UCSF Helen Diller Family Comprehensive Cancer Center

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

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

This policy covers the development, approval, and maintenance procedures of oncology-related, interventional IITs.

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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). For the purpose of this policy, these IITs will be referred to as HDFCCC IITs.

Scope

This policy applies to all oncology-related, interventional IITs both single and multicenter, 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."

Oncology-related: As defined by the UCSF PRMS, "clinical research projects conducted at the HDFCCC and its affiliates studying participants with cancer or those at risk for cancer, and providers of care to cancer patients (including clinical providers, caregivers or personal support, and health systems)."

Background

Responsibility for overall compliance with UCSF-sponsored IITs rests with the Principal Investigator (PI). To ensure compliance with federal, state, University, collaborating partners, and HDFCCC policies, protocol development and maintenance of all HDFCCC IITs for oncology-related protocols must align with the elements outlined in this policy.

The Protocol Development (PD) unit, a division of the Clinical Research Support Office (CRSO) at the HDFCCCC, works on HDFCCC-supported, UCSF-sponsored IITs. PD involvement begins at the Site Committee concept review stage. The PD Manager is the point person for discussing questions, workflows, and timelines for developing CRSO-managed interventional UCSF IITs (contact mailto:CRSOIND@ucsf.edu).

Procedures

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

1.0 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.

1.1 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)/ 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.

1.2 HDFCCC Data and Safety Monitoring Committee (DSMC)

PIs and their study teams are required to meet all training requirements set by the HDFCCC DSMC Education and Training Office. Specific to UCSF-sponsored IITs, all therapeutic and non-therapeutic 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 (or delegate) must review the protocol for safety and monitoring language prior to Protocol Review & Monitoring Committee (PRMC) submission (Appendix 1).

For HDFCCC IITs that enroll participants at any international site, the PI/study team must follow the HDFCCC DSMC Policy on Minimum Standards for Partnerships with International Clinical Research Organizations (CROs) to ensure oversight of all international sites, including training of all staff and hiring of an international CRO as appropriate.

1.3 Statistical Considerations

All interventional HDFCCC 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 and Monitoring Committee (PRMC) Review Policy and Protocol Review Committee Review Forms.

The HDFCCC provides statistical support during the protocol development process for UCSF-sponsored IITs if needed. Requests for the services of the HDFCCC Biostatistics Core may be made through an online request.

1.4 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.

For all IDS-related inquiries, please use the IDS Intake Form located at ids.ucsf.edu. The IDS internal website can also be used to locate updated SOPs, fee schedules, contact information, and updates related to IDS.

1.5 Diversity

All HDFCCC 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 templates.

1.6 Multicenter Trials (MCT)

The following requirements apply to multicenter HDFCCC IITs:

- Non-UCSF sites must be reviewed and approved by the DSMC.
- 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.

2.0 Protocol Review and Monitoring System (PRMS) Approval

All oncology-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 and Monitoring Committee (PRMC). For Site Committee and PRMC submission and review processes, please refer to the PRMS's Site Committee Review Policy and PRMC Review Policy.

3.0 Regulatory Approvals

HDFCCC IITs are subject to IRB and FDA approval and reporting as listed in the References section of this policy.

4.0 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.

5.0 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
- OnCore calendar build
- Medicare Coverage Analysis (MCA) final check
- Contract execution with collaborating partners through UCSF Legal

6.0 Study Operations and Maintenance

6.1 Approval of OnCore Electronic Case Report Forms (eCRFs) for Patients Prior to the Start of Enrollment in IITs

All participant data must be entered into OnCore or an equivalent EDC system. To facilitate timely data entry and subsequent safety reviews, the study calendar and eCRFs modules must be approved and signed off by the study team prior to the start of enrollment.

