CLINICAL INVESTIGATOR'S MANUAL

USC Norris Comprehensive Cancer Center

Developed By

Clinical Investigations Support Office (CISO)

Table of Contents

Essential Contacts 4
Commonly Used Abbreviations 6
Introduction and Purpose 7
SECTION I: Clinical Investigations Support Office (CISO) 7
SECTION II: USC Norris Comprehensive Cancer Center Committees 9
SECTION III: Submitting a Study Protocol for Review and Approval 10
3.1 CIC and IRB Approval 10
3.2 Additional Approvals and Resources for Clinical Trials 17
3.2.1 Clinical Trial Unit (CTU) 17
3.2.2 Radiation Safety Committee (RSC) 17
3.2.3 Institutional Biosafety Committee (IBC) 18
3.2.4 Office of Compliance for Conflict of Interest 18
3.2.5 CAFÉ (the Cancer Center Database) 18
3.2.6 Tissue Procurement Process for Approved Clinical Research 19
3.2.7 Radiology Services 19
SECTION IV: Protocol Activation Process 20
4.1 Open to Accrual 20
SECTION V: Protocol Review And Monitioring Process 22
5.1 Clinical Investigation Committee (CIC) 22
5.2 Quality Assurance Monitoring Committee (QAMC) 24
5.3 Data and Safety Monitoring Committee (DSMC) 26
5.4 Phase I Committee 27
SECTION VI: Investigator's Responsibilities 29
6.1 Informed Consent Process 29
6.2 Amendments 29
6.3 Communication 29
6.4 Patient Eligibility and Follow-up 30
6.5 Required Research Training 30
6.6 National Cancer Institute (NCI) Registration 30
6.7 SWOG Registration 30
6.8 Subject Registration in Café 30
SECTION VII: CISO Research Staff Support of Study 31
7.1 Regulatory Manager 31
7.2 Study Coordinator (SC) 31
7.3 Data Manager (DM) 31
7.4 Business Manager (BM) 32
SECTION VIII: Protocol Development 32
8.1 Investigator Initiated Trial (IIT) 33
8.1.1 Scientific Validity 33
8.1.2 Assessment of Resources 33
8.1.3 Financial Feasibility 33

8.1.4 Recruitment Potential 33
8.1.5 Competing Trials 33
8.1.6 Statistical Design 34
8.2 Important Resources for Developing IIT Protocol 34
8.2.1 Protocol and Informed Consent Template 34
8.2.2 Biostatistics Core 34
8.2.3 Cancer Research Informatics Core (CRIC) 34
SECTION IX: Frequently Asked Questions 35
Appendices 38
Appendix I: What is a Clinical Trial? 38
Ia Research Categories for Clinical Studies 38
Ib Study/Protocol Classification 38
Ic Clinical Trial Phases 39
Id Study Type 39
Appendix II: Disease Specific Program Group List 40
Appendix III: Study Status Update Notification 44
Appendix IV: Pre-site Visit (Site Qualification) Form 45
Appendix V: NCCC Clinical Trial Accrual Monitoring Policy 46
Appendix VI: Tissue Procurement Forms 48
VIa Application for Tissue 48
VIb Translational Pathology Core Facility Tissue Procurement Forms 50
VIc Price List of Services 52
Appendix VII: Template Language for Documenting Subject Consenting Process 54
Appendix VIII: Helpful Links 55
Appendix IX: CIC Protocol Submission Checklist 56

Essential Contacts

Committee/Department	Name	Contact
Clinical Investigations Support Office (CISO)	**Anthony El-Khoueiry, MD** Medical Director	elkhouei@med.usc.edu 323-865-3967
	Sikander Ailawadhi, MD Assistant Medical Director	ailawadh@usc.edu 323-865-3913
	Kay Johnson, RN Associate Director	johnson_k@med.usc.edu 323-865-0457
	Zeno Ashai, MPH Assistant Director	Zeno.ashai@med.usc.edu 323-865-0463
	Nonna Snider Quality Assurance Supervisor	Nonna.snider@med.usc.edu 323-865-0420
	Manuel Gimenez Business Manager	mgimenez@usc.edu 323-865-0453
	Criselda Chang Administrative Assistant	chang_c@med.usc.edu 323-865-0451
Clinical Investigation Committee (CIC)	**Syma Iqbal, MD** Co-Chair	iqbal@med.usc.edu 323-865-3907
	Ann Mohrbacher, MD Co-Chair	mohrbach@usc.edu 323-865-3924
	Zeno Ashai, MPH CIC Coordinator	Zeno.ashai@med.usc.edu 323-865-0463
	CIC Helpdesk	CIC@med.usc.edu 323-865-0463 323-865-0451
Quality Assurance and Monitoring Committee (QAMC)	**Eila Skinner, MD** Chair	skinner@med.usc.edu 323-865-3705
	Susan Groshen, PhD Co-Chair	Susan.Groshen@med.usc.edu 323-865-0375
	Nonna Snider QAMC Coordinator	Nonna.snider@med.usc.edu 323-865-0420
Data Safety and Monitoring Committee (DSMC)	**Debasish Tripathy, MD** Chair	tripathy@usc.edu 323-865-3900
	Richard Sposto, PhD Co-Chair	rsposto@chla.usc.edu 323-361-8582
	Nonna Snider DSMC Coordinator	Nonna.snider@med.usc.edu 323-865-0420
Phase I Committee	**Anthony El-Khoueiry, MD** Chair	el-khoueir@med.usc.edu 323-865-3967
	Sarah Cole, MS Phase I Coordinator	Sarah.Cole@med.usc.edu 323-865-0820

Committee/Department	Name	Contact
Biostatistics Core	**Susan Groshen, PhD** (GU, Hematology and DT)	Susan.Groshen@med.usc.edu 323-865-0375
	Richard Sposto, PhD (Pediatrics, Women Studies)	rsposto@chla.usc.edu 323-361-8582
	Dongyun Yang, PhD (GI Studies)	Dongyun.Yang@med.usc.edu 323-865-0414
	Denice Tsao-Wei, MS	tsaowei@med.usc.edu 323-865-0370
	Lingyun Ji, MS	Lingyun.Ji@med.usc.edu 323-865-0375
Cancer Research Informatics Core (CRIC)	**Aarti Vaishnav** Director	Vaishnav_a@med.usc.edu 323-442-7711
	Café Helpdesk	cafehelp@usc.edu
Institutional Review Board (IRB)	**Darcy Spicer, MD** Chair	dspicer@usc.edu 323-266-2233
	Sandy Jean Director	sjean@usc.edu 323-276-2231
	iStar Helpdesk	istar@usc.edu

Commonly Used Abbreviations

CIC – Clinical Investigations Committee
CISO – Clinical Investigations Support Office
NCCC – Norris Comprehensive Cancer Center
CRF – Case Report Form
DSMC – Data and Safety Monitoring Committee
DSCPRF – Disease Specific Clinical Program Review Form
DSTL – Disease Specific Trial List
FDA – Food and Drug Administration
GCP – Good Clinical Practice
HS – Human Subject
HIPAA – Health Insurance Portability and Accountability Act
HRA – Health Research Association
ICF – Informed Consent Form
SNIF – Significant New Information Finding
IND – Investigational New Drug
IRB – Institutional Review Board
POC – Phase One Committee
QAMC – Quality Assurance Monitoring Committee
SAE – Serious Adverse Event
SIV – Site Initiation Visit
SWOG – Southwest Oncology Group
RTOG – Radiation Therapy Oncology Group
ACOSOG – American College of Surgeons Oncology Group
NSABP – National Surgical Adjuvant Breast and Bowel Project
GOG – Gynecologic Oncology Group
CTSU – Clinical Trial Support Unit
RC – Research Coordinator
QA – Quality Assurance
IB – Investigator's Brochure
DLT – Dose Limiting Toxicity
MTD – Maximum Tolerated Dose
IIT – Investigator Initiated Trial
NCI – National Cancer Institute
CIRB – Central Institutional Review Board
CDA – Confidential Disclosure Agreement
ICOI – Institutional Conflict of Interest
CIRC – Conflict of Interest Review Committee
PSC – Protocol Submission Checklist
SC CTSI – Southern California Clinical and Translational Science Institute

Introduction and Purpose

Congratulations! You have taken the initiative to educate yourself on the process of conducting a clinical trial at the USC Norris Comprehensive Cancer Center. The purpose of this manual is to provide you, the Principal Investigator, along with your project managers or administrators, with an overview of the processes set up at USC Norris Comprehensive Cancer Center for conducting clinical trials. This manual will describe the various processes, committees and departments that you will work with throughout the submission, approval and conduct of your trial. It also highlights important resources available to you as you design and conduct your studies.

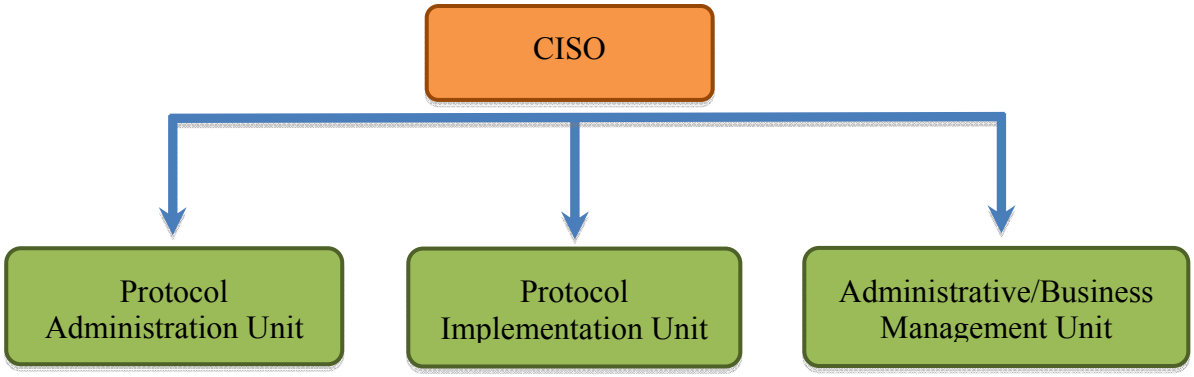
SECTION I: Clinical Investigations Support Office (CISO)

The Clinical Investigations Support Office (CISO) serves as a centralized unit to oversee the clinical research infrastructure and assist investigators in their conduct of clinical trials and translational research projects. The mission of CISO and its associated committees is to promote, support, and oversee the development and conduct of clinical and translational studies aimed at advancing cancer care for patients. CISO is committed to excellence, integrity, compliance and preservation of patient safety in all its operations.

CISO serves as the central point of the entire clinical research infrastructure and as the single point of entry for all investigators involved in clinical research. There are many benefits to a robust centralized clinical research administration in the Cancer Center, and these are beyond the scope of this document. In brief, the main advantages that CISO provides are:

- **Efficiency**
  - Centralized administrative unit
  - Centralized management of resources
  - Streamlined processes and operations
- **Quality**
  - Standardized staff training and oversight
  - Standard operating procedures
  - Staff education
- **Compliance**
  - Quality assurance and auditing capabilities
  - Regulatory services
  - Assistance with monitoring visits and audits
- **Competitive Edge**
  - Economy of scale
  - Systematic approach to improvement of research infrastructure and environment
  - Organized and strategic collaborations

In order to fulfill its mission, CISO has three main operational units: Protocol Administration, Protocol Implementation, and Administrative/Business Management. CISO also provides the administrative and logistical support for all clinical research related committees in the Cancer Center, most importantly the Clinical Investigations Committee (CIC), Quality Assurance Monitoring Committee (QAMC) and Data Safety Monitoring Committee (DSMC).



