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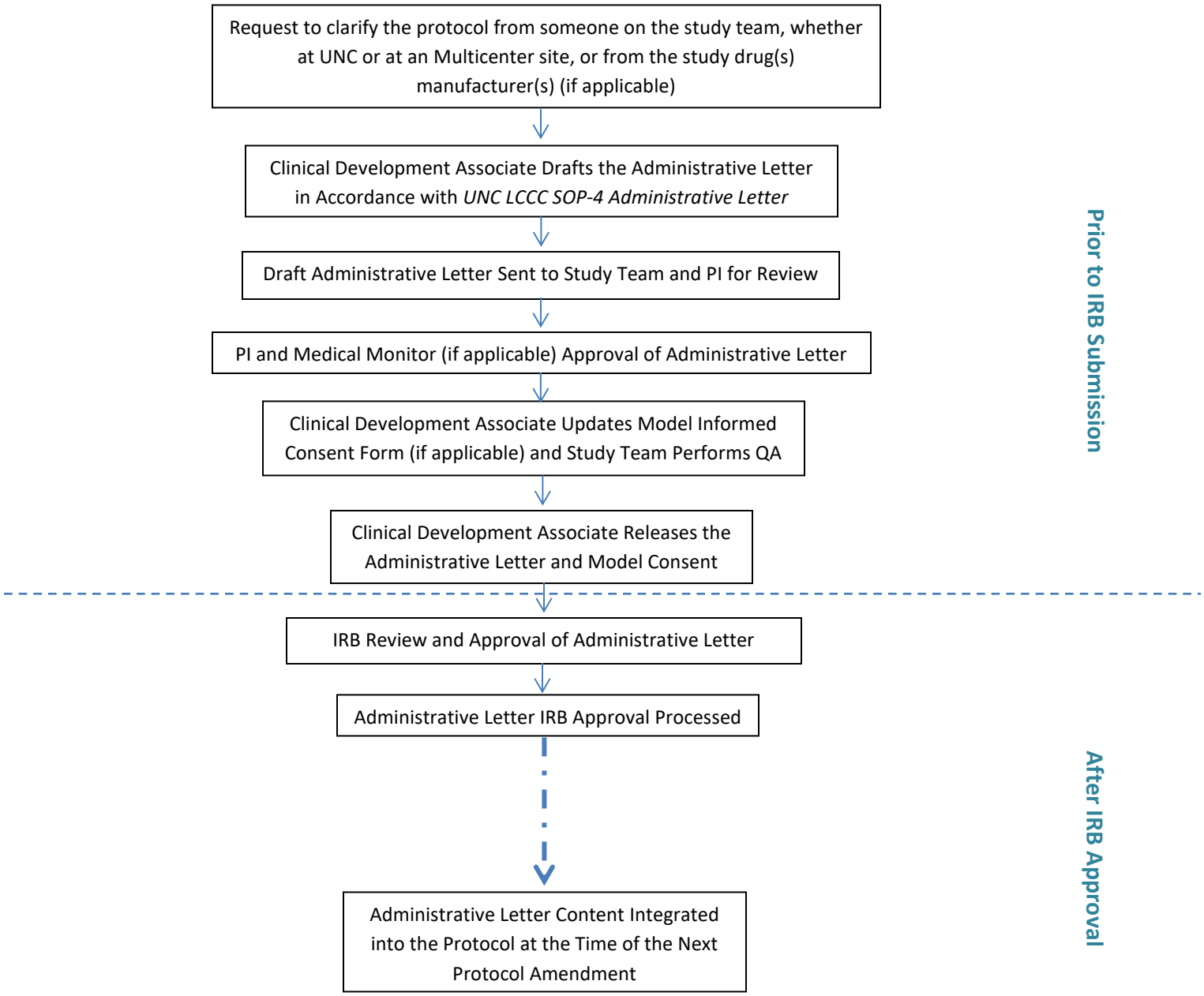

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I. Request to Clarify the Protocol from Someone on the Study Team, Whether at UNC or at an Multicenter Site, or from the Study Drug(s) Manufacturer(s) (if applicable)

The Medical Monitor and PI of the study will screen all requests with the Clinical Development Manager or a member of the Clinical Development team to determine if an administrative letter could suffice in lieu of an amendment, regardless of whether the issue will be addressed in a future amendment.