6.2 OnCore Data Entry

All HDFCCC IITs are registered in the HDFCCC central clinical trial management system (CTMS), OnCore, at the time of PRMC 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: dates of consent/withdrawal, treatment start/stop, on/off study, and NIH reporting requirements (patient-level or partial patient accrual[1])

Patient-level accrual	Partial Patient
• Study Identifier (e.g., Lead Org, NCI, CTEP, or DCP Protocol ID Number) • Participating Site Identifier • Study Participant Identifier • Zip Code (if U.S.) • Country • Date of Birth (MM/YYYY) • Sex (Biological sex assigned at birth) • Ethnicity • Race(s)	• Participating Site Identifier • Study Participant Identifier • Registration Date

• Registration Date • Disease Code • Disease Site Code (only for participants reported with ICD-O-3 disease coding)	

[1] Partial patient accrual reporting is to be used when full patient-level accrual has not been collected because of the scientific design of the study.

- Adverse Event/Serious Adverse Event reporting as stated in protocol
- Protocol violations
- Monitoring visits
- 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.

6.3 Completion of Baseline Condition OnCore Electronic Case Report Forms (eCRFs) for Patients Enrolled in IITs

Knowing the baseline characteristics of the study participants allows investigators to assess how closely these match other participants, and, therefore, how generalizable the study results will be. Baseline data are measured as close as possible to the time participants are randomly allocated to study groups and, in all cases, should be measured before the allocated treatment commences. Information collected after the commencement of study treatment may have been altered by the treatment itself and is not regarded as baseline.

For all HDFCCC IITs, at the beginning of a participant's screening visit, the provider will summarize the current state of health for the study participant, which is considered "baseline" data.

6.4 Protocol Amendments

All protocol amendments must be submitted to PRMS, IRB, and FDA (if applicable) throughout the life of the study (until IRB study closure). 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.

6.5 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.

Policy Exemptions

None.

References

FDA Guidelines:

- 42 CFR 11
- FDA IND Applications
- FDA IND Exemptions
- FDA IND Protocol Amendments
- FDA IDE Required Elements
- FDA E3 Structure and Content of Clinical Study Reports
- Cancer Drug and Biological Products - Clinical Data in Marketing Applications
- 42 CFR 410.16

NIH/NCI Policies:

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

UCSF IRB Policies:

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

HDFCCC Clinical Research Policies:

- PRMS Site Committee Review Policy
- PRMS PRMC Review Policy
- PRMS Amendment Submission Policy
- PRMS Protocol Closure Policy
- IND/IDE Central Management Policy
- UCSF HDFCCC Data and Safety Monitoring Plan (current version)
- Policy for Data and Safety Monitoring of Phase 1 Studies (current version)
- Policy for Data and Safety Monitoring of Phase 2 or 3 Studies (current version)
- HDFCCC Website: Conducting Research on Participants Diagnosed with, or at Risk for, Cancer

Appendices

Appendix 1: Interventional UCSF-Sponsored IIT Activation Table

Policy Approval

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

Signed by:
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Nicholas Butowski, MD
Clinical Research Support Office Medical Director
Helen Diller Family Comprehensive Cancer Center

8/23/2024
Date

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Appendix 1 – Interventional UCSF-Sponsored IIT Activation Table

IIT Start Up Tasks	Sequence	
	CRSO	Non-CRSO
PD work request submitted by study team	Step 1	N/A
Site Committee (SC) concept review and approval	2	1
IIT Planning Meeting[1]	3	N/A
SC protocol review and approval	4	2
DSMC review and approval	5	3
PRMC submission and approval	6	4
FDA submission and FDA comments addressed (as applicable)	7	5
BioSafety submission and Inpatient BMT nurse manager letter of support (if applicable)	8	6
After responses to PRMC and FDA are completed, PD releases protocol to study team for remaining pipeline work request	9	N/A
Request submitted for remaining pipeline work. Work is completed 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	7
IRB submission (after FDA submission and PRMC approval)	11	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[2]	14	11
Study Calendar and eCRFs in OnCore approved by the Protocol Project Manager (PPM) or Clinical Research Manager (CRM)[3]	15	12
APeX build complete[4] and UCSF participant enrollment begins	16	13
Multicenter trials *(NOTE: in addition to the unique steps below, all multicenter trials must complete the steps above. Steps below can begin after UCSF IRB approval)*[5]		
Multicenter Trials (MCT) PI Feasibility Questionnaire completed	1	N/A
Study team kick-off meeting	2	N/A
Subsite study start up can begin start-up packet, subsite kick-off meeting, and feasibility questionnaire	3	1
UCSF approval of sub-site ICF(s) for IRB review[6] and IRB submission	4	2
Sub-site(s) IRB approval	5	3

[1] Held for greater than minimal risk IITs to streamline communications and decrease amendments and time to activation.