- Provides consultation regarding protocol development and design
- Assists with IND applications
- Provides Regulatory Managers who navigate the protocols through the various steps of review (CIC, IRB)
- Maintains a protocol tracking system
- Develops and manages patient registration/data management tools

- Provides and manages staff for study conduct including:
  - Study coordinators
  - Data managers
  - Specimen coordinators
- Provides centralized data and quality assurance oversight
- Provides centralized research staff oversight and training

- Assists investigators with interactions with HRA and the Department of Contracts and Grants
- Oversees budget development and staff salary buckets
- Provides personnel management

SECTION II: USC Norris Comprehensive Cancer Center Committees

As you develop and conduct a clinical or translational study, you will interact with several oversight committees within the Cancer Center; these committees collectively constitute the Protocol Review and Monitoring System mandated by the NCI Cancer Center Support Grant (CCSG). A detailed description of each committee and how it pertains to study monitoring is provided in Section V.

Research Committee	Committee Roles
Clinical Investigations Committee (CIC)	• Scientific peer-review committee for clinical and translational studies at Norris Comprehensive Cancer Center (NCCC) • All interventional studies (clinical, translational, prevention, quality of life, etc.) involving cancer patients MUST be reviewed by CIC prior to IRB submission* • Meets twice a month • The CIC meeting schedule and submission deadlines are available at: http://uscnorriscancer.usc.edu/Core/CISO/ViewPending.aspx. • All studies submitted for CIC review must be reviewed and approved by "Disease Specific Clinical Program" with ≥50% of group member approval. The approval is submitted by "Disease Specific Clinical Program Chair" (see Appendix II for Disease specific group list) • All investigators are required to sign up for minimum of four CIC meetings per year during which they serve as peer-reviewers
Quality Assurance and Monitoring Committee (QAMC)	• Reviews accrual and protocol progress • Reviews and oversees audits, compliance, data accuracy, and institutional protocol amendments • Meets once a month • Reports results of the reviews to CIC and CISO
Data Safety and Monitoring Committee (DSMC)	• Real time (within 24 hours) review of Serious Adverse Events (SAEs) • Reviews institutional trials for safety, scientific progress including interim analyses, and overall study conduct based on study reports prepared by CISO and PI • Reviews new protocols at time of initial CIC review to ensure an adequate Data and Safety Monitoring Plan is included • Meets quarterly • Reports results of the reviews to CIC and IRB when actions are needed
Phase I Committee	• Reviews all patients on institutional Phase I studies • Reviews all adverse events during the "dose-limiting toxicity observation period" in order to make decisions about dose escalation or de-escalation, cohort expansion, subject evaluability for DLT, and confirmation of maximum tolerated dose attainment • Meets every 2 weeks (may vary depending on need)

*IRB will decline review of studies not approved by CIC; the only exception to the rule is for studies that involve a limited number of cancer patients and in which the main scientific question is NOT cancer related.

SECTION III: Submitting a Study Protocol for Review and Approval

For information on developing an Investigator Initiated Trial (IIT) concept and protocol, please see section VIII.

3.1 CIC and IRB Approval

Step 1: **Contact CISO for Protocol Submission**

Submit your protocol along with the informed consent, investigator brochure, and any other related documents (such as sponsor budget, CDA, etc.) to the CIC coordinator at CIC@med.usc.edu. You can also submit it to Zeno Ashai or Criselda Chang. They can be contacted at zeno.ashai@med.usc.edu or chang_c@med.usc.edu.

Step 2: Disease-Specific Clinical Program Review**

The Disease-Specific Clinical Program Review is a required step to ensure that there is programmatic buy-in and support for the study. The focus of this review should be on whether the study fits within the programmatic scientific and research goals, that adequate programmatic resources are available (including patient numbers), and that trials are prioritized adequately; the program is asked to minimize competing trials or provide appropriate justification for opening competing studies. The process by which this review takes place is up to program (some programs have formal monthly meetings; others have weekly informal review of their research plans, etc.). Documentation of this review is included in the CIC Protocol Submission Checklist as detailed in Step 3. The Chair of the Disease-Specific Clinical Program signs off to verify that the Disease-Specific Clinical Program review has occurred. The signature by the program chair confirms that at least 50% or more of the members of the program have approved the proposed study.

****The Disease-Specific Clinical Program Review can take place before or after step 1; the only requirement is that it occurs before the submission of the CIC Protocol Submission Checklist.**

Step 3a: Completion of CIC Protocol Submission Checklist

Once you complete step 1, you will receive an email containing a link to the CIC protocol Submission Checklist (PSC). The purpose of the checklist is to provide all the necessary information to document the disease specific clinical program review, perform the scientific and operational review by CIC and CISO, and initiate the contract and budgeting process. It serves as an efficient SINGLE POINT OF ENTRY for all clinical trials in the USC NCCC. As part of the checklist, a list of potentially competing trials is provided by CISO; the PI is asked to verify whether an existing trial on that list competes with the proposed one, and then provide

justification for opening a competing study. Competing studies have to be ranked by priority order by the Disease-Specific Clinical Program.
The first part of the checklist is completed by the PI. The PI submits the form to the Disease Specific Clinical Program Chair to provide verification and outcome of the programmatic review described in step 2.

ALL ELEMENTS OF THE CIC PROTOCOL CHECKLIST MUST BE COMPLETED PRIOR TO MOVING FORWARD WITH YOUR STUDY. IF YOU DO NOT HAVE A COMPLETED CIC PROTOCOL CHECKLIST, NO FURTHER PROGRESS CAN BE MADE AND THE PROTOCOL WILL NOT BE REVIEWED (see Appendix IX for CIC Protocol Submission Checklist).

Step 3b: Contract and Budget Development

Completion of the CIC Protocol Submission Checklist is the trigger to initiate the contract and budget development. This takes place in parallel to the CIC and IRB reviews. The CISO Business Manager (Manuel Gimenez) submits the protocol documents via True 2.0 for budget and contract development (a HRA database). Protocols that have non-industry grant funding or federal funding usually require review by the Department of Contracts and Grants. The same process generally applies in those cases. The CISO Business Manager will work with your division or department administrator in the case of protocols requiring DCG review. By accessing True 2.0 real-time status of the budget and contract can be ascertained. If you are interested in the status of your budget, contact the CISO Business Manager at mgimenez@usc.edu.

Step 4: CIC Review

Once the CIC PSC is received, the protocol will be scheduled for Clinical Investigations Committee (CIC) review. No more than ten (10) protocols can be reviewed per meeting, so protocols will be processed on a first-come first-served basis. The deadline for the submission of both new and re-submitted protocols to the CIC is the second and fourth Friday of the month prior to the next month's Wednesday and Thursday meetings, respectively. The CIC meeting schedule and submission deadlines are available at:

http://uscnorriscancer.usc.edu/Core/CISO/ViewPending.aspx.

- There are two types of reviews:
    - Full review: Each study undergoes scientific and operational review. Two peer-reviewers, one statistician and one operational reviewer from CISO are assigned to review the protocol.
    - Modified review: Cooperative Group, CTEP reviewed and sponsored, and specimen studies, all require one peer-reviewer and one operational reviewer to conduct a modified scientific review. The review is focused on, but is not limited to, study feasibility and prioritization.

- Complete study package which includes Protocol, Sponsor and USC formatted ICF, CIC PSC, is sent a week before the meeting to assigned reviewers and CIC members who are required to attend the meeting. The reviewers are selected by the CIC Co-Chairs and the CIC Coordinator. The reviewers are required to complete and submit the reviews 24 hours before the scheduled CIC meeting. The CIC Coordinator makes every effort to ensure that all reviews are received for the meeting. If all the written reviews are not received one day before the CIC meeting, the study is deferred and reviewed at the next CIC meeting.

- Investigators are encouraged to attend the CIC meeting to present their study to committee members.

- CIC reviewers are kept anonymous. The investigator, if present, is requested to leave the meeting during study discussion and voting. All studies are given a priority score and risk assessment for monitoring, with the exception of cooperative group studies which are not given a priority score. The risk assessment will determine the frequency of monitoring by the QAMC.

- The possible outcomes of the CIC review are:

    - Approved
    - Contingent approval-response required- approval by Chair
    - Contingent approval-response required-approval by Chair + designated reviewer
    - CIC re-review required
    - Deferred
    - Disapproved

Step 5: Response to CIC Stipulations

Within a week from CIC review, the investigator will receive a memo with comments/stipulations from the CIC. The PI is expected to respond to the CIC stipulations within one month of receiving the memo. The PI may request an extension of an additional two months. If the PI does not respond, the study will be placed in the **"closed file"**. To reopen the study, the PI will be required to complete a new protocol submission and start the entire process of CIC review again, as if submitting a new study.

Step 6: **CIC Approval**

After responding to the CIC stipulations, the CIC Coordinator/Regulatory Manager will send the PI's response to the appropriate CIC reviewers who have up to a week to review the response and send their recommendation to the Coordinator.

If the PI's response to stipulations is satisfactory, the PI will receive a final approval memo from the CIC.

Table 1 below provides an overview of steps and documents required for protocol submission depending on the type of study.

Table 1: Study Group and Steps Required for Protocol Submission

Protocol Submission Requirements	Investigator Initiated Study (IIT)	Cooperative Group/ Consortium study	Industry Study	Purpose	Provided by	Completed by	Submitted to CISO by
Pre-Site* Evaluation			X	Performed by sponsor for site selection and to evaluate site qualification for the trial.	Sponsor	CISO Regulatory Manager	
Protocol, Informed Consent Form (ICF)	X	X	X	To inform potential subject about the study	Sponsor and/or Investigator	Sponsor and/or Investigator	PI
Sponsor Budget, CDA			X	To develop the USC budget and contract for industry studies	Sponsor	PI and HRA	PI
CIC Protocol Submission Checklist €	X	X	X	To ensure that USC NCCC has an adequate, potentially eligible patient population for a specific trial, the investigators have to coordinate with other members of the Disease-Specific Clinical Research Program to review all potential concepts and trials as a group in order to strategically and effectively develop a portfolio of high quality and well-accruing trials. Assists the PI and group members in identifying potentially competing clinical studies. This is a listing of all open trials and trials pending activation.	CISO	PI	Disease Specific Clinical Program Chair (see appendix III)

NOTE TO PI: Submit protocol, ICF and regulatory documents for industry trials (i.e., Form 1572, Financial Disclosure, CTA, CDA, etc.) to CIC@med.usc.edu. CISO will start the CIC review process upon receipt of this information.

*For all industry studies, the sponsors perform a pre-site visit to evaluate site qualification for the trial. Sponsor can request a Teleconference site qualification in lieu of on site visit. After pre-site evaluation, if the site is qualified, the sponsor sends a site selection notification to the PI. CISO arranges pre-site visits. During pre-site visit, sponsor is given a detailed tour of the facility including USC Norris Cancer Center, LAC+USC Medical Center (HCC if required), the clinics, Norris and IDS pharmacies, Clinical Trial Unit, day hospital, monitoring room. The pre-site visit also includes meeting with the PI and pharmacists. After the visit, the sponsor is required to sign a pre-site visit form acknowledging receipt of visit information and USC NCCC

clinical trial policies and procedures. A copy of the signed form is given to the sponsor and original is kept in the regulatory binder. See Appendix IV for a sample of Pre-site Visit form

€Electronic form CIC-PSC will be generated by CISO upon receipt of protocol and ICF. The investigator is responsible for completion and submission of the form to the relevant Disease-Specific Clinical Program Chair. The Chair approves and submits the form. Approval from Disease-Specific Chair reflects ≥50% approval of the members of disease-specific group. **Note: The study will not proceed until the form is received.** A template of this form is provided in Appendix IX

Step 7: **Institutional Review Board (IRB) Submission**

There are four Institutional Review Boards at the University of Southern California (one on the University Park Campus, and three on the Health Sciences Campus). These IRBs review and approve research in accordance with Department of Health and Human Services (DHHS) regulations in 45 CFR 46. For studies involving products regulated by the Food and Drug Administration (FDA), the USC IRBs review research and comply with the requirements set forth in 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812. In addition, the IRBs comply with HIPAA and its regulations set forth in 45CFR 160 and 164 and California law as it pertains to human subjects' research.