The following types of changes are sufficient to drive an amendment and should NOT be included in an administrative letter:

- Change in dose (including addition of a new dose level which is higher or lower), frequency of dosing, duration of treatment

- Addition or deletion of an Investigational Product (IP) for protocol directed treatment
- Increase in the number of subjects to be enrolled
- Study design change 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)

Examples of clarifications that may be addressed in an administrative letter:

- Changes addressed in an administrative letter must be either logistical/administrative changes or clarifications that do not change the original meaning of the text. For example:

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- The time and events table includes creatinine as part of serum chemistries and the study assessment section omits it
- A brief window (e.g. +/- 2 days) is allowed for study visits, but this is not specified in the protocol
- Addition/Removal of a new Co-InvestigatorChange in Medical Monitor

II. Clinical Development Associate Drafts the Administrative Letter in Accordance with *UNC LCCC SOP-4 Administrative Letters*

The Clinical Development Associate (Protocol Development Associate or IND Specialist) drafts an administrative letter using the administrative letter template (DT-4).

Example administrative letter:

Administrative Letter

DATE: June 23, 2016
STUDY: 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
IND NUMBER: 14688

Dear Investigator:

This administrative letter is to document the change in 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.

This is an administrative protocol change and does not significantly affect the safety of subjects, study scope, or scientific quality of the protocol. Accordingly, it may be implemented immediately, or as per your institutional IRB policy.

The clarifications/changes made to the protocol are as follows:

1. **Serum Pregnancy tests must occur within 72 hours of lymphodepletion**
    a. Foot note #3 in the time and events table of Protocol Amendment 1 indicates that serum pregnancy tests will occur 72 hours prior to infusion of ATLCAR cells. However, pregnancy testing is listed as occurring within 72 hours prior to infusion of lymphodepleting chemotherapy in section 6.2.2 of the protocol. This letter clarifies that pregnancy testing should occur within 72 hours of lymphodepletion.
2. **Certificate of Analysis (CofA) will be generated at the completion of required studies for production/QA of cells. The CofA will be available prior to the planned infusion.**

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a. Section 6.2.1 (Pre-procurement) lists that the CofA will be generated at this time point. However, the time and events table and Appendix C list CofA as being available at the time of ATLCAR.CD30 infusion. This letter clarifies that the CofA will be available prior at the time of ATLCAR.CD30 infusion.

3. **The list of co-Investigators has been updated with the addition of Yara Park, MD and Christopher Dittus, DO, MPH and the removal of Peter Voorhees, MD.**

Please maintain a copy of this administrative letter with your protocol. Please provide a copy to your Investigational Review Board as per your institutional policy.

III. Draft Administrative Letter Sent to Study Team and PI for Review

The Clinical Development Associate Distributes the Administrative Letter to applicable study team members for review:

- Study Coordinator
- Regulatory Associate
- Clinical Data Management Associate
- In-House Monitor
- Multicenter Project Manager (if applicable)
- Multicenter Regulatory Associate (if applicable)

It is particularly helpful if the individual requesting the administrative letter performs QA to confirm his/her concerns are addressed. The study team is typically given 48 hours to review unless the administrative letter is urgent and the timeline for review is included in the email to the team requesting their review.

IV. PI and Medical Monitor (if applicable) Approval of Administrative Letter

The PI and Medical Monitor (if applicable) approve the administrative letter and then the Regulatory Associate signs the administrative letter.