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

[3] Must occur prior to start of enrollment in all IITs so that data can be entered into OnCore for the DSMC monitors to review.

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

[5] 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.

[6] For study teams working with the CRSO, PD reviews and approves 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.

Sub-site(s) budget and contract negotiation and execution	6	4
Sub-site(s) initiation visits	7	5
Sub-site(s) documented into OnCore	8	6
Sub-site(s) added into UCSF IRB application and IRB approval letter added in UCSF IRB application	9	7

Summary of Changes

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

Version Date: 08/23/2024

Section(s)	Summary of Change	Rationale
Definitions	Added definition for “oncology-related”	Clarify which studies the HDFCCC protocol development will support.
Background	Removed “interventional” requirement	HDFCCC protocol development team may support any HDFCCC supported, UCSF-sponsored IIT, including both interventional and non-interventional
1.3	Added process for HDFCCC Biostatistics core requests	Added workflow.
1.4	Added process for IDS requests	Added workflow
1.6	Non-UCSF sites must be approved by the DSMC	DSMC reviews the capabilities of all external sites prior to site selection to ensure they site can fulfill the requirements of the study.
5.0	Added OnCore calendar build	Calendars must be built for all trials with procedures eligible to be billed to insurance. Calendars are set-up to facilitate the billing process.
6.1	Added entire section. Text replaces decommissioned “Guidance Document for the Requirement of the Approval of OnCore Electronic Case Report Forms Prior to the Start of Enrolment in Investigator-Initiated Trials” (version 26.September.2013)	All IITs must have an EDC system in place to capture data for the study. The system should be set-up prior to the start of enrolment.
6.2	Added additional elements for OnCore data entry	To meet the needs of the NCI data reporting, DSMC monitoring and HDFCCC reporting, additional data entry requirements were added.

6.3	Added entire section. Text replaces decommissioned “Guidance for Completion of Baseline Conditions CRF for Patients on Investigator-Initiated Therapeutic Oncology Clinical Trials” (version 04.27.2012)	All HDFCCC IITs must collect baseline information from all study participants so that events, end-points and safety can be evaluated once the participant starts the treatment/intervention.
Entire policy	Updated formatting	Updated formatting to be in alignment with the Policy on Clinical Research Policies.
Appendix 1	Updated table	Added additional steps in the list of tasks to clarify the workflow.

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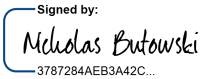
Nicholas Butowski Nicholas.Butowski@ucsf.edu MD University of California, San Francisco Security Level: Email, Account Authentication (Optional)	Signed by:  3787284AEB3A42C... Signature Adoption: Pre-selected Style Using IP Address: 128.218.42.137	Sent: 8/23/2024 12:52:56 PM Viewed: 8/23/2024 1:09:04 PM Signed: 8/23/2024 1:09:07 PM
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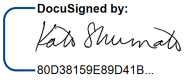
Katherine Shumate kate.shumate@ucsf.edu Chief of Staff, Director of Administration University of California, San Francisco Security Level: Email, Account Authentication (Optional)	DocuSigned by:  80D38159E89D41B... Signature Adoption: Uploaded Signature Image Using IP Address: 128.218.42.19	Sent: 8/23/2024 1:15:01 PM Viewed: 8/23/2024 4:47:38 PM Signed: 8/23/2024 4:47:59 PM
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Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

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Witness Events	Signature	Timestamp

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Completed	Security Checked	8/23/2024 4:47:59 PM

Payment Events	Status	Timestamps