University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center

Policy for Protocol Development and Maintenance of Interventional Investigator Initiated Trials Sponsored by the University of California San Francisco

Purpose

The purpose of this Helen Diller Family Comprehensive Cancer Center (HDFCCC) policy is to outline the protocol development, approval, and maintenance requirements for oncology-related, interventional investigator initiated trials (IITs) sponsored by the University of California San Francisco (UCSF).

Scope

This policy applies to oncology-related, interventional therapeutic and non-therapeutic IITs, both single and multi-center, sponsored by UCSF.

Definitions

- ***Interventional Clinical Trial:*** *As* defined by the National Cancer Institute *(NCI), "Individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, treatment, behavioral, or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed."*

Background

Overall compliance for UCSF-sponsored IITs is the responsibility of the Principal Investigators (PIs). Protocol development and maintenance for all UCSF-sponsored IITs must consider the elements described in this policy to ensure compliance with federal, state, University, collaborating partner, and HDFCCC standards and policies.

The Protocol Development (PD) unit, a division of the Clinical Research Support Office (CRSO), works on interventional UCSF-sponsored IITs managed and staffed by CRSO programs. PD involvement begins after initial Site Committee protocol review. The PD Manager is the point person for the discussion of questions, workflow, and timelines for the development of CRSO-managed interventional UCSF IITs (contact CRSO@ucsf.edu).

Procedures

Refer to Appendix 1 for an outline of the activation process for interventional UCSF-sponsored IITs.

1. Required Protocol Elements

The Site Committee of record is responsible for ensuring that the protocol requirements described below are included in new IITs. The Site Committee Chair/Co-Chair will acknowledge that all elements have been included and reviewed as part of the Chair or Co-Chair Summary of Review form.

a. HDFCCC Protocol Templates

HDFCCC protocol templates must be used for all interventional oncology-related IITs. These templates are designed to meet the requirements for HDFCCC policies and procedures, Good Clinical Practice (GCP), Institutional Review Board (IRB) review, Food and Drug Administration (FDA) submission, and National Institutes of Health (NIH)/National Cancer Institute (NCI) guidance.

HDFCCC protocol templates detail the minimum sections that all protocols should include. Resources, references, and suggestions for consideration when developing various sections are embedded within the protocol templates. Where applicable, HDFCCC protocol boilerplate language is provided in the template to ensure that all IIT protocols meet the standards defined by the groups above. All revisions made to a protocol after it has been submitted to any regulatory body should be made in a new protocol version with a new date. Protocol dating and versioning should match that described in the PRMS Amendment Submission Policy.

b. HDFCCC Data and Safety Monitoring Committee (DSMC)

PIs and their study teams are required to meet all training requirements set by the HDFCCC DSMC. Specific to UCSF-sponsored IITs, all therapeutic and nontherapeutic protocols must incorporate the Data and Safety Monitoring Plan (DSMP) templates from the most recent version of the NCI-approved DSMP to detail the delineation of responsibilities and a description of the data and safety review process that must be followed during the life of the trial. The DSMC Director must review the protocol for safety and monitoring language prior to Protocol Review Committee (PRC) submission.

For UCSF IITs that enroll participants at any international site, the PI/study team must follow the HDFCCC DSMC policy to ensure oversight of all international sites, including training of all staff, and hiring of an international Contract Research Organization (CRO) as appropriate.

c. Statistical Considerations

All interventional UCSF-sponsored IITs must have a trained statistician designated as the study statistician. The study statistician is named on the protocol cover page and is responsible for drafting the protocol statistical analysis plan, objectives, endpoints, sample size and power estimate during study activation.

Prior to Site Committee protocol approval, these statistical components of the protocol should be comprehensive and complete. For HDFCCC protocol

statistics requirements and review processes, refer to the PRMS Protocol Review Committee (PRC) Review Policy and Protocol Review Committee Review Forms.

The HDFCCC provides statistical support during the protocol development process for UCSF-sponsored IITs, if needed. Contact the HDFCCC Biostatistics Core statistician assigned to your disease program.

d. Investigational Drug Services (IDS)

UCSF IDS may be consulted for IIT protocols with unique or special requirements. Any requests to IDS will be reviewed within 10-business days and the IDS Consultation Fee will apply.

e. Diversity

UCSF IIT protocols must include a statement regarding equitable participant recruitment or justification for excluding a specific population. Suggested phrasing is available in the IIT protocol template.

f. Multi-center Trials (MCT)

The following requirements apply to multi-center UCSF-sponsored IITs:

- UCSF IRB approval of the study protocol and consent form must be obtained prior to opening the study at any participating site.
- The study protocol should address any site-specific information regarding laboratory facilities, testing, shipping, ordering, data entry, or any other study components that may differ across sites.
- The Coordinating Center should be identified and a Scope of Work document should be completed to clearly assign study responsibilities across the various study collaborators.