Please note: *Some funding sources may require review or receipt of administrative letters.*

The CD Associate would then submits amendment to funding source(s), to obtains 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 CD Associate should review the contract, which can be found in a study-specific folder in the finance folders:

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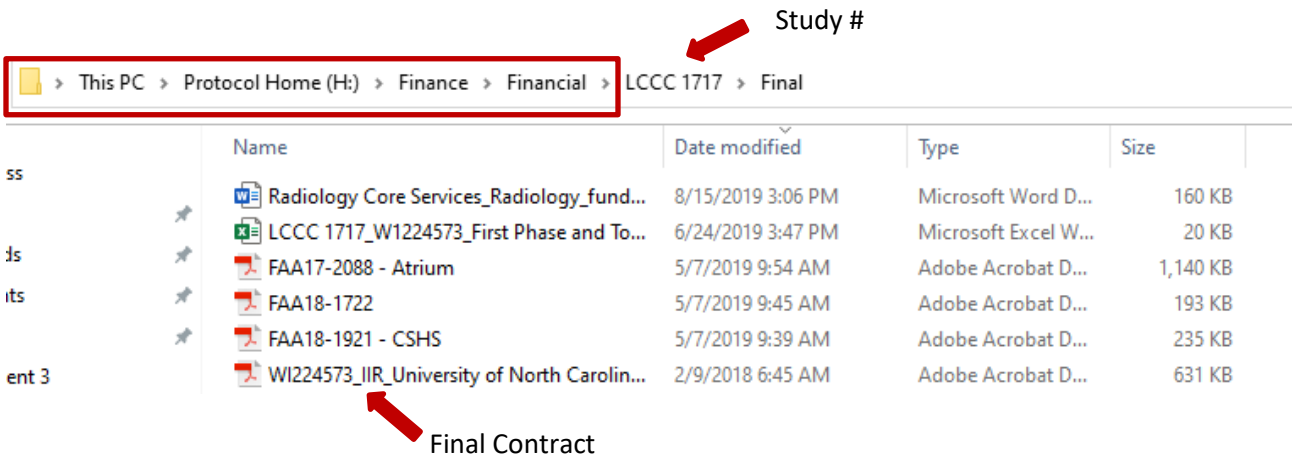

- CD Associate can find the list of Medical Science Liaisons (MSLs) who can either accept the submission via email or direct the CD Associate on how to submit the protocol for review here: **R:\LCCC_CPO Development\Administrative\MSL Contact List**
    - *Please Note:* This list should be updated by the CD Associate if a new contact is discovered during the amendment review process.
- 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 CD Associate requests the following individual to submit through the portal on their behalf:
    - For multicenter trials: Multicenter project manager
    - For single center: Study coordinator

V. Clinical Development Associate Updates Model Informed Consent Form (if applicable) and the study team performs QA

The Informed Consent Form (ICF) should be updated to reflect the protocol changes. Additional changes, as required, may be incorporated into the ICF at this time.

The ICF should be updated using the track change function of Microsoft Word. A final clean and tracked versions should be saved.

The consent drafts are reviewed by the study team.

For a Multicenter IIT Study:

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

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For Single Center IIT Study:

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

VI. Clinical Development Associate Releases the Administrative Letter and Model Consent (if applicable)

A **FINAL** copy of the administrative letter and model consent form is **released b**y a member of the Clinical Development Team.

- If it is an administrative letter only (no ICF updates), then the CD Associate who wrote and/or finalized the letter will release it

- If the informed consent form has been updated, the CD Associate who updated the ICF will release the final documents.

For a Multicenter IIT Study:

- A **FINAL** copy of the administrative letter is **released** to: Multicenter regulatory associate; Project Manager; CPO Multicenter Listserv; Clinical Data Management Associate; 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** administrative letter 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 LCCC IND Protocol Amendment- Change in Protocol WIs for additional details)

For a Single Center IIT Study:

- A **FINAL** copy of the administrative letter is **released** to: UNC Regulatory Associate; Clinical Data Management Associate; In-house Monitor; PI
- A **FINAL** copy of the model consent form is **released** to: UNC Regulatory Associate

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Example notification of release of new administrative letter 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,

Attached find administrative letter #1 to protocol amendment #2 (dated October 27, 2019) for the above-mentioned study. A clarification was made about the timing of the start of radiation therapy. The Adult Informed Model Consent was also updated to accommodate changes in the amendment.

