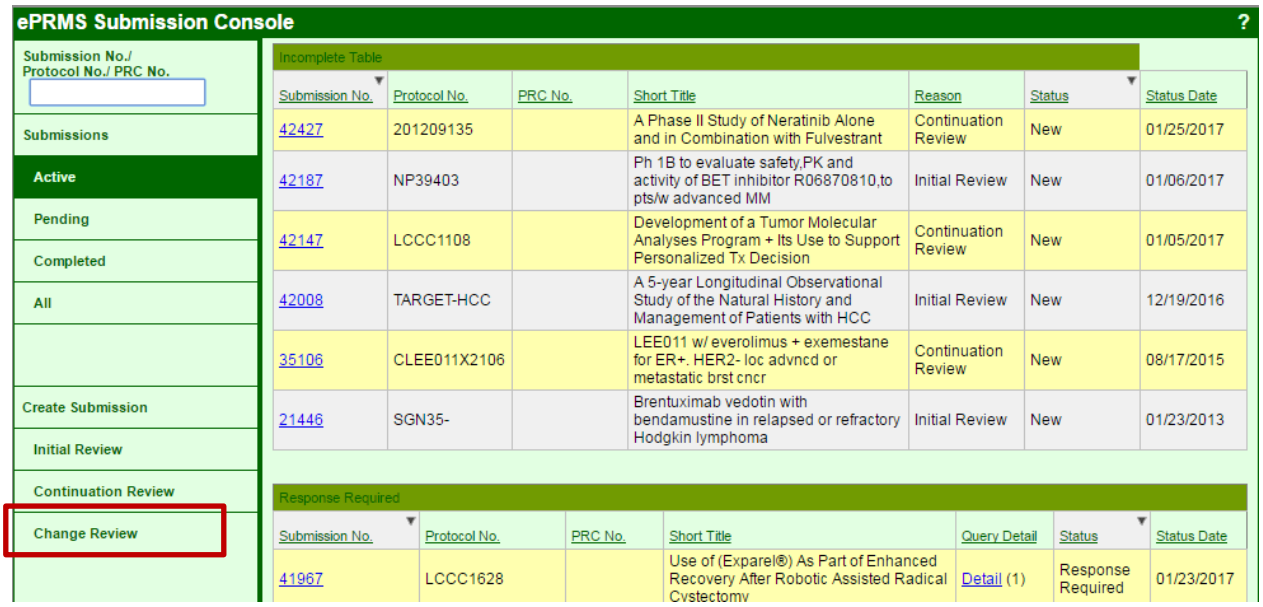
- Select ePRMS at the top of the OnCore screen