2. Protocol Review and Monitoring System (PRMS) Approval

All oncology and oncology-risk related protocols must be approved for scientific merit, prioritization and feasibility by PRMS before IRB approval. Two levels of review are required: 1) Site Committee and 2) Protocol Review Committee (PRC). Approved studies must submit all revisions to protocols to PRMS for the life of the trial, per PRMS policy, until IRB closure. For Site Committee and PRC submission and review processes, please refer to the PRMS Site Committee Review Policy and the PRMS PRC Review Policy.

3. Regulatory Approvals

UCSF-sponsored IITs are subject to Institutional Review Board (IRB) and FDA approval and reporting as listed in the References section of this policy.

4. ClinicalTrials.gov and Clinical Trials Reporting Program (CTRP)

As defined in 42 CFR 11.10(a-b), the NIH, FDA, and International Committee of Medical Journal Editors require PIs to register and update interventional IITs with ClinicalTrials.gov. Additionally, all interventional trials conducted at the HDFCCC must be registered in CTRP and report accruals quarterly to meet the NCI DT4 requirement. PIs can contact the HDFCCC Research Compliance Team with questions about ClinicalTrials.gov and CTRP.

5. Requirements for Opening to Accrual

Prior to opening to accrual at UCSF or participating subsites, all applicable regulatory, billing, and contractual requirements must be completed, including:

- FDA authorization and IRB approval
- Medicare Coverage Analysis (MCA) final check
- Contract execution with collaborating partners through UCSF Legal

6. Study Operations and Maintenance

a. OnCore Data Entry

All UCSF-sponsored IITs are registered in the HDFCCC central clinical trial management system (CTMS), OnCore, at the time of PRC submission, and must continue to be updated in real-time and maintained for the duration of the study until IRB closure. Expected updates include:

- Study status changes (e.g., IRB approved, open to accrual, closed to accrual, etc.)
- Accrual reporting – including dates of consent/withdrawal, treatment start/stop, and on/off study
- Adverse Event/Serious Adverse Event reporting as stated in protocol
- IND/IDE submission and renewal information (Refer to IND/IDE Central Management Policy)
- Study staff changes
- New funding sources
- Change in the study management team.

b. Protocol Amendments

All protocol amendments are submitted to PRMS, IRB, and FDA (if applicable) throughout the life of the study. Certain protocol changes may also require subsequent updates to the study's ClinicalTrials.gov and CTRP registrations. Protocol amendments should also be reviewed by DSMC and IDS, when applicable. Refer to the PRMS Amendment Submission Policy for Summary of Changes and versioning/dating requirements.

c. Administrative Memos

Variations to the protocol to convey new information or instructions can only be implemented after IRB approval of a formal protocol amendment, and not via an administrative memo. When protocol changes are necessary to immediately eliminate or reduce an apparent hazard to the safety of research participants or others, according to UCSF IRB, those changes may be initiated without prior IRB approval and then must be reported to the IRB/HRPP after initiation within the mandatory time frame and must be followed by a protocol amendment.

References

FDA Guidelines

- 42 CFR 11
- FDA IND Applications
- FDA IND Exemptions
- FDA IND Protocol Amendments
- FDA IDE Required Elements

NIH/NCI Policies

- NIH Policy on the Use of Single IRB
- NCI Data Table 4

UCSF IRB:

- Protocol Violations or Incident Page (Reporting Requirements Chart for Immediate Protocol Change to Protect Participant Safety)
- IRB Review Requirements and Submissions

HDFCCC:

- PRMS PRC Review Policy
- PRMS Site Committee Review Policy
- PRMS Amendment Submission Policy
- PRMS Protocol Closure Policy
- IND/IDE Central Management Policy
- HDFCCC Website: Conducting Research on Subjects Diagnosed with, or at risk for, Cancer

Alternate Procedure

None.

