Effective Date: 12/1/2017	Single Subject Exceptions, v1

Policy

This policy addresses the process that Lineberger Comprehensive Cancer Center (LCCC) uses to determine the permissibility of single subject exceptions and delineates alternative courses of action when single subject exceptions are not permitted.

Rationale

Many institutions and external IRBs have policies on single subject exceptions (SSEs) to both protect the integrity of the study data, promote a healthy risk/benefit ratio for subjects and ensure FDA compliance. Without such a policy in place, LCCC as the sponsor of our studies, and LCCC investigators who are tasked with overseeing the conduct of the research, are placed at an increased risk. As a result of recent comment and guidance from FDA, CTEP and NCI, we are instituting a policy on single subject exceptions to protect the integrity of our studies and to protect our investigators. Single subject exceptions are often misconstrued as a method of "wiping the slate clean" of an upcoming deviation. However, whether or not a single subject exception has been granted, both FDA and IRB still view this event as a deviation to the protocol.

Policy Statement

Lineberger Comprehensive Cancer Center Investigator Initiated Trials

Eligibility SSEs are not permitted for Lineberger Comprehensive Cancer Center (LCCC) Investigator Initiated Trials (IITs) under any circumstances (both for IND and IND exempt IITs).

If the PI feels strongly that an eligibility SSE is necessary and is not truly deviating from the parameters of the protocol, then the recommended course of action is creation of a protocol administrative letter clarifying the eligibility exception in question. Please note that an administrative letter can only be used to clarify an eligibility criterion, not to change an eligibility criterion. For example, if patients with ≥ Grade 2 AEs from prior treatment are excluded, but the eligibility criteria also allows hemoglobin levels > 9, then the eligibility criteria may be clarified to indicate that the intent was to exclude patients with ≥ Grade 2 AEs except hematological toxicities. Prior to IRB submission and approval, this administrative letter must be approved by the PI, IND PI (if applicable), IND Specialist (if applicable), the Assistant Director of Quality Assurance and Regulatory, and Director of Protocol Development (if applicable) as listed in Lineberger SOP #4 (Administrative Letters). The administrative letter must be incorporated into the next protocol amendment. Although SSE are not permitted in any other circumstances, a protocol amendment may be pursued in lieu

of an exception after proper regulatory review. For IND trials, many changes to the protocol must be reviewed by FDA according to 21CFR312.30 (see below).

SSEs not related to eligibility may be granted after proper regulatory and LCCC sponsor review. As above, for IND trials, many changes to the protocol must be reviewed by FDA according to 21CFR312.30 (see below). A SSE may be viewed as either a divergence from the protocol (deviation) or an amendment to the protocol for a single subject. Consultation with the IND specialist should occur when determining what amendments and/or single subject exception requests must be sent to the FDA per regulation. Per 21CFR312.30:

> A Sponsor of an IND application is expected to submit a protocol amendment in cases when there are changes in the existing protocol that significantly affect safety of subjects, scope of the investigation, or scientific quality of the study. For example, changes requiring an amendment to an IND application may include:
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> - Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
> - Any significant change in the design of a protocol (such as the addition or elimination or a control group)
> - Addition of a test or procedure intended to improve monitoring for, or reduce the risk or, a side effect or adverse event; or elimination of a test intended to monitor safety.
> - **Note:** A protocol change intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that FDA is subsequently notified by protocol amendment and the reviewing IRB is also notified

For IND exempt IITs, the delineated above criteria will also help determine when a more stringent review of the SSE request is warranted. The attached decision tree delineates the LCCC process for evaluating whether the submission of a single subject exception on LCCC IITs at either UNC or an affiliate site is permissible or the other options that may be pursued if the submission of a single subject exception is not permissible. In all cases, SSEs (except those intended to avoid apparent immediate hazard to the subject), administrative letters and protocol amendments must be approved by the IRB prior to implementation.

Cooperative Group Trials

In most cases, the cooperative groups do not allow for single subject exceptions. NCI CIRB does not review or approve any planned deviations (exceptions). The Cancer Therapy Evaluation Program (CTEP) does not allow protocol deviations of any type. If a change to a CTEP-approved protocol is necessary, the Protocol Chairman may submit an amendment to

the protocol. The amendment must be approved in writing by CTEP prior to its implementation. In all cases, SSE requests should be reviewed by the UNC National and Cooperative Group Coordinator or the Assistant Director of Quality Assurance and Regulatory.

Pharmaceutical Sponsored Trials and Trials Sponsored by Other Academic Institutions

All types of SSEs for industry-sponsored trials or other academic institution sponsored trials need to be routed to the industry sponsor or other academic institution for approval prior to implementation. Additionally, the IRB must review and approve the single subject exception prior to implementation.

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Date

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Revision History

Version No.	Date	Authors/Approvers	Changes
1	11/06/2017	K. Morrison, S. Raboin, C. Lee	New Policy