- USC IRBs have the authority to approve, disapprove, or suspend human subject research projects. No USC faculty, staff, or student may conduct human subjects' research without first obtaining approval from the appropriate IRBs at either the Health Sciences or University Park Campuses.

- USC IRBs have the authority to observe, or have a third party observe, the consent process and the conduct of the research

Step 7a: iStar Application Submission to IRB

After final CIC approval, the study is ready for IRB submission. A CISO Regulatory Manager assigned to the study is responsible for IRB submission and completion of all regulatory documents.

The Regulatory Manager submits new study applications through iStar (online IRB Application System) which include a description of the research methodology and procedures, advertisements/flyers, and other relevant materials such as protocol, informed consent, investigators brochure (if applicable), HIPPA form, lab agreement form and lab utilization form.

Step 7b: Electronic Signatures

Once the iStar application is complete, a 'study ready notification' is sent to the Investigator and Co-Investigators to agree to participate in the study. All Co-Investigators must sign before the PI can submit the study. The study also undergoes various department approvals. Investigators' participation and department approval are submitted electronically. It usually takes 1-2 weeks for all Co-Investigators, PI and departments to sign off on the study. It is the PI's responsibility to

assist CISO in ensuring that all Co-Investigators sign off in a timely fashion in order to avoid delays.

Step 7c: IRB Review

New submission (non-exempt protocols) sent to the IRB undergo one of the following reviews:

- Full Board Review
- Facilitated Review
- Expedited Review

The determination of the type of review is made by the IRB and is based on the provisions of the federal regulations. New submissions may be processed by expedited review (one reviewer) or may require review at a convened meeting of the appropriate USC IRB (reviewed by the committee).

The University of Southern California IRB has designated the NCI Central Institutional review board (CIRB) as the IRB of record for adult Phase III cancer cooperative group trials as a participant in the CIRB initiative. New protocols that have been reviewed and approved by NCI CIRB undergo facilitated review at USC.

The possible outcomes of IRB review are:

- Approved
- Approved with Contingencies
- Deferred
- Disapproved

Step 7d: Response to IRB Contingencies

After the initial IRB review, the investigator and study contact person receive IRB notification electronically via iStar specifying the action taken by the IRB. The IRB letter outlines the decision taken by the IRB and specifies the contingencies and modifications required for IRB approval. The Regulatory Manager works closely with the investigator to address IRB contingencies and is responsible for submitting contingency response to IRB.

Table 2 and Table 3 below provide an overview of the steps required for IRB submission, review process and responsible parties.

Step7e: IRB Approval

Once all of the contingencies are satisfied, IRB final approval is received via iStar notification to the investigator and study contact person (Regulatory Manager) listed in the application. The IRB approval letter lists all the documents which receive final IRB approval, i.e., protocol, ICF, IB, HIPPA, and any additional documents applicable to the study. The letter also notes a beginning approval date and an ending approval date. The beginning approval date is the day

final approval is granted. The IRB approval date can never be more than 364 days from the date of the last IRB review.

Table 2: Documents Requirement for IRB Submission

Study Group	Protocol, ICF[Λ], IB[α] & Budget[¥]	Supporting Documents (Lab Agreement, Lab Utilization)*	IND application*	Grant [€]
Investigator Initiated Study (IIT)	X	X	X (Most of the time)	X
Cooperative Group/ Consortium Study	X	X		
Industry Study	X	X		

[Λ]Informed Consent form (ICF) for all industry trials and some consortium trials require approval from the sponsor prior to IRB submission. The Regulatory Manager submits the ICF to the Sponsor for approval.

[α]Investigator's Brochure (IB) is required for investigational drugs. If the drug is FDA approved for that indication, the package insert is submitted instead.

[¥] The budget process will begin once a CIC Protocol Submission Checklist is received in CISO. The CISO Business Manager will submit the study in True 2.0 to start the budget process. True 2.0 an electronic Health Research Association (HRA) database for contracts and budgets and provides status information of contract and budget. For Cooperative group/consortium studies the budget is generated for a Medicare analysis.

*CISO will prepare the supporting documents and send it to the investigator for signatures and submit Investigational New Drug (IND) application when necessary.

Table 3: IRB Submission Process for All Study Groups

Responsible Person	IRB Application	Electronic Sign Off *	Consistency Checklist [¥]	Response to Contingencies [€]
Regulatory Manager	X			X
Investigator/Co-PI		X		X
HRA			X	

*All studies are submitted to the Institutional Review Board (IRB) electronically via iStar. Investigators will receive an email from iStar with a link to sign off on the study. Studies are signed off electronically via iStar.

[¥]A Consistency Checklist provides the cost and injury language for the ICF which is consistent with the language in the final contract. A Consistency Checklist is required prior to submitting the responses to contingencies to the IRB.

[€]The Regulatory Manager will contact the investigator if the complexities of the contingencies require input from the investigator. The PI DOES NOT respond to IRB directly.

The entire approval is complex and time consuming. CISO is dedicated to ensuring that this process proceeds smoothly without delays. ***CISO and Cancer Research Informatics Core (CRIC)* have developed an electronic protocol tracking tool that accounts for every step that a protocol goes through from initial receipt in CISO until study is open to accrual***. The Regulatory Manager in CISO ensures that the tracking tool is constantly and accurately updated. The investigator receives monthly updates about the status of each of their studies in the queue in the form of a summary table generated from the electronic tracking tool. An example of this update can be found in Appendix III.

Please note that CISO charges a one-time administrative fee for all new protocols; federally funded studies such cooperative group and CTEP sponsored trials are exempt. The fee covers all

the administrative functions associated with the initial review and set-up of a protocol, as well as the work associated with the IRB submission. The fee is itemized and the breakdown can be provided upon request; the total fee usually reaches around 5000 US Dollars. HRA negotiates this fee on CISO's behalf with sponsors. Investigator initiated studies may have this fee reduced on a case by case basis depending on the funding source and the priority of the study.

*CRIC function is described in Section 8.2.

3.2 Additional Approvals and Resources for Clinical Trials

Certain studies require additional approvals from various units and committees, depending upon study specific requirements. For example, if study requires complicated PK draws or other assessments requiring prolonged patient stay, the CTU may be used, and requires CTU approval. Below is the overview of such units and committees and information on how and when to obtain approval.

3.2.1 Clinical Trial Unit (CTU)

The Clinical Trials Unit (CTU), part of the NIH-funded Southern California Clinical and Translational Science Institute (SC CTSI) is an important resource for studies that require intensive pharmacokinetic (PK) and/or pharmacodynamic (PD) blood draws, as well as studies that may require intensive monitoring (such as serial EKGs, etc.). The CTU is also equipped with a core laboratory that can perform complex specimen handling.

Please check "yes" in the box that asks if CTU is needed if:

- Your study involves serial and frequent blood draws (beyond 2 or 3 draws that could be done in the day hospital or clinic).
- Your study involves serial blood draws for PD markers with complex specimen handling.
- Your study requires intensive monitoring with EKGs, vitals, etc.

If you are unsure, please contact CISO to discuss and speak with the associate or assistant directors, Kay Johnson at Johnson_k@med.usc.edu or Zeno Ashai at zeno.ashai@med.usc.edu.

Once your protocol is CIC approved, CISO will begin the CTU application on your behalf and may ask for your assistance with specific questions, especially the MD orders for your study. The application will not be accepted at CTU until there is contingent IRB approval. CTU will generally accept the CIC review as the only scientific review. An operational review by the CTU takes place before giving final approval for all studies. Please note that final CTU approval is only given once the study is IRB approved as well**.**

3.2.2 Radiation Safety Committee (RSC)

All studies that use radiation exposure for investigational purposes that is not clinically indicated and/or that differs from standard clinical practice, requires Radiation Safety Committee (RSC)

approval. This includes CT scan/PET scans, etc. that are being done for research purposes and that are not considered standard of care for the study.

- The RSC "Application for Use of Radiation Producing Devices in Clinical Research" is submitted to the RSC with a copy of the IRB application, the Informed Consent Form(s), and sponsor's protocol (if applicable). The Radiation Safety Committee meets at least quarterly.
- CISO Regulatory Manager completes and submits the RSC application.
- All new studies that use radiation in an investigational manner must receive approval by the RSC in addition to IRB approval prior to initiating the study. The two approvals are from separate entities and are not dependent on each other.

3.2.3 Institutional Biosafety Committee (IBC)

All studies that involve biohazardous materials require Institutional Biosafety Committee (IBC) approval and must be registered with the IBC. Biohazardous materials include recombinant DNA, potentially infectious microorganisms, bacteria-derived toxins, human cell lines, tissue, blood or other human/nonhuman primate material.

- All new studies that use biohazardous material must receive approval by the IBC in addition to IRB approval prior to initiating the study.
- IBC meets once a month. The IBC reviews all research protocols involving biological materials and known chemical carcinogens. IBC approval is given for a period of one year. The Regulatory Manager completes and submits the IBC application.

3.2.4 Office of Compliance for Conflict of Interest

Research studies can have either institutional conflict of interest (ICOI) or investigator conflict of interest. ICOI or investigator conflict of interest is indicated in the iStar application.

- The Regulatory Manager works with the investigator to complete a Statement of Outside Interests Related to Research form for iStar application and submits to the Conflict of Interest Review Committee (CIRC) for review and determination.
- The memo from the CIRC committee is uploaded to the iStar application. The IRB will not approve the study until the conflict has been reviewed by the CIRC Committee, the memo has been uploaded to iStar, and there is an acceptable management plan.
- At USC, when a human subjects research project involving greater than a minimal risk has had institutional interests (ICOI) identified, it must undergo a second IRB review by Cedars Sinai Medical Center under a Memorandum of Understanding. The recommendations provided by the second review, pertinent only to human subject's issues, are advisory to the USC IRB.

3.2.5 CAFÉ (the Cancer Center Database)

- For ITT studies, eCRFs must be developed prior to opening a trial to enrollment. For resources and information on developing eCRFs see section 8.2.2 and 8.2.3.

- Café Tracker provides step-by-step protocol status information in real time from time of receipt of protocol by CISO till the study is open to accrual. The Regulatory Manager assigned to the study is responsible for updating the Café Tracker. At the beginning of each month, the investigators receive an automated email from the Regulatory Manager generated by CAFÉ providing the status of their studies. Investigators also receive email reminders with deadlines for CIC protocol submission forms and CIC stipulation submission. These email reminders help investigators to track the progress of their studies. The reminder and status emails stop once the study is open to accrual.

3.2.6 Tissue Procurement Process for Approved Clinical Research

Request for tissue samples from LAC+USC County and Norris are processed through Moli Chen who works for Dr. Sue Ellen Martin in the USC Norris Comprehensive Cancer Center Translation Pathology Core. For fresh frozen tissue, an Application must be filled out and signed by the PI. A copy of the Protocol and the IRB approval must be attached for every Application. Regulatory Manager is responsible for the submission of these forms. After approval by Pathology, requests may be made for fresh or frozen patient's samples by the SC.

There is usually a charge for this resource and its services, which should be established at the time that the protocol budget is being developed.

To procure fresh or frozen tissue for a patient, the SC will fill out the appropriate request form, scan along with the signed Informed Consent and email both to Moli at mhchen@usc.edu or hand deliver to room 2357. To procure slides/blocks for a patient, the SC or Data Manager will fill out the appropriate Requisition Form, scan along with the signed Informed Consent and email both to Moli at mhchen@usc.edu or hand deliver to room 2357.

The Application Form, the Request/Requisition Forms for tissue procurement and the Price List for Services from pathology are attached under Appendix VI.

3.2.7 Radiology Services

If you wish to conduct research studies utilizing Radiology services at either the lower level of the Healthcare Consultation Center II (HCCII) or the PET Center located on the 3rd floor of the Healthcare Consultation Center I (HCCI), please email Diana Shycoff at shycoff@med.usc.edu). Your email should include the following items:

- Current copy of the sponsor's protocol, grant application, or proposal describing the requirements of the study.
- The account number to charge these services to (Contracts & Grants # or HRA #).
- Imaging manual, if applicable.
- IRB number.
- A brief description of the Radiology services you wish to utilize.