Appendices

Appendix 1: Interventional UCSF-Sponsored IIT Activation Table

Policy Approval

This policy was approved by the following personnel on the following dates:

DocuSigned by:
Charalambos Andreadis
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10/30/2019

Charalambos Andreadis, MD
Clinical Research Support Office Medical Director
Helen Diller Family Comprehensive Cancer Center

Date

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10/28/2019

Jennifer Clarke, MD
Protocol Review Committee Chair
Helen Diller Family Comprehensive Cancer Center

Date

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10/28/2019

Eric Small, MD
Chief Scientific Officer,
Helen Diller Family Comprehensive Cancer Center

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Kate Shumate, MPA, CCRP
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APPENDIX 1: INTERVENTIONAL UCSF-SPONSORED IIT ACTIVATION TABLE

IIT Start Up Tasks	Sequence	
	CRSO	Non-CRSO
Site Committee (SC) concept review and approval (optional)	Step 1	Step 1
SC protocol review and approval	2	2
Multicenter Trials (MCT) PI Feasibility Questionnaire completed (for MCTs only)	3	N/A
PD work request by study team	4	N/A
DSMC review of all non-CRSO protocols to ensure compliance to HDFCCC monitoring and safety reporting requirements	N/A	3
FDA submission and FDA comments addressed (as applicable)	5	4
PRC submission and approval	6	5
BioSafety submission and Inpatient BMT nurse manager letter of support (if applicable)	7	6
After responses to FDA completed, PD releases protocol to study team for remaining pipeline work request	8	N/A
IRB submission (after FDA submission and PRC approval)	9	7
Request submitted for remaining pipeline work. Work completes in the following order while IRB submission is underway: OnCore calendar build → Medicare Coverage Analysis (MCA) → Ancillary budget requests → Main budget development → MCA final check → Contracts (if applicable)	10	8
At budget negotiations, study team begins study conduct preparation, as applicable (i.e., nursing orders, eCRF creation, kits preparation, etc.)	12	9
Contracts/ agreements executed (if applicable)	13	10
Open to Accrual documented in OnCore and notification to study team[1]	14	11
APeX build complete[2] and UCSF participant enrollment begins	15	12
Multi-center trials *(NOTE: in addition to the unique steps below, all multi-center trials must complete the steps above. Steps below can begin after UCSF IRB approval)* [3]		
Study team kick off meeting	A	N/A
UCSF approval of sub-site ICF(s) for IRB review[4] and IRB submission	B	A
Sub-site(s) IRB approval	C	B
Sub-site(s) budget and contract negotiation and execution	D	C
Sub-site(s) initiation visits	E	D
Sub-site(s) documented into OnCore	6	5
Sub-site(s) IRB approval letter added in UCSF IRB application	7	6

[1] IITs can open to accrual when all UCSF requirements are met: SC, PRC, FDA, IRB, MCA, budget, and contract execution (as applicable). Per UCSF billing compliance policy, participants cannot enroll until APeX is built.

[2] APeX build must be in place, per UCSF billing compliance policy, to enroll participants on study.

[3] Subsite startup begins only after UCSF study has been approved by IRB. Although not required, it is preferred that subsites start after budget development to provide subsites a full startup packet inclusive of budget.

[4] For study teams working with the CRSO, PD will review and approve sub-site ICFs. For non-CRSO study teams, the study team is expected to review and approve subsite ICFs before sub-sites obtain their local ICF approval.

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Summary of Changes

Policy Title: Policy for Protocol Development and Maintenance of Interventional Investigator Initiated Trials Sponsored by the University of California San Francisco

Version Date: 10/23/2019
Revision Number: 1

Page No.: 1	**Sections:** Purpose, Scope, Definitions
Original Text	**Purpose** The purpose of this Helen Diller Family Comprehensive Cancer Center (HDFCCC) policy is to outline the protocol development, approval, and maintenance requirements for oncology-related, interventional therapeutic and non-therapeutic investigator initiated trials (IITs), both single and multi-center, sponsored by the University of California San Francisco (UCSF).
New Text	**Purpose** The purpose of this Helen Diller Family Comprehensive Cancer Center (HDFCCC) policy is to outline the protocol development, approval, and maintenance requirements for oncology-related, interventional ~~therapeutic and non-therapeutic~~ investigator initiated trials (IITs), ~~both single and multi-center,~~ sponsored by the University of California San Francisco (UCSF). ***Scope*** ***This policy applies to oncology-related, interventional therapeutic and non-therapeutic IITs, both single and multi-center, sponsored by UCSF.*** ***Definitions*** • ***Interventional Clinical Trial: As defined by the National Cancer Institute (NCI), "Individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, treatment, behavioral, or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed."***
Reason for Change	• 'Scope' and 'Definitions' sections added to align with standard HDFCCC policy format. • Transferred information from 'Purpose' to new 'Scope' section. • Added NCI definition of interventional clinical trial.