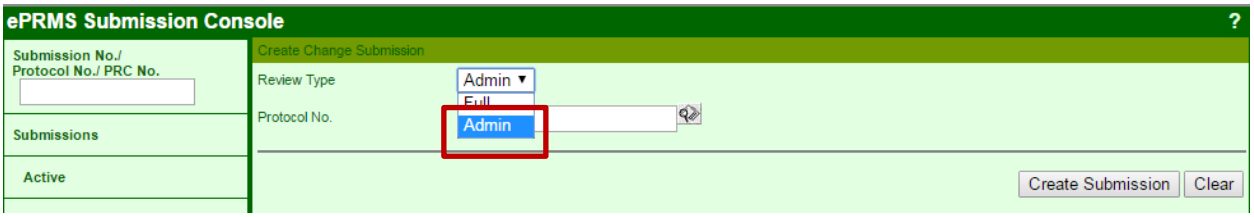
- Click on Submission Console



- Select Change Review



- Select Administrative Review



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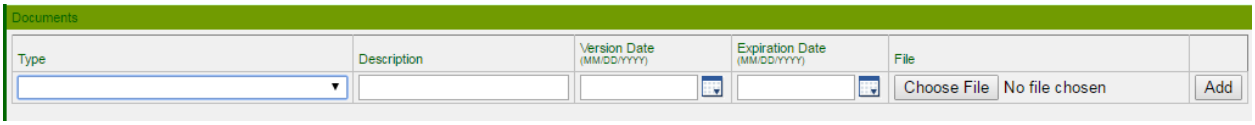
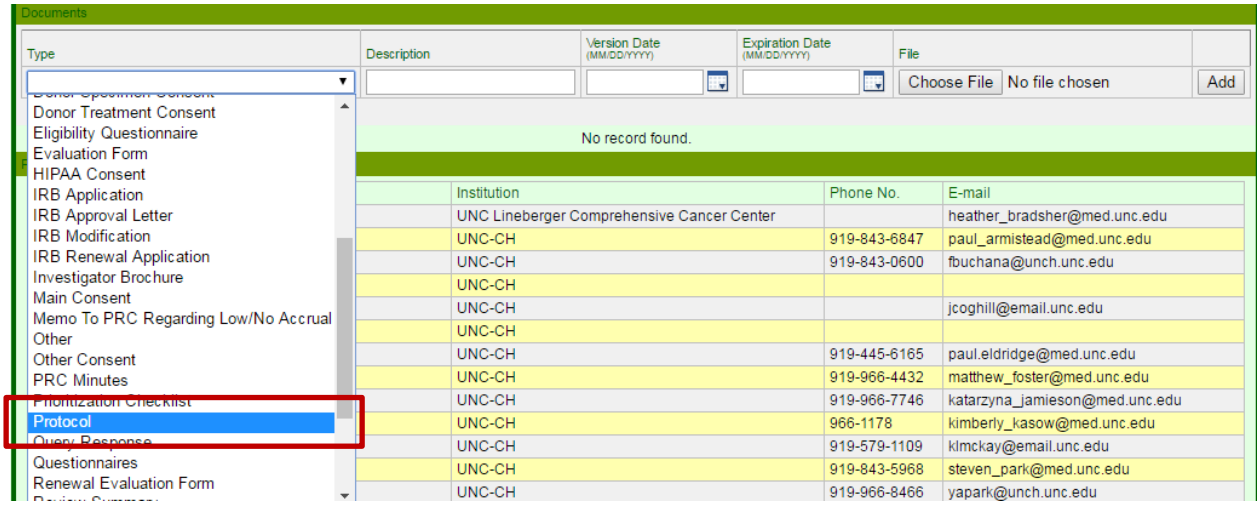
- Enter your study number and click create submission

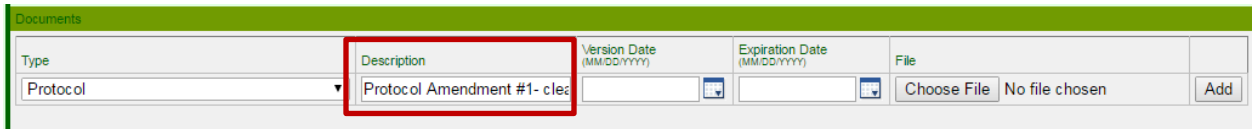
- Attach the protocol in the attachment section by completing the following:



  - Select the Document Type as protocol



  - Enter protocol description- Example: Protocol Amendment #1-clean



  - Enter version date

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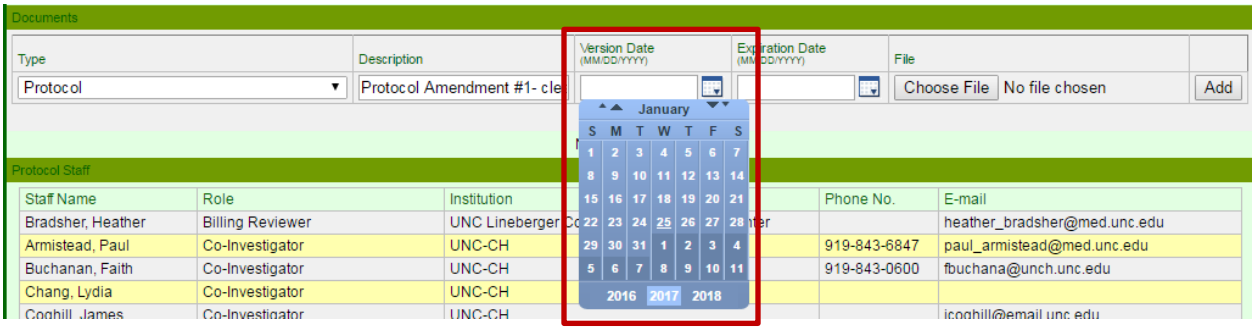
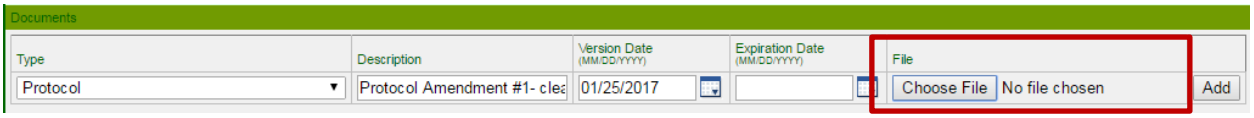
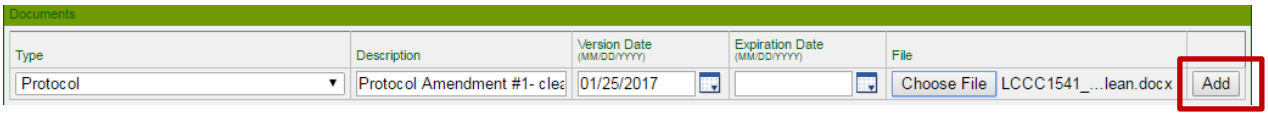


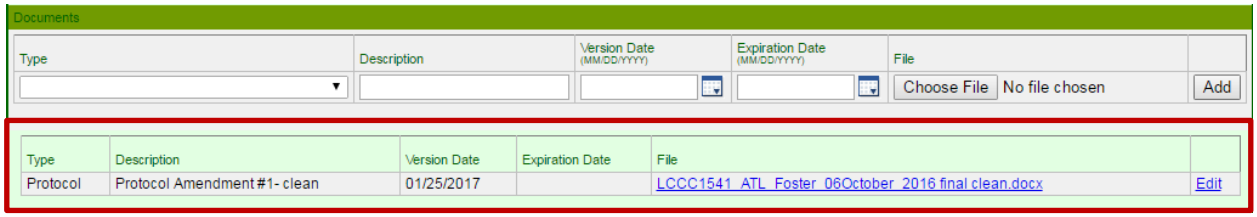
- Select the clean version of the protocol by clicking choose file



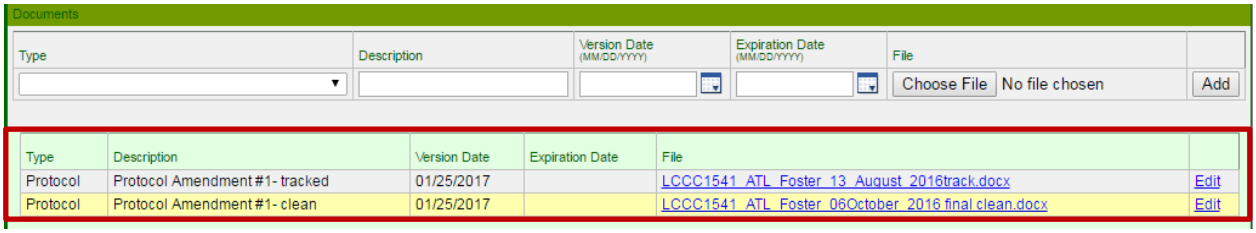
- Click add to attach the protocol



- The document should appear below



- Repeat the above steps to attach the tracked changed version of the protocol, but in the description indicate that this version is tracked. Example: Protocol Amendment #1- tracked