The Regulatory Manager will contact Diana Shycoff at least one month before study initiation for assistance in setting up the study at these two locations. You may contact Diana at the same time you submit your study to the IRB. If the study involves standard of care Radiology services,

you do not need to contact her. After receiving the information, Diana will schedule a protocol specific meeting with the appropriate people at HCCII to facilitate the protocol set-up process. The person most familiar with the protocol requirements must also attend this meeting (Study Coordinator and/or Regulatory Manger). The radiology team is also included in the SIV and a visit in radiology is scheduled during the SIV.

SECTION IV: PROTOCOL ACTIVATION PROCESS

4.1 Open to Accrual

After all appropriate protocol approvals have been completed, the study is ready of activation. The following is required before enrollment can begin.

Institutional Trials: Investigator initiated/institutional trials must have final approval of all required committees (CIC, IRB, CTU, Café eCRFs and RSC if applicable), a signed contract and drug available on site. The PI should work with CISO to complete an internal study initiation meeting with the study staff; this meeting can be arranged by the CISO Regulatory Manager in charge of the study.

CTEP Sponsored or California Consortium Trials: Study approval is required from all committees prior to activation and drug must be on site. The Regulatory Manager will submit the proper regulatory documentation to the consortium coordinating center and will then notify the pharmacist to order the drug to be shipped to the site. No SIV is required for most of the CTEP sponsored studies, however, there are a few which may require a teleconference SIV. The regulatory manager assigned to the study will arrange the SIV. The PI is encouraged to review the study with the research staff for studies that have no formal sponsor SIV.

Cooperative Group Trials: For activation of cooperative group trials, notification of IRB approval must be sent to CTSU to register the study before a patient can be enrolled. No SIV is required but the PI is encouraged to review the study with the research staff; the Regulatory Manager will submit the proper regulatory documentation to the coordinating center. Drug will be shipped when the first patient is enrolled and registered at the coordinating center.

Industry Trials: For activation of industry trials, it is required to have study approval, finalized contract, drug at site and SIV. The Regulatory Manager or the Regulatory Assistant will arrange the SIV. Prior to the SIV, the sponsor contract and budget should be approved and signed; usually the drug or device to be tested is not shipped until after the SIV has been held and all regulatory documents are received by the sponsor.

Table 4 below provides an overview of each study type requirement for activation

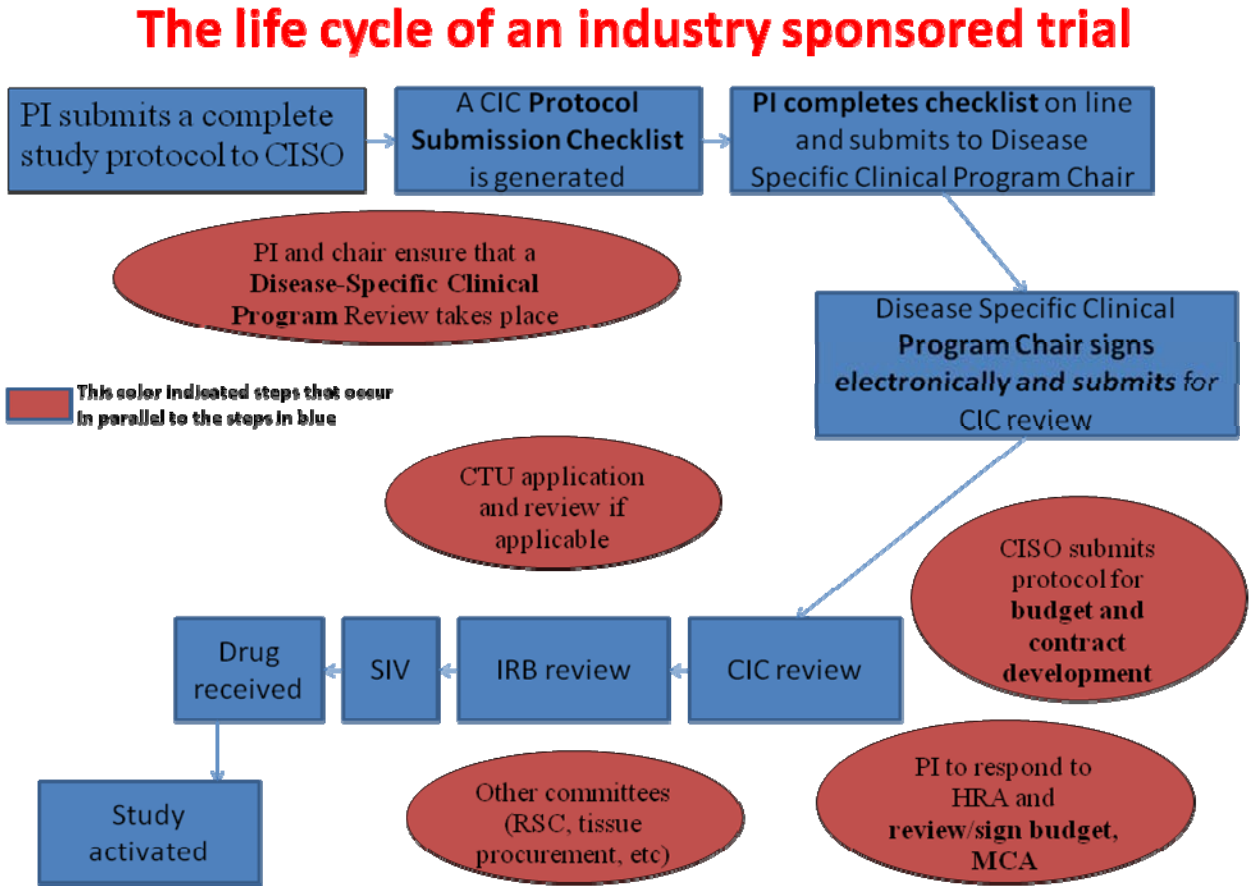
Table 4

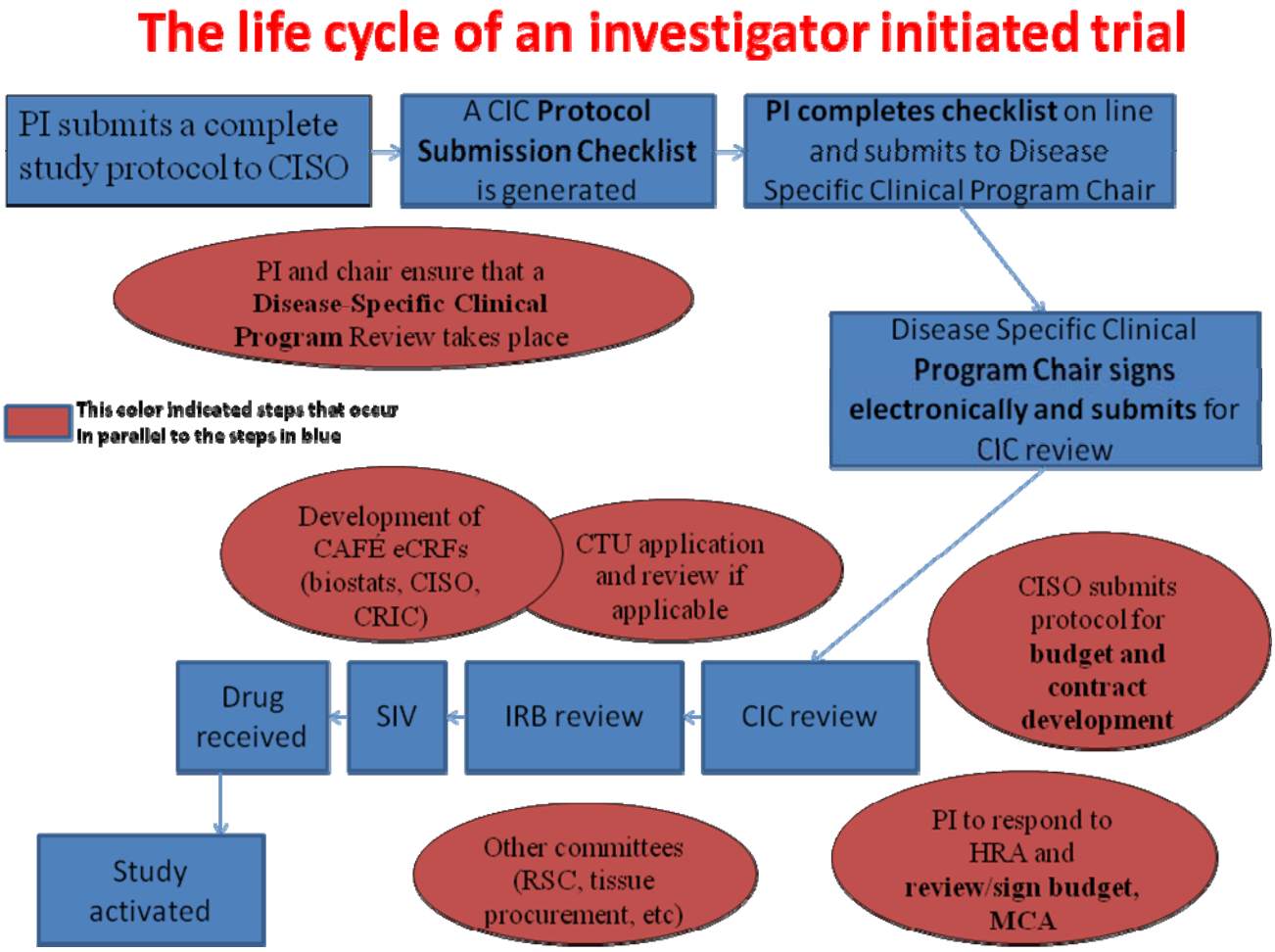
Study Group	IRB Approval & Other Appropriate Committees	Site Initiation Visit	Drug Received	Contract Finalized	Regulatory Documents	Site Registration	eCRF** Development
Investigator Initiated Study (ITT)	X	X$^{\Omega}$	X	X			X
Cooperative Group	X					X	
Consortium Study	X	X*	X		X*	X	
Industry Study	X	X	X	X	X		

$^{\Omega}$Investigator can have SIV for IIT; the regulatory assistant schedules the SIV.

*Some consortium studies require site initiation visits and regulatory documents (Form 1572, Financial Disclosure, etc.); the Regulatory Manager assigned to the study arrange the meeting and provides the requested regulatory documents to the coordinating center.

**USC's Biostatistics Core and the Cancer Research Informatics Core (CRIC) work with the investigator in developing in-house CRFs for all IIT.





SECTION V: PROTOCOL REVIEW AND MONITIORING PROCESS

There are four Cancer Center committees which together form the NCI-mandated protocol and review monitoring system at the NCCC. These committees are the Clinical Investigations Committee (CIC), the Quality Assurance Monitoring Committee (QAMC), the USC NCCC Data and Safety Monitoring Committee (DSMC), and the Phase I Committee.

5.1 Clinical Investigation Committee (CIC)

The objectives of the Clinical Investigation Committee (CIC) are to implement a multi-disciplinary scientific peer-review system that ensures internal oversight of both the scientific and research aspects of clinical trials and optimally engages the institution's clinical resources. This system of review ensures that clinical research trials at the USC Norris Comprehensive Cancer Center are of the highest scientific quality and integrity by review of the scientific merit, priorities and progress. Specific aims of the Committee are:

- To maintain a review committee with sufficient breadth of expertise and size to critically and scientifically review ALL clinical cancer research protocols.
- To conduct a thorough scientific review of clinical research protocols using specific criteria for review.
- To facilitate prompt initiation of approved protocols by interfacing with the IRB and other relevant institutional or external entities to ensure compliance with local and federal regulations.
- To ensure and oversee a system of prioritization of clinical research protocols conducted at the USC NCCC.
- To work closely with CISO in conducting a feasibility and operational review of all submitted protocols; this part of the review ensures the availability of adequate resources and infrastructure to conduct the proposed research as well as the adequacy of the funding and support personnel.
- To monitor the progress of clinical research protocols to ensure scientific progress and ensure closure as required by interim analysis and stopping rules or adverse events.
- *CIC has the executive authority to close or suspend any study in the USC NCCC* for lack of accrual (see accrual policy) or for concerns regarding scientific progress, study conduct or patient safety. In this capacity, the CIC works closely with QAMC, DSMC, CISO and IRB.