Page No.: 1	**Section:** Background
Original Text	The Protocol Development (PD) unit, a division of the Clinical Research Support Office (CRSO), works on interventional UCSF IITs managed and staffed by CRSO programs. PD involvement begins after initial Site Committee (SC) protocol review. The PD Manager is the point person for the discussion of questions, workflow, and timelines for the development of CRSO-managed interventional UCSF IITs.
New Text	The Protocol Development (PD) unit, a division of the Clinical Research Support Office (CRSO), works on interventional UCSF***-sponsored*** IITs managed and staffed by CRSO programs. PD involvement begins after initial Site Committee ~~(SC)~~ protocol review. The PD Manager is the point person for the discussion of questions, workflow, and timelines for the development of CRSO-managed interventional UCSF IITs ***(contact CRSO@ucsf.edu).***
Reason for Change	• Editorial revisions • Added CRSO central inbox as contact for Protocol Development Manager.
Page No.: 2	**Section:** Required Protocol Elements - Statistical Considerations
Original Text	All interventional UCSF IITs must have a trained statistician designated as the study statistician. The study statistician is named on the protocol cover page and is responsible for drafting the protocol statistical analysis plan, objectives, endpoints, sample size and power estimate. At the time of Site Committee protocol review, the statistical components of the protocol should be comprehensive and complete. For HDFCCC protocol statistics review processes, refer to the Site Committee and Protocol Review Committee Policies. Refer to the Site Committee and Protocol Review Committee Review Forms for protocol statistics requirements. Contact the HDFCCC Biostatistics Core or the statistician associated with your disease program for assistance.
New Text	All interventional UCSF***-sponsored*** IITs must have a trained statistician designated as the study statistician. The study statistician is named on the protocol cover page and is responsible for drafting the protocol statistical analysis plan, objectives, endpoints, sample size and power estimate ***during study activation***. ~~At the time of~~***Prior to*** Site Committee protocol approval, these statistical components of the protocol should be comprehensive and complete. For HDFCCC protocol statistics requirements and review processes, refer to the ~~Site Committee and Protocol Review Committee~~ Policies***PRMS Protocol Review Committee (PRC) Review Policy*** ***and*** ~~Refer to the Site Committee and Protocol Review Committee~~ ***Protocol Review Committee*** Review Forms ~~for protocol statistics requirements~~. ***The HDFCCC provides statistical support during the protocol development process for UCSF-sponsored IITs, if needed.*** Contact the HDFCCC Biostatistics Core statistician ***assigned to*** ~~associated with~~ your disease program.

Reason for Change	• Clarified that the HDFCCC funds Biostatistics Core statisticians to draft statistical components of protocol during study startup. • Clarified completed protocol statistics are required prior to Site Committee approval. • Removed references to Site Committee statistical review.
Page No.: 4	**Section:** ClinicalTrials.gov and Clinical Trials Reporting Program (CTRP)
Original Text	As defined in 42 CFR 11.10(a-b), the NIH, FDA, and International Committee of Medical Journal Editors require PIs to register and update interventional IITs with CT.gov. Additionally, all interventional trials conducted at the HDFCCC must be registered in CTRP and report accruals quarterly to meet the NCI DT4 requirement. PIs can contact the HDFCCC Research Compliance Team with questions about CT.gov and CTRP.
New Text	As defined in 42 CFR 11.10(a-b), the NIH, FDA, and International Committee of Medical Journal Editors require PIs to register and update interventional IITs with C~~T~~***linicalTrials***.gov. Additionally, all interventional trials conducted at the HDFCCC must be registered in CTRP and report accruals quarterly to meet the NCI DT4 requirement. PIs can contact the HDFCCC Research Compliance Team with questions about C~~T~~***linicalTrials***.gov and CTRP.
Reason for Change	Removed any shorthand for ClinicalTrials.gov.
Page No.: 4	**Section:** Study Operations and Maintenance – Protocol Amendments
Original Text	All protocol amendments are submitted to PRMS, IRB, and FDA throughout the life of the study.
New Text	All protocol amendments are submitted to PRMS, IRB, and FDA ***(if applicable)*** throughout the life of the study.
Reason for Change	• Clarified that protocol amendments are only submitted to FDA if applicable (for FDA-regulated trials).
Page No.: 6	**Section:** Policy Approval
Original Text	N/A
New Text	***Policy contact:*** ***Andrea Skafel, Clinical Research Support Office Director*** ***Andrea.Skafel@ucsf.edu; +1 415 502 5805***
Reason for Change	• Added policy contact