- Please include statistician signoff with amendment review application

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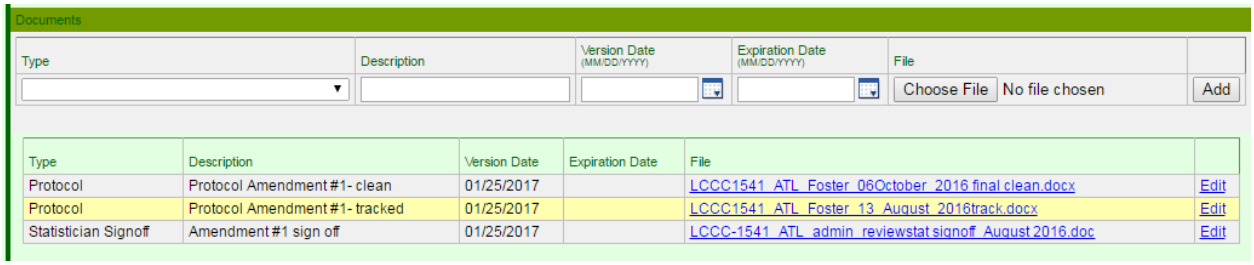
- For each amendment check in with the biostatistician listed on the front of the protocol via email to determine if updates are required to the statistics
- If Biostatistician sign off is required attached it in ePRMS



- When everything is attached click send

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APPENDIX F: SUMMARY OF RESPONSIBILITIES PER ROLE AT CPO

Role	Responsibilities
Multicenter Sites	• May request a protocol amendment • Receive protocol amendment and updated model consent (if applicable)
Biostatistician	• May request a protocol amendment • May be tasked with amending the protocol as determined by the Clinical Development Manager and PI • QAs the protocol amendment for changes to the statistics • Provides biostatistician sign-off for the protocol amendment
CTU Laboratory Coordinator	• May request a protocol amendment • Receive notification of upcoming protocol amendment from the UNC Regulatory Associate • Update the Lab Manual • Receive IRB approval notification from the UNC Regulatory Associate • If there were IRB requested changes that affect the lab, then the lab manual is updated accordingly • Release new lab manual
Clinical Protocol Development Team (CPD Associate, OR IND Specialist)	• May request a protocol amendment • May be tasked with amending the protocol as determined by the Clinical Development Manager • Initiates study team review of the amendment • May QA the protocol amendment • Secure PI and Biostatistician (if applicable) approval • Submits amendment to funding source for approval • Submits to PRC for approval (if applicable) • Release amendment to study team
Clinical Data Management	• May request a protocol amendment • QAs the protocol amendment • Determines if the protocol amendment will impact the eCRFs and/or calendar • Receives the FINAL version of the protocol amendment from CPD Associate • Updates the eCRFs and/or calendar • Receives notification from the Regulatory Associate that the IRB has approved the amendment • Double Checks that the IRB did not require any additional updates to the protocol that will affect the eCRFs

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	• Releases updated eCRFs • Updates Clinicaltrials.gov • Releases update of clinicaltrials.gov for review by the Regulatory Managers • Emails Regulatory Associate confirming that the entry on clinicaltrials.gov has been completed
Clinical Development Manager	• May request a protocol amendment • Notifies the CPD team of an upcoming protocol amendment • May be tasked with amending the protocol as determined by the PI • May QA the protocol amendment • May help to coordinate funding source review of the amendment by helping to provide contact information
Epic Coordinator	• Receives the FINAL version of the protocol amendment from the UNC Regulatory Associate • Updates OnCore for addition of new arms, etc. • Receive IRB approval notification from UNC Regulatory Associate • Updates OnCore with any IRB required changes if applicable • Releases the OnCore updates
Financial Analyst	• Reviews the amendment to determine if the amendment has a financial impact (this typically results from an update to the time and events table in the protocol) • Requests input from the PI on routine vs. study-related procedures • Revises the BCA • Submits the revised BCA to OCT • Re-negotiates the budget with the funding source • QAs the ICF cost section being sure to harmonize it with the approved budget from the sponsor • Receives notification from the Regulatory Associate that the IRB has approved the amendment
Funding Source	• May provide new information resulting in a protocol amendment (ex: updated IB) • Reviews the protocol amendment if required by the contract
IDS	• May request a protocol amendment • Receives the FINAL and IRB ready version of the protocol amendment from UNC Regulatory Associate • Updates Relevant Documents • Receives notification from UNC Regulatory Associate that the IRB has approved the amendment • If there were IRB requested changes that affect the IDS documents, then updates the documents accordingly