It is extremely important for investigators to realize that the CIC is not only an oversight committee, but also a critically important resource; the CIC members and reviewers are experienced trialists and scientists who can provide very important feedback that improves the study design and conduct, and therefore benefit the investigator's research.

- **CIC Members**

There are 34 voting CIC members which investigators, statisticians and staff broadly representing departments and divisions actively participating in Cancer Center programs and research. CIC voting members also include two patient representatives.

Members are required to attend at least one CIC meeting per quarter. An electronic sign-in sheet is sent at the beginning of the year and quarterly thereafter to each member to ensure attendance to the CIC meetings. Once a member has signed up for a meeting an automated reminder is sent a week before the meeting and another on the day of the meeting.

The committee relies on the attendance of the members who have committed to the meeting. Without a quorum, the meeting is canceled and protocols are deferred.

- **CIC Meeting**

Dr. Syma Iqbal and Dr. Ann Mohrbacher Co-Chair the CIC. The committee meets the first Wednesday and the third Thursday of each month. A quorum of five voting members is required for the meeting to proceed.

- To ensure an objective and thorough review, protocols are assigned to reviewers who signed up for the meeting, allowing for adequate review and discussion of the study.
- Reviewers are required to submit a written review a day before the CIC meeting. *Failure to submit the review on time results in an unduly delay in study review and will also result in disciplinary action from the NCCC.*
- Investigators submitting protocols for review are encouraged to attend the CIC meeting to present their protocol to members and answer any questions or concerns. After presenting the study, the PI is excused from the discussion and leaves the room. The PI does not participate in the committee review, decision and voting process. If there are Co-Investigators present in the meeting, they are also excused during the review process. If there is not a quorum, the Co-Investigators may be asked to participate in the review and vote.
- During the meeting, the study is presented briefly by the PI, Co-PI or one of the reviewers; the reviews are then presented by the reviewers is they are present, or by the CIC Co-Chair on their behalf; a statistical review is presented by a statistician; an operational review is presented by CISO.
- Reviewers are kept anonymous both during the meeting and on the CIC memo to the investigator.
- Each month CIC also reviews a list of studies which received final CIC approval and studies that have exceeded the CIC stipulation deadline. Studies which have passed the CIC stipulation deadline are closed by CIC.
- The minutes of the last QAMC meeting are presented and if requested or required, action will be taken by Committee. The CIC also reviews any IIT protocol amendments at the recommendation of the QAMC.
- The minutes of the last DSMC meeting are also submitted to the CIC if DSMC deems it necessary for the CIC to take action on specific studies.

5.2 Quality Assurance Monitoring Committee (QAMC)

The Quality Assurance Monitoring Committee (QAMC) of NCCC meets monthly. Its primary function is to review study accrual, adherence to protocol-mandated recruitment, treatment and follow-up, data accuracy, and institutional protocol amendments. It is also entrusted with performing and overseeing internal audits.

- **USC NCCC Clinical Trials Accrual Monitoring Policy**

QAMC reviews protocol accrual during scheduled annual or semi-annual protocol reviews. The schedule is based on its Risk Assessment that was stipulated by the CIC.

- At the scheduled QAMC protocol review, if accrual is found to be less than 50% of expected accrual during the preceding 12 months, a memo is sent to the PI requesting an explanation for the lack of accrual. If the explanation is not satisfactory, or if no response is received (within 30 days for studies with less than 10% of accrual or 90 days for the studies with accrual between 10% and 50%), a second memo is sent informing the PI that the protocol will be presented

to the CIC with the recommendation for closure. The CIC will discuss the recommendation and vote on enacting it.

- At the scheduled QAMC protocol review, if a protocol has exceeded its planned total accrual a memo will be sent to PI asking PI to justify over-accrual through a proper protocol amendment or to close the study. If a response is not received within 30 days, a second memo is sent informing the PI that the protocol will be presented to the CIC with a recommendation for closure. The CIC will discuss the recommendation and vote on enacting it.

See Appendix V for USC NCCC Clinical Trial Accrual Monitoring Policy.

- **QAMC Audit**

  - All open, institutional and California Cancer Consortium trials are audited by the QAMC once a year. Twenty percent of patients accrued during the past 12 months – and a minimum of 2 patients – are selected. If deemed necessary, additional patients may be audited. The audit involves a review of the research chart and electronic source documents to evaluate eligibility (including failure to obtain appropriate informed consent) and required baseline procedures or tests; documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome. In addition, for investigative agents, a drug audit is also performed for these patients by the Research Pharmacist.
  - The investigator receives a report summarizing the results of the audit and, if appropriate, suggestions are provided for improving the conduct of the trial. PI responses will be required if deficiencies are identified. These responses are reviewed at the next QAMC meeting. Copies of all audit reports are sent to the PI and the CIC for review and the DSMC at the time of the annual progress report review.
  - If audits uncover serious concerns related to study conduct or scientific validity, the QAMC will notify CIC and recommend that study be suspended until the issues are addressed.

- **Institutional Protocol Amendments**

All institutional amendments are reviewed by the QAMC at the monthly meeting, or in an expedited fashion by the QAMC Chair or designee. If it is deemed that significant safety or scientific issues are present, the amendment is forwarded for full CIC review.

Protocol Violations

All Major Violations occurring in any active study, as well as minor protocol violations occurring on Industry studies, if requested by the Sponsor, are reported in Café and reviewed by the Quality Assurance Committee at monthly meetings. In addition, violations which affect patient safety or study outcome are reported to the IRB in real time.

- The Study Coordinator is responsible for completing the violation in the Café database. The required information includes an explanation of how the violation occurred, description of the outcome and any corrective actions taken to avoid such violation in the future.
- If the QA Coordinator or PI or QAMC determine that the Major Violation may affect patient safety or study outcome, the Study Coordinator is asked to submit the protocol violation via iStar to the IRB.
- Reported violations are reviewed and discussed at the next monthly QAC meeting. If thought necessary, the QAC sends a memo to the PI suggesting a specific modification of procedure or study clarification. This will require a protocol amendment. If the PI does not respond or if the violations continue, the QAC reports this to the Clinical Investigations Committee (CIC) with a recommendation to either close the study or suspend accrual until the problems can be resolved.
- Repeated violations and patterns as well as the number and type of violations per study are reviewed by the QAC and CISO management. These data may result in identifying the need for counseling, re-training or disciplinary action.

5.3 Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) is an independent body responsible for the safety of study subjects through the review of new protocols to ensure an adequate adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials.

Investigators Responsibilities for DSMC Review

The data required for the DSMC quarterly safety reviews and annual protocol reviews will be compiled by the Clinical Investigation Support Office (CISO), but PIs and their staff will be asked to provide additional specific information and respond to periodic queries regarding adverse events in a timely fashion. PIs are asked to assist the DSMC in performing its duties by facilitating the following:

- Provide a copy of any protocol-specified interim analysis to the DSMC within 4 weeks of generating such report.
- Answer any queries generated by the DSMC during real-time SAE review within the stipulated timeframe.
- At the time of DSMC annual review, provide the following to the DSMC Coordinator:
  - A brief capsule of the overall progress on the trial, including any issues with accrual, conduct of the study and/or subject outcomes.
  - Any publications and presentations pertaining to the study since the last DSMC review.
  - Any changes in standards of care or major changes in the field relevant to the study since the study approval.

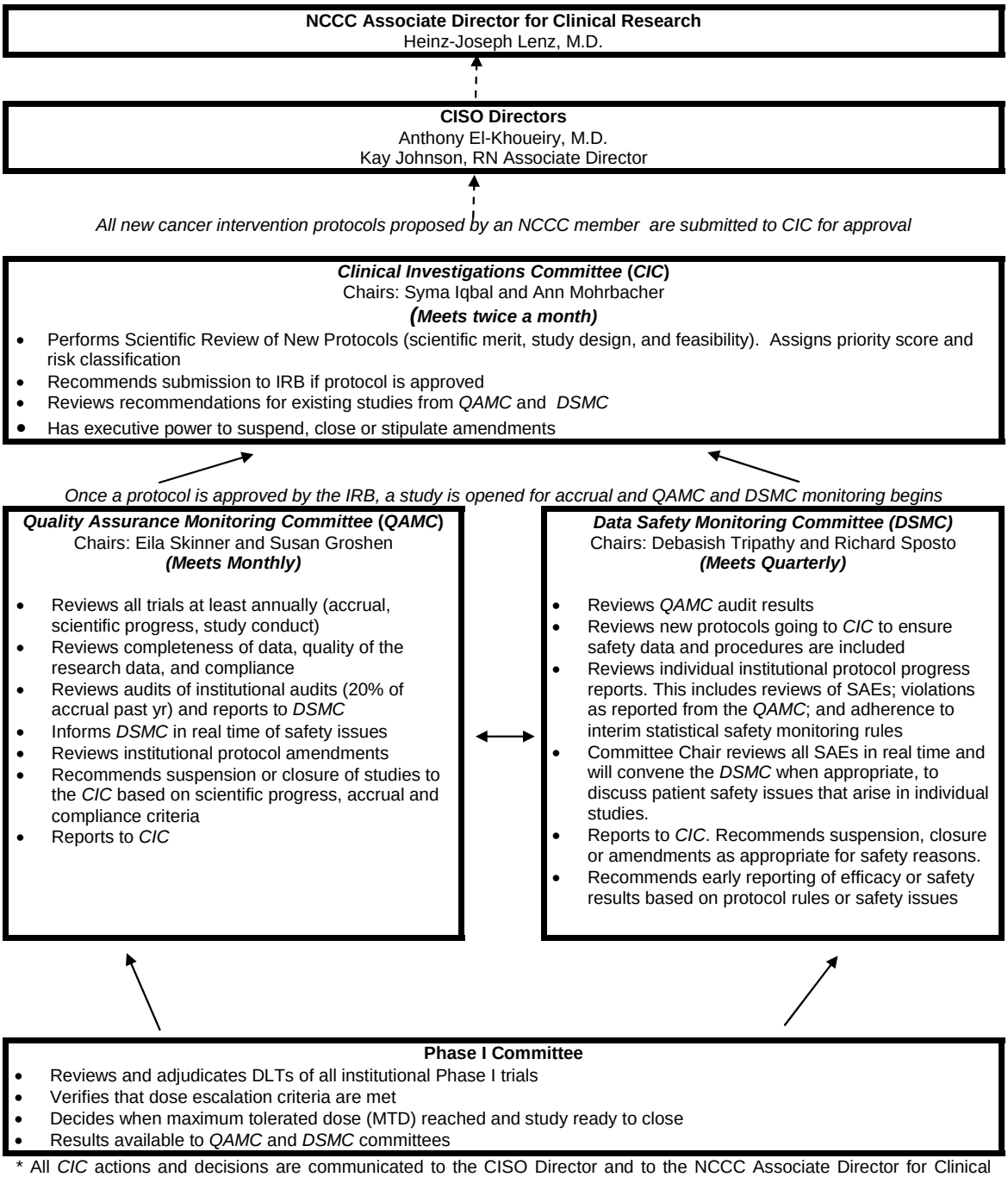
- Answer any queries generated during the preparation of annual protocol review report within the stipulated timeframe.
- Review toxicities report generated by the DSMC Coordinator in a timely manner.
- Review and sign the annual safety protocol review report prepared by the DSMC Coordinator prior to the DSMC scheduled meeting.