Attached are:

- LCCC 1725 Administrative Letter #1 (dated 10/27/2019)
- LCCC 1725 Adult Model 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,

OR

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,

Attached find administrative letter #1 to protocol amendment #2 (dated October 27, 2019) for the above-mentioned study. This letter reflects a change in the medical monitor.

Attached is the following:

- LCCC 1725 Administrative Letter #1 (dated 10/27/2019)

No other documents will be changed at this time.

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

Best,

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VII. IRB Review and Approval of Administrative Letter

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

VIII. Administrative Letter IRB Approval Processed

UNC Regulatory Associate will email the study team per typical regulatory team processes to inform of IRB approval of the submitted administrative letter and the approval is processed in OnCore.

Please Note: *This email should also clearly indicate which subjects require re-consent.*

Please Note: *Clinicaltrials.gov may need updating. Please refer to the Clinicaltrials.gov work instructions for aid in the process.*

IX. Administrative Letter Content Integrated into the Protocol at the Time of the Next Protocol Amendment

The Clinical Development Associate guarantees that when the protocol is next amended the clarifications included in the administrative letter are integrated into the updated protocol if it is still applicable. Please refer to **SOP #2 Amending CPO IIT** and the accompanying work instructions for additional details.

X. RESOURCES

Code of Federal Regulations IND Protocol Modifications (21CFR312.30):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.30

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

IND Application Reporting: Protocol Amendments:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362503.htm

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Appendix I: Roles and Responsibilities

Role	Responsibilities
Biostatistician	• May Request an Administrative Letter
Clinical Data Management Associate	• May Request an Administrative Letter • QAs Administrative Letter • Notified of IRB Approval
Clinical Development Associate (Clinical Protocol Development Associate OR IND Specialist)	• May Request an Administrative Letter • May screen request for administrative letter • Drafts the administrative letter • Updates the informed consent form (if applicable) • Secures funding source approval of the administrative letter (if applicable) • Secures PI approval of the administrative letter • Releases administrative letter to the study team\ Guarantees that Administrative Letter Content is Integrated into the Protocol at the time of the next Protocol Amendment
CTU Laboratory Coordinator	• May Request an Administrative Letter
Funding Source	• May Request an Administrative Letter • May review and approve
IDS	• May Request an Administrative Letter
Multicenter Project Manager	• May Request an Administrative Letter • QA Administrative Letter (if applicable) • QA Consent Form (if applicable) • Notified of IRB Approval (if applicable)
Multicenter Regulatory Associate	• May Request an Administrative Letter • QA Consent Form (if applicable) • Distributes Administrative Letter to Multicenter sites • Notified of IRB Approval (if applicable)
Multicenter Sites	• May Request an Administrative Letter
Principal Investigator and/or Medical Monitor	• May Request an Administrative Letter • Screens all requests for Administrative Letters • Approves Administrative Letter • Notified of IRB Approval

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Role	Responsibilities
Regulatory Documents Specialist/ Regulatory Assistant	• Notified of upcoming administrative letter • Docks Administrative Letter submission in OnCore • Notified of IRB Approval • Processes IRB Approval
Regulatory Associate	• May Request an Administrative Letter • May Draft Administrative Letter if so Delegated by Clinical Development • May Update Consent Form (if applicable) if so Delegated by Clinical Development • Prepares IRBIS Modification Submission • Processes IRB Approval
Study Coordinator	• May Request an Administrative Letter • May QA Administrative Letter • QAs Consent Form • Notified of IRB Approval