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	• Updated IDS practices initiated
IND Specialist	• May request a protocol amendment • Receives notification of an upcoming protocol amendment and checks that it is docked in OnCore • May be tasked with amending the protocol as determined by the Clinical Development Manager • May QA the protocol amendment • Receives notification from the Regulatory Associate that the amendment has been scheduled for full board review, has received a stipulation letter • Receives notification from the Regulatory Associate that the IRB has approved the amendment • Runs an external committee lapse report to determine what IND actions are outstanding
OnCore Specialist	• Updates coverage analysis and billing calendar in OnCore
Principal Investigator	• May request a protocol amendment • Screens protocol amendment requests to determine if there is an amendment driver • Recommends the use of an administrative letter if there isn't a sufficient amendment driver • May be tasked with amending the protocol a • QAs the protocol amendment • Approves the protocol amendment • QAs the ICF • Receives notification from UNC Regulatory Associate that the IRB has approved the amendment
Regulatory Documents Specialist/ Regulatory Assistant	• Docks the IND submission in OnCore • Docks the IRB submission in OnCore • Receives notification from UNC Regulatory Associate that the IRB has approved the amendment • Processes the IRB submission of the protocol amendment change in protocol
Regulatory Associate	• May request a protocol amendment • Consults with PI to determine if an IB update should trigger a protocol amendment • May be tasked with amending the protocol as determined by Clinical Development Manager • QAs the protocol amendment • Notifies the Regulatory Documents Specialist and/or Regulatory Assistant that docking is required for an IRB submission • Creates subject reimbursement forms (if applicable)

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	• Distributes the IRB ready version of the protocol to the Beacon Coordinator, Financial Analyst, Data Management, CTU Lab Coordinator, UNC Hospital Beacon Analyst, Tissue Procurement Facility, IDS and Study Coordinator • Prepares IRB modification submission • Receives IRB stipulation letter and/or approval letter OR information from IRBIS indicating that the amendment has been scheduled for full board review and notifies the IND Specialist • Notifies the study team and IND Specialist of IRB's approval of the protocol amendment and of any changes IRB made to the protocol during their review • Updates Clinicaltrials.gov • Emails Clinical Data Management to request update to their applicable sections of clinicaltrials.gov • Confirms Clinical Data Management updates to clinicaltrials.gov are complete • Processes the IRB submission of the protocol amendment change in protocol • QA of Regulatory Assistant entries in OnCore for the IRB submissions
Study Coordinator	• May request a protocol amendment • QAs the protocol amendment • Receives the finalized protocol amendment from UNC Regulatory Associate • QAs the final ICF, sent by UNC Regulatory Associate • Receives the IRB ready version of the protocol amendment from UNC Regulatory Associate • Updates the CTSU Flowsheets • Receives notification from UNC Regulatory Associate that the IRB has approved the amendment • If there were IRB requested changes that affect the flowsheets, then updates the flowsheets accordingly
Tissue Procurement Facility	• Receives the IRB ready version of the protocol amendment from the Regulatory Associate • Makes updates to any process flows to reflect the protocol amendment • Receive IRB approval notification from UNC Regulatory Associate • If there were IRB requested changes that affect TPF, then TPF flow is updated accordingly • Updated TPF procedures are initiated
Project Manager	• May request a protocol amendment • QAs the protocol amendment • QAs the ICF • Receives notification from the Regulatory Associate that the IRB has approved the amendment

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Multicenter Regulatory Associate	• May request a protocol amendment • Receives the FINAL and ready version of the protocol amendment from PD Associate and/or IND Specialist • Updates the site-specific ICF templates if necessary • Receives IRB approval notification from UNC Regulatory Associate • Distributes the updated ICF models to all participating sites • QAs site specific ICF updates (if applicable) • Receives the site-specific IRB approval letters • Distributes the protocol amendment to all participating sites
UNC Hospital Beacon Analyst	• Receives the FINAL version of the protocol amendment from the Regulatory Associate • Updates the Beacon Build • Receives notification from UNC Regulatory Associate that the IRB has approved the amendment • If there were IRB requested changes that affect the Beacon build, then updates the beacon build accordingly • Releases the Beacon build

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APPENDIX G: CHEAT SHEETS

The following are cheat sheets to explain some of the tasks related to UNC RA, Multicenter RA, and Project Manager on how to handle protocol amendment

UNC Regulatory Associate Cheat Sheet

What are my responsibilities when working with a protocol amendment?