If the annual protocol review report is not available for review due to delays by the PI in providing the information listed above, the study may be put on hold.

5.4 Phase I Committee

- All institutional Phase I trials are reviewed by the Phase I Committee that meets twice a month. It is responsible for reviewing and adjudicating all dose-limiting toxicities, dose escalations and appropriateness of the escalation, cohort expansion, subject replacements and confirmation of attainment of maximal tolerated dose. Each patient is reviewed individually after the end of their DLT/assessment period and evaluability/replacement and DLT are determined, as specified in the protocol.
- All findings are documented in Café. Special toxicities are queried as needed and a summary is prepared and made available to the CIC, QAMC and DSMC.
- The Phase I committee also maintains a waiting list of all patients waiting for slots and assigns slots to patients as they become available.

Figure 1. Protocol Monitoring and Review System



* All *CIC* actions and decisions are communicated to the CISO Director and to the NCCC Associate Director for Clinical Research

SECTION VI: INVESTIGATOR'S RESPONSIBILITIES

The investigator is responsible for, and is expected to be actively engaged, in supervising all aspects of their clinical or translational protocols. Such engagement ensures high study conduct quality is essential for the successful completion of the trial.

6.1 Informed Consent Process

Only the PI, Co-PIs, fellows, Nurse Practitioners if applicable, listed in the IRB application as responsible for consenting patients can consent the subjects. The person in charge of the informed consent process with the patient MUST document in the medical record the entire consenting process including the fact that the study was discussed, alternatives reviewed, questions were answered, and the subject agreed to participate after having an adequate understanding of the all issues discussed.

All subjects should be consented on an IRB approved and valid stamped ICF. IRB approved ICFs are stamped with approval and expiration date. All approved ICFs are posted on the Café website. IRB approved documents CANNOT be changed/deleted or altered.

Please see Appendix VII for example of proper documentation of consent in the patient's progress notes.

If a mistake is made on any form pertaining to the trial, it should be crossed out, initialed, and dated. **Do NOT use white out.**

6.2 Amendments

All protocol amendments, revisions to ICF or IB should be sent to the Regulatory Manager in CISO or forwarded to CISO for IRB submission. Amendments must be submitted to the IRB within 90 days of receipt. It is possible that the PI is the only person who receives the protocol amendment documents; therefore, it is imperative that the PI be pro-active in ensuring that the CISO Regulatory Manager receives these documents as well.

If the amendment contains new information for the enrolled patients, subjects should be re-consented with the revised IRB approved ICF or a significant new information finding (SNIF). The Quality Assurance (QA) manager will generate an email informing the study team if re-consenting is required.

6.3 Communication

Any notification or piece of communication received by the PI from the sponsor must be immediately forwarded to the Regulatory Manager in CISO.

6.4 Patient Eligibility and Follow-Up

The Investigator is responsible for ensuring subject and protocol compliance throughout the study duration. During the conduct of the study, serious adverse events (SAEs), toxicities, dose modifications must be properly documented in the medical record. Research staff follow strict Standard Operating Procedures for all these processes. SOPS are developed by CISO and available in CAFÉ. The USC Norris Comprehensive Cancer Center policy is not to allow any protocol waivers or deviations unless they are necessary for patient safety. A detailed SOP in this regard is available.

6.5 Required Research Training

All investigators and study staff involved in research are required to complete several training courses and obtain certificates. All certifications are done online. Below is the list of certifications required with web links.

- **HIPAA (Health Insurance Probability and Assurance Act) Privacy Rule Education Program**: http://ooc.usc.edu
- **Human Subjects (HS) Education Program (**CITI Human research Curriculum): http://www.citiprogram.org
- **Good Clinical Practice (GCP):** http://www.citiprogram.org

An iStar account is required to complete HS and GCP certifications. To obtain an account, send an email to istar@usc.edu or contact CISO office for assistance.

6.6 National Cancer Institute (NCI) Registration

All investigators are required to register with NCI annually. As part of this registration process, investigators sign a 1572 Statement of Investigator form, complete Supplemental Information Form and a Financial Disclosure form, and provide a copy of their current CV. The Investigator is responsible for submission and renewal of NCI registration.

6.7 SWOG Registration

Investigators who are interested in participating in SWOG Cooperative group trials must have SWOG membership. CISO can facilitate and submit the SWOG application for you. Please provide a copy of your CV and Human Subject Certificate to Ms. Kay Johnson at Johnson_k@med.usc.edu. Within a few days you will receive a complete SWOG membership application for signatures to sign and return to Ms. Johnson for submission to SWOG. Your application will be reviewed and approved by the SWOG Executive Committee at their semi-annual meeting. Afterwards you will receive a letter of acceptance from SWOG.

6.8 Subject Registration in Café

All subjects are registered in Cafe. Café serves two general purposes: it is both a Clinical Trials Management System (CTMS) and an Electronic Data Capture (EDC) tool. In other words, it is an electronic database designed to manage and track protocols, capture patient enrollment, and allow entry of patient protocol specific data in order to analyze clinical and translational research data collected from institutional studies. It is also utilized for tissue microarray data capture, epidemiologic studies, prevention trials, laboratory management, tissue repositories, and administrative systems at USC (http://cafe.usc.edu).

For IITs, eCRFs are available in Café and all study related data is entered by the DM in Café. After the CIC initial review, CISO informs the Biostatistics Core to develop eCRFs for all IITs. The Biostatistics Core statisticians works closely with the investigator, members of CRIC and CISO staff in developing eCRFs.

SECTION VII: CISO Research Staff Support of Study

7.1 Regulatory Manager

A Regulatory Manager is assigned to each new study received by CISO. The Regulatory Manager is responsible for submitting the protocol to the IRB, tracking the study approval process and maintaining regulatory documents. The Regulatory Manager is also responsible for submitting protocol amendments, annual renewals, and external SAE review and reporting.

7.2 Study Coordinator (SC)

Each study is assigned two study coordinators (one for LAC and another for Norris). The exception is for the research staff involved in hematology and radiation oncology clinical trials where one coordinator works at both clinical sites. The Study Coordinators are usually assigned to disease-specific clinical programs, but they are occasionally shared across programs. The SC plays a central role in study conduct along with the PI; their responsibilities include: ensuring that all procedures required by the study are set-up, determining patient eligibility, ordering and ensuring completion of all study related procedures, monitoring and documenting toxicity, administering treatment or other interventions per protocol guidelines, submitting internal serious adverse events and protocol violations. The SCs are centrally managed by CISO and follow CISO Standard Operating procedures. The PI and disease specific clinical programs should relay all concerns about SC performance to the appropriate supervisors in CISO.

7.3 Data Manager (DM)

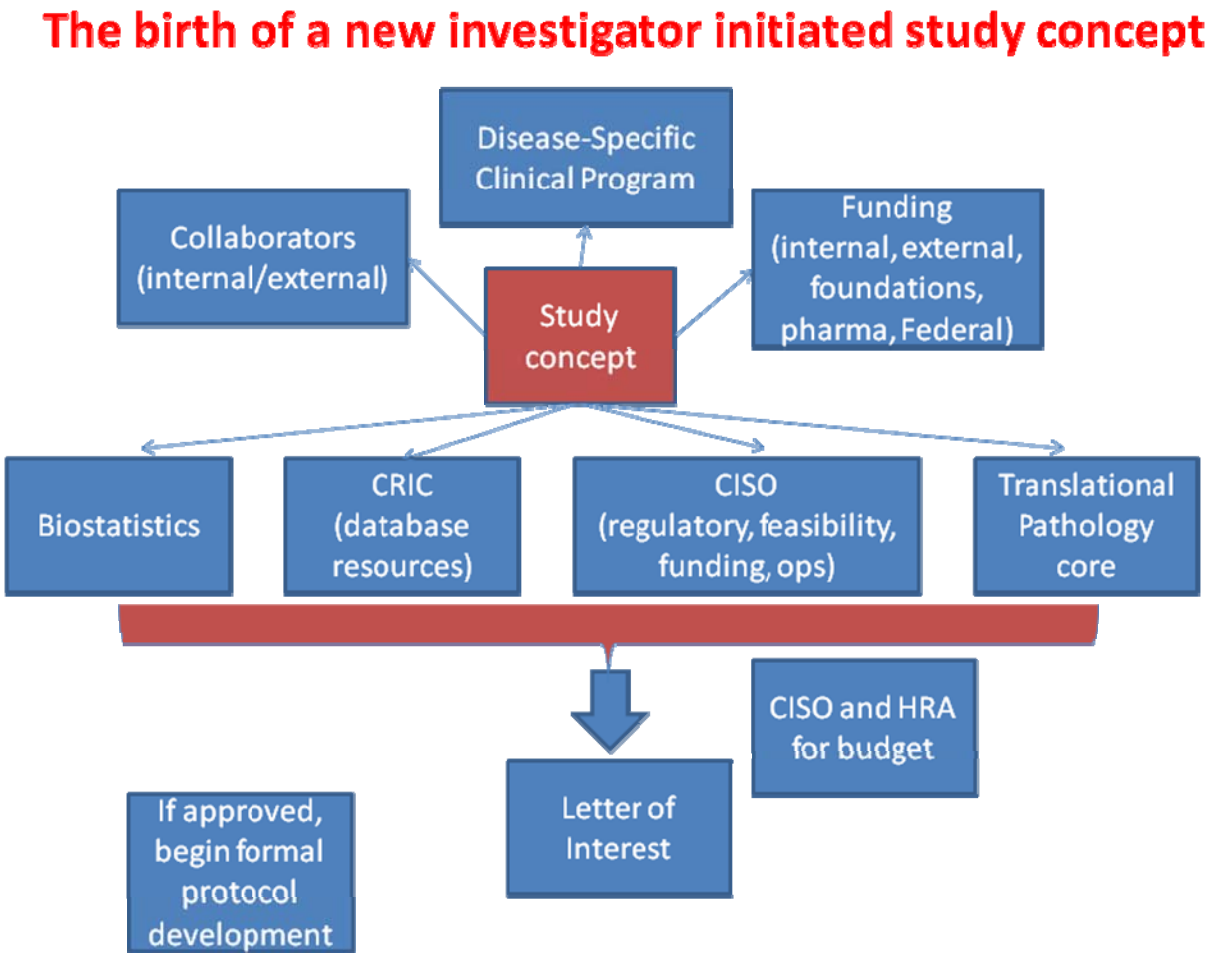
Each study is assigned two DMs (one for LAC and another for Norris) (except for hematology staff). DMs enter clinical data obtained from subject participation onto Case Report Forms (CRFs) (electronic or paper). DMs are responsible for coordinating the monitoring visits with the sponsors. There are designated DMs for each disease group and Phase I studies. The DMs and SCs work together in disease specific teams; each disease specific team is located in the same physical area in order to foster team spirit and adequate communication.

7.4 Business Manager (BM)

The CISO Business Manager works closely with the investigator and HRA in developing and finalizing the budget with the sponsor. The BM is responsible for submitting budget and contract documents (CDA, CTA, sponsor budget template) to HRA via True 2.0. HRA begins working on the CTA, contract and budget after receipt of required documents in True 2.0. Investigators are required to send all budget and contract documents to the CISO business manager, along with a sponsor contact.

NOTE: Please DO NOT contact HRA directly for CTA, CDA and budget. All contract and budget processes are handled by the CISO Administrative/Business Management UNIT. This is the only way that we can ensure adequate tracking of all studies and ensure that the loop is closed on all submissions.

SECTION VIII: Protocol Development



8.1 Investigator Initiated Trial (IIT)

Before proceeding with the research you wish to conduct, you must first consider four different factors to determine if the study is feasible.

8.1.1 Scientific Validity

The investigator is responsible for ensuring that the scientific question to be answered by the study is relevant and important for the advancement of the understanding or treatment of a specific cancer or disease. In addition to a thorough review of the published literature, the investigator is encouraged to seek internal and external collaborations with basic scientists, radiologists, pathologists, statisticians or others as needed to ensure that the science and design are of the highest quality.