- You may be asked to write a protocol amendment by Clinical Development Manager. You will follow this working instruction and SOP-2 while preparing the amendment.
- QA the protocol amendment draft when requested by CPD Associate and/or IND Specialist
- QA an updated consent form when requested by CPD team. Don't forget to check CAPAs promised to IRB during your review. Send a copy of the IRB approved CAPA to CPD team to help them in incorporating the CAPAs, when possible.
- Distribute FINAL copies of the amendment to UNC cross-functional team
- Ask Finance Analysts for updated Routine vs. Research spread sheet, when applicable
- Ensure PI information is correct on the first page of the consent
- Notify the Regulatory Documents Specialist and/or Regulatory Assistant that docking is required for an IRB submission
- Prepare IRB modification to submit the amendment and consent form
- Distribute the IRB ready version of the protocol to the Beacon Coordinator, Financial Analyst, CTU Lab Coordinator, UNC Hospital Beacon Analyst, Tissue Procurement Facility, IDS and Study Coordinator
- Notify Clinical Development if IRB issues major stipulations regarding the protocol and consent form.
- Notify the study team and IND Specialist of IRB's approval of the protocol amendment
- Update Clinicaltrials.gov
- Email Clinical Data Management Associate to request update to their applicable sections of clinicaltrials.gov
- Confirms Clinical Data Management updates to clinicaltrials.gov are complete
- Processes the IRB submission of the protocol amendment change in protocol

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Multicenter Regulatory Associate Cheat Sheet

What are my responsibilities when working with a protocol amendment?

- Notify Clinical Development Manager, PI, IND Specialist if participating sites are requesting changes in the protocol.
- QA the protocol amendment draft when requested by CPD team. Don't forget to include any questions/comments received by sites that could improve the protocol.
- QA the updated consent form when requested by CPD team. Don't forget to include any questions/comments received by sites that could improve the protocol.
- Distribute FINAL copies of the amendment and updated consent forms to all participating sites, including UNC.
- Prepare re-consenting plan with PI, if a protocol amendment or updated consent include information that might impact patient's willingness to continue participation in a study
- Distribute re-consenting plan to all participating sites
- Review site-specific changes in consent forms from participating sites. Notify Regulatory Manager if a site substantially changes the original model released by sponsor.
- Check for new IBs and send to participating sites
- Receives IRB stipulation from participating sites and notify IND Specialist, in case a change in the protocol is required
- Update Clinicaltrials.gov

Project Manager Cheat Sheet

What are my responsibilities when working with a protocol amendment?

- Review site inquiries regarding protocol procedures.
- Notify Clinical Development Manager, PI, CPD team if participating sites are requesting changes in the protocol.
- QA the protocol amendment draft when requested by CPD team. Don't forget to include any questions/comments received by sites that could improve the protocol.
- QA the updated consent form when requested by CPD team. Don't forget to include any questions/comments received by sites that could improve the protocol.

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APPENDIX H: RESOURCES

Code of Federal Regulations IND Annual Reports (21CFR312.33):
https://gov.ecfr.io/cgi-bin/text-idx?SID=1d75922673ae72d5a005f8e2ca1e3b1b&mc=true&node=se21.5.312_133&rgn=div8

Code of Federal Regulations IND Protocol Modifications (21CFR312.30):
https://gov.ecfr.io/cgi-bin/retrieveECFR?gp=&SID=8afe7f88b0db526df0a7571d168e0119&mc=true&n=sp21.5.312.b&r=SUBPART&ty=HTML#se21.5.312_130

SOP 8110: Submission of Paper Regulatory Applications to CBER:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079467.htm