8.1.2 Assessment of Resources

Resources needed for a study can range from the availability of the patient population, to the ability to perform all study related procedures and tests, and to having adequate staff. CISO can advise or assist with identifying and organizing all these resources. It is important to involve CISO early in the protocol development process by contacting the Protocol Administration Unit (Kay Johnson at Johnson_k@med.usc.edu or Zeno Ashai at zeno.ashai@med.usc.edu). If the protocol requires an IND, CISO will submit IND application and annual reports to FDA.

8.1.3 Financial Feasibility

What are the costs of the study and who or what will be funding it? Is there a grant or some kind of support, i.e., financial or drug. CISO Business Manager and the Health Research Association (HRA) will work together to create a budget. The budget process will begin once study is submitted to CIC; the process is explained above section III.

8.1.4 Recruitment Potential

Are there enough subjects available to complete the study? Who would be eligible? Where will you recruit them? Do you need healthy volunteers as well as those who need treatment? Will you recruit subjects outside of the university?

8.1.5 Competing Trials

Are there any competing trials currently open or in the pipeline which will impact accrual to the new trial? How does this new study fit in the disease-specific clinical program and how will it be prioritized in relation to the ongoing trials? The Disease-Specific Clinical Program Review should include a prioritization of the proposed study in relationship to existing trials. As part of the CIC Protocol Submission Checklist, a list of potentially competing trials is provided and the PI is asked to verify whether a trial is competing or not, and then provide justification for opening a competing study.

8.1.6 Statistical Design

The Investigator should work with a Biostatistician from the USC Norris Comprehensive Cancer Center Biostatistics Core early in the protocol development stage. The biostatistician helps in study design, analysis plan and writing of the protocol.

8.2 Important Resources for Developing IIT Protocol

8.2.1 Protocol and Informed Consent Template

The protocol should explain the purpose of the study and how it will be carried out. If the study is multi-institutional (i.e., other sites outside of USC), keep in mind that the protocol should be translatable to other institutions. It is suggested to create a schematic or flow chart for the trial to accompany the protocol. A visual aid is useful in clarifying the sequential steps in the trial as well as giving a quick, comprehensive overview.

CISO has developed a sample protocol for Phase I and Phase II. The protocol samples can be found online at: http://www.uscnorris.com/Core/Ciso/CisoDocSearch.aspx or contact Kay Johnson at Johnson_k@med.usc.edu or Zeno Ashai at zeno.ashai@med.usc.edu for assistance.

Informed Consent Form (ICF) – an ICF template from the IRB can be found here: http://www.usc.edu/admin/provost/oprs/hsirb/forms/

8.2.2 Biostatistics Core

The Biostatistics Core helps with the study design, analysis, protocol development and writing; as well as development of case report forms (CRFs). The Biostatistics Core works with the investigators throughout the study to ensure that relevant data are collected from the subjects for analysis to generate meaningful results. The investigator should contact the Biostatistics Core at the earlier stages of protocol development.

For IIT in Genitourinary, Hematology and Developmental Therapeutics studies contact Dr. Susan Groshen at Susan.Groshen@med.usc.edu or 323-865-0375.

For ITT in Pediatrics, and Women studies contact Dr. Richard Sposto at rsposto@chla.usc.edu or 323-361-8582.

For IIT in Gastrointestinal studies contact Dr. Dongyun Yang at Dongyun.Yang@med.usc.edu or323-865-0414.

8.2.3 Cancer Research Informatics Core (CRIC)

The USC Norris Comprehensive Cancer Center's Cancer Research Informatics Core (CRIC) is a centralized unit charged with the provision of the informatics research support. CRIC has developed a common application framework that is extensible and is known locally as Café. It is

an object-oriented development environment that combines common objects with study-specific data entry form(s) libraries with common and study specific metadata. Reporting Services is used to create Reports and Dashboards. Currently, Café supports data capture for protocol management, patient management, and patient enrollment. Information is also collected on protocol amendments, protocol sponsors, other participating organization, PI contact information, SAEs, etc. The in-house Café based CTMS system is called Café-Patients and Café-Protocols.

For IIT, the Biostatistics Core develops case report forms (CRFs) with PI and CISO input and approval. Cancer Research Informatics (CRIC) then creates the final forms as eCRFs displayed in Café. If your study involves a database of some sort, it is important to include CRIC in the initial steps of study development.

Section IX. Frequently Asked Questions

Q: I have received a Synopsis and CDA from the sponsor- what do I need to do?

A: If you are interested in the study, forward all documents with sponsor contact to CISO Business Manager, Manny Gimenez, who will submit the CDA to HRA for processing. You will receive notification from HRA to sign the CDA.

Q: What do I need to do for a pre-site visit?

A: Within a week of receipt of documents you will receive an email from CISO Regulatory Assistant requesting your availability for pre-site visit. You should provide at least a few dates and time with your availability; pre-site visit can't be scheduled if dates are not provided.

Q: How do I know that our site is selected by the sponsor?

A: After the pre-site visit, sponsor sends a follow-up letter indicating site selection or rejection.

Q: Whom should I contact for CIC submission?

A: You can submit your study documents (Protocol, ICF) to CIC@med.usc.edu or Zeno Ashai at zeno.ashai@med.usc.edu.

Q: Can I do CIC and IRB submission simultaneously?

A: No, study require final CIC approval prior to IRB submission.

Q: I have received CIC Protocol Submission Checklist, how do I complete and submit?

A: All forms are submitted electronically. The email you receive with the form contains step by step instructions on how to complete these forms.

Q: I have received a CIC memo after my protocol review, what does this memo means?

A: The CIC memo provides the CIC's decision and summary of the study review along with a detailed list of the stipulations that require a response from you. You are required to respond to CIC memo to obtain final CIC approval. See section IIB.

Q: My study received final CIC approval, is it open to accrual?

A: No, the study is now ready for IRB submission.

Q: How long does it take to receive IRB approval?

A: Study is assigned a date for initial review approximately 4 weeks from the date study is received by IRB. It takes about 8-10 weeks for final IRB approval.

Q: I have received an iStar 'study ready notification' what do I need to do?

A: If you are listed as a Co-PI in a study, login to iStar and agree to participant. If you are the PI of the study wait for all the Co-PIs to sign off and then submit the study to IRB.

Q: Why do I have to provide my Curriculum vitae (CV) and license?

A: Curriculum vitae and/or other relevant documents are required from the investigator(s) and sub-investigators to document investigators' qualifications and eligibility to conduct trials and/or provide medical supervision of subjects.

Q: When is RSC approval required?

A: Studies that use radiation exposure for investigational purposes (exposure that is not clinically indicated and/or that differs from standard clinical practice) require radiation safety committee (RSC) approval.

Q: What is a consistency checklist?

A: HRA uploads the Consistency Checklist. It compares, and verifies that the contractual language in the sponsored research agreement is consistent with language in the informed consent document and the protocol. The IRB does not grant final approval to begin research until it receives a completed and signed Consistency Checklist from HRA.

Q: How can I expedite the process of consistency checklist?

A: You can contact CISO Business Manager, Manuel Gimenez Or Study Regulatory Manager for the status of checklist and request to expedite the process with HRA. The CISO Business Manager requests weekly updates from HRA.

Q: I have been receiving emails from sponsor about the study, what should I do?

A: Contact the Regulatory Manager assigned to the study for the status of the study. You will receive an automatically generated Café email Status Update of the study at the beginning of every month until study is open to accrual.

Q: How do I know which protocol version and ICF is approved at IRB?

A: The latest approved protocol version and ICF are uploaded on Café website. You can also obtain the documents from iStar or contact the regulatory manager assigned to the study.

Q: I hold an IND for my IIT, what are my responsibilities?

A: If you hold an IND you are responsible for submitting study updates and renewals per FDA guidelines. CISO assists you in generating study updates. Contact Kay Johnson, CISO Associate Director for this purpose.

Q: Study monitor for my study is having issues with data reporting and compliance whom should I contact?

A: You may contact the QA Supervisor, Nonna Snider at 865-0420 or Kay Johnson at 865-0457.

Appendices

Appendix I: What is a Clinical Trial?

A clinical trial is a bio-medical or health-related research study, with a pre-defined protocol, which (a) involves human subjects, and (b) involves an intervention (therapeutic, diagnostic, or for disease prevention). Often the terms "clinical study" and "protocol" are used interchangeably. The clinical study or clinical trial is the research investigation; the protocol is the document that specifies all the steps and requirements necessary to complete the proposed research. There are three (3) different research categories (Appendix Ia), Six (6) different classifications (Appendix Ib) and four phases (Appendix Ic) in total that occur in sequence. Studies are grouped into four (4) types (Appendix Id).

Ia: Research Categories for Clinical Studies

Categories	Description
Agent or Device	Intervention, whether preventive or therapeutic, using an agent or device
Other Intervention	Any other type of intervention, whether preventive or therapeutic, such as behavioral modifications or nutrition protocols
Non-Interventional	Protocols not requiring any intervention (this is not a clinical trial – although it is clinical research)

Ib: Study/Protocol Classification

Ancillary or Companion (Linked Studies)	Auxiliary studies that are stimulated by, but are not a required part of, a main clinical trial and that utilize patient or other resources of the main trial to generate relevant information
Correlative	Laboratory based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc.
Epidemiologic, Observational, or Outcome	Studies among cancer patients and healthy populations that involve no intervention or alteration in the status of the patients
Prevention Trial	Trials for the modulation of cancer risk and inhibition of cancer progression using chemopreventive drugs, nutritional, dietary, behavioral, or other interventions
Screening, Early Detection, or Diagnostic Trials	Trials directly testing the efficacy of devices, techniques, procedures, or tests for earlier or more accurate detection and diagnosis of disease
Supportive Care Trial	Trials intended to improve the comfort and quality of life for the patient using drugs, nutritional, dietary, behavioral, or other interventions
Therapeutic Trial	Trials with therapeutic intent using drugs, radiation, surgery, other biological agents, behavioral, or other interventions

Ic: Clinical Trial Phases

Phase	Description
I	The objective is to determine safety, correct dosage, MTD (maximum tolerated dose) and side effects for an investigational agent or regimen. Study is done on a small group of participants
II	The study objective is to determine investigational agent's treatment activity and further evaluate its safety and toxicity profile.
III	Randomized trials that compare the investigational agent to standard treatments.
IV	Post-marketing studies determine the drug's risks, benefits, and optimal use

Id: Study Type

Type	Description
Investigator Initiated Study (ITT)	Protocol concept is conceived and written by the investigator. The investigator acts as sponsor and is responsible for study conduct and FDA regulations. The funding for the study may be from industry or other sources. These studies are monitored internally. Studies sponsored by an industry partner but where the PI contributed significantly to the concept development and writing of the study, and where the intellectual property is shared between the USC and the PI. Studies that are multi-institutional but originated by collaborative efforts among several PIs across institutions may be designated as investigator initiated if they meet the above criteria.
Cooperative Group	A study designed, sponsored and monitored by one of the NCI Clinical Trials Cooperative Group programs, such as SWOG, GOG, RTOG and others. USC is a member institution of SWOG (with grant funding from SWOG) but also participates in studies from other cooperative groups, usually through the CTSU mechanism.
NCI Consortium Study	A NCI consortium is a group of institutions whose funding comes from a U01 grant (for Phase I studies) or a Phase II contract with NCI (N01 grant). Studies are institutionally written by consortium investigators and are externally peer reviewed by NCI. Studies are monitored by a coordinating center for the consortium. USC is member of the California Cancer Consortium (CCC) that consists of USC, UC Davis and City of Hope. Pennsylvania State University, the University of Pittsburgh, and the Wayne State Karmanos Cancer Centers are part of the consortium for Phase II trials.
Industry Study	Study is conceived, written, monitored and sponsored by a pharmaceutical company. Sponsor holds the IND and is responsible for all FDA requirements.

Appendix II: Disease Specific Program Group List

Disease Specific Program Group List		
Disease Group		**Email**
Developmental Theraputic (Sarcoma, melanoma, skin cancers (SCC, Basal, Merkel) lung, head + neck, Brain)		
Group Leader	Mike Wong, MD	mike.wong@med.usc.edu
Members	Barbara Gitlitz, MD	gitlitz@usc.edu
	James Hu, MD	jameshu@usc.edu
Hematology		
Group Leader	Preet Chaudhary, MD	pchaudha@usc.edu
Members	Anil Tulpule, MD	tulpule@usc.edu, tulpule_a@ccnt.usc.edu
	Ann Mohrbacher, MD	mohrbach@usc.edu
	Casey O'Connell,MD	coconnel@usc.edu
	Howard Liebman, MD	liebman@usc.edu
	Ilene Weitz, MD	iweitz@usc.edu
	Parkash Gill, MD	igill@usc.edu
	Sikander Ailawadhi, MD	ailawadh@usc.edu
	Vinod Pullarkat, MD	vinod.pullarkat@med.usc.edu
Colorectal Surgery		
Group Leader	Anthony Senagore, MD	anthony.senagore@med.usc.edu
Members	Andreas Kaiser, MD	kaiser_a@ccnt.usc.edu; akaiser@usc.edu
	Glenn Ault, MD	ault@usc.edu

Breast Oncology		
Group Leader	Debu Tripathy, MD	tripathy@usc.edu
Members	Agustin Garcia, MD	Agustin.Garcia@med.usc.edu; aagarcia@usc.edu
	Dennis Holmes, MD	Dennis.Holmes@med.usc.edu; dholmes@usc.edu
	Diana Chingos	Diana.Chingos@gmail.com
	Heather MacDonald, MD	hmacdona@usc.edu
	Michael Press, MD	press@usc.edu
	Christy Russell, MD	carussel@usc.edu
	Stephen Sener, MD	Stephen.Sener@med.usc.edu
	Pulin Sheth, MD	pulin_sheth@yahoo.com
	Darcy Spicer, MD	dspicer@ccnt.usc.edu
	Richard Sposto, PhD	rsposto@chla.usc.edu
Gynecological Oncology		
Group Leader	Lynda Roman, MD	lroman@usc.edu
Members	Agustin Garcia, MD	Agustin.Garcia@med.usc.edu; aagarcia@usc.edu
	Huyen Pham, MD	hqpham@usc.edu
	Yvonne Lin, MD	ylinliu@usc.edu
GU (Urology+ Oncology)		
Group Leader	Jacek Pinski, MD	pinski_j@ccnt.hsc.usc.edu
Members	David Quinn, MD	diquinn@usc.edu
	Amir Goldkorn, MD	agoldkor@usc.edu
	Mitchell Gross, MD	mitchell.gross@usc.edu
	Simak Daneshmand , MD	daneshma@usc.edu
	Tanya Dorff, MD	dorff@usc.edu
Radiology		
Group Leader	Ed Grant, MD	edgrant@usc.edu
Members	Meng Law, MD	eulaw@usc.edu
	Patrick Colletti, MD	colletti@usc.edu
	Hossein Jadvar, MD	jadvar@usc.edu
	Linda Hovanessian-Larsen, MD	lhlarsen@usc.edu
	Suzanne Palmer, M.D.	spalmer@usc.edu

GI Oncology		
Group Leader	Heinz-Josef Lenz, MD	lenz@usc.edu
Members	Anthony El-Khoueiry, MD	el-khoueiry_a@ccnt.usc.edu; elkhouei@usc.edu
	Syma Iqbal, MD	iqbal_s@ccnt.usc.edu
Radiation Oncology		
Group Leader	Paul Pagnini, MD	pagnini@usc.edu
Members	Afshin Rashtian, MD	afshin.rashtian@usc.edu
Solid Tumors or Phase I		
Group Leader	Anthony El-Khoueiry, MD	el-khoueiry_a@ccnt.usc.edu; elkhouei@usc.edu
Members	Agustin Garcia, MD	Agustin.Garcia@med.usc.edu; aagarcia@usc.edu
	David Quinn, MD	diquinn@usc.edu
	Mike Wong, MD	mike.wong@med.usc.edu
	Barbara Gitlitz, MD	gitlitz@usc.edu
	Heinz-Josef Lenz, MD	lenz@usc.edu
	Preet Chaudhary, MD	pchaudha@usc.edu
	Vinod Pullarkat, MD	vinod.pullarkat@med.usc.edu

CHLA Pediatric Oncology		
Group Leader	Leo Mascarenhas, MD, MS	lmascarenhas@chla.usc.edu
Group Leader (Backup)	Marcio Malogolowkin, MD	mmalogolowkin@chla.usc.edu
Members	Stuart Siegel, MD	Ssiegel@chla.usc.edu
	Robert Seeger, MD	rseeger@chla.usc.edu
	Judith Villablanca, MD	jvillablanca@chla.usc.edu
	Araz Marachelian, MD	Amarachelian@chla.usc.edu
	Eric Bubbers, MD	Ebubbers@chla.usc.edu
	Paul Gaynon, MD	Pgaynon@chla.usc.edu
	Teresa Harned, MD	Tharned@chla.usc.edu
	John Jack Quinn, MD	jjquinn@chla.usc.edu
	David Freyer, DO, MS	dfreyer@chla.usc.edu
	Yves DeClerck, MD	ydeclerck@chla.usc.edu
	Cecilia Fu, MD	cfu@chla.usc.edu
	Richard Ko, MD	Rko@chla.usc.edu
	Robert Brown, MD	rjbrown@chla.usc.edu
	Rima Jubran, MD	Rjubran@chla.usc.edu
	Jonathan Finlay, MD	Jfinlay@chla.usc.edu
	Anat Epstein, MD	Aepstein@chla.usc.edu
	Shahab Asgharzadeh, MD	SAsgharzadeh@chla.usc.edu
	Girish Dhall, MD	GDhall@chla.usc.edu
	William May, MD	WMay@chla.usc.edu
	David Tishler, MD	DTishler@chla.usc.edu
	Kathleen Meeske, PhD	kmeeske@chla.usc.edu
	Ernest Katz, PhD	ekatz@chla.usc.edu
	Sharon O'Neil, PhD	SONeil@chla.usc.edu
	Rajkumar Venkatramani, MD	RVenkatramani@chla.usc.edu
	Hung Tran, MD	HTran@chla.usc.edu
	Kathleen Ruccione, MPH, RN, CPON, FAAN	KRuccione@chla.usc.edu
	Jacquelyn Baskin, MD	JBaskin@chla.usc.edu

Appendix III: Study Status Update Notification

Dear ....,

Below is a short status summary for the protocol TEST002.

Protocol Title:

Action Date	Action	Responsible Party
9/2/2009	CISO Received your Protocol	PI
	CIC Checklist was Received	PI
6/9/2009	First Expected Review Date	CISO
12/10/2004	Protocol discussed in CIC Meeting. (Final Status: Administratively approved)	CISO
6/1/2006	Protocol discussed in CIC Meeting. (Final Status: Approved with minor changes)	CISO
5/15/2008	Protocol discussed in CIC Meeting. (Final Status: Revisions required - CIC re-review required)	CISO
9/17/2008	Protocol discussed in CIC Meeting. (Final Status: Withdrawn by PI)	CISO
9/2/2009	Final CIC Status - Approved	CISO
	I-STAR study ready notified sent to signoff	CISO
	IRB Submission	CISO
	IRB Review (Review Status: Pending)	IRB
	Sponsor Budget template sent to HRA	CISO
	Sponsor Budget template received	HRA
7/15/2009	Consistency Checklist Uploaded to ISTAR	HRA
3/5/2007	IRB Final Approval	CISO
	Study Drug Received	Pharmacy
3/3/2007	Open to Accrual	CISO
9/3/2009	Overall Status - Open to Accrual	CISO

Thank you,

Appendix IV: Pre-Site Visit (Site Qualification) Form

UNIVERSITY OF SOUTHERN CALIFORNIA/KENNETH NORRIS, JR. COMPREHENSIVE CANCER CENTER
Kenneth Norris, Jr. Cancer Hospital & Research Center - 1441 Eastlake Ave., Los Angeles, CA 90033 Tel. (323) 865-3000
USC University Hospital - 1500 San Pablo St., Los Angeles, CA 90033 (323) 442-8500
Los Angeles County/USC Medical Center - 1200 N. State St., Los Angeles, CA 90033 Tel. (323) 226-6395

Pre- Site Visit

Investigator: _____ **Visit Date:** _____

Protocol No: _____ **Study Drug:** _____

CRA Name: _____ **CRA Email:** _____

CRA Phone # _____ **Institution:** University of Southern California

Summary of Pre-Site Visit

Description	Y/N	Comments
1. Site Visit		
Meeting with Investigator		
Meeting with Pharmacists (Norris)		
Meeting with Pharmacists (IDS)		
2. *Protocol submission process overview*		
3. *Personnel contact information*		
4. *Facilities*		
Norris Cancer Center		
LAC-USC county		
Clinical Trials Unit (CTU) for studies involving multiple PKs		
5. Drug shipment and process		Study drugs shipped to both locations
Pharmacy-dispensing		
6. Physical facilities for patient care		
7. Storage of CRF's during/after study		
8. Monitoring visit procedure		No internet access is provided by USC. Study CRAs are advised to bring their own internet wireless card and their own laptop to access their system.
9. Monitoring Letter		
10. Signing Monitoring Log		
11. Electronic Data access form		
12. Attach additional comments and supporting documentation as appropriate.		

CRA Name/ Title **Signature:**

Company Name **Date:**

Page 8 of 8

Appendix V: NCCC Clinical Trial Accrual Monitoring Policy

USC UNIVERSITY OF SOUTHERN CALIFORNIA

Quality Assurance Monitoring Committee

CLINICAL TRIALS ACCRUAL MONITORING POLICY

DATE: March 1, 2011

The following is the USC Norris Comprehensive Cancer center clinical trials accrual monitoring policy.

At the time of initial protocol submission to the CIC, PI is asked to provide the following information to the CIC:

- Total planned accrual; estimated accrual per year; estimated years of accrual.

NCCC QAMC will review studies for accrual as follows:

- All USC investigator-initiated intervention trials every 6 months counting from the open to accrual date.
- All USC investigator-initiated specimen and database collecting trials every 12 months counting from the open to accrual date.
- All protocols (intervention, specimen, database) that are not USC-investigator-initiated every 12 months, counting from the open to accrual date.

Criteria For Slow Accrual*

- At any review: if accrual is < 50% but > 10% of projected accrual, a memo will be sent to the PI, copied to disease specific group, notifying of the slow accrual and requesting to provide an action plan within 30 days of receiving such memo.
  - A reminder will be sent to the PI on a monthly basis for a total of 3 months if response is not received.
  - If response is not received within 3 months from the initial memo date, QAMC will submit study closure recommendation to the CIC and the study will be closed.
- At any review: if accrual is 10% or less of projected accrual, a memo will be sent to the PI, copied to disease specific group and CIC, notifying of the slow accrual and recommending study closure.
  - Unless a strong argument can be made to keep the study open, the study will be closed within 1 month of sending such memo to the PI.
  - If it is decided to keep the study open, the study accrual will be re-reviewed in 6 months with the same stipulations as stated above.
  - If response is not received within 30 days from the initial memo date, QAMC will submit study closure recommendation to the CIC and the study will be closed.
- At any review: if a trial is found to have < 50% of projected accrual after more than one review, QAMC will estimate the time that it will take to complete accrual to the trial. If that estimate is more than twice the planned accrual period, a memo will be sent to the PI, copied to disease specific group, notifying about slow accrual and recommending study closure.
  - Unless a strong argument can be made to keep the study open, the study will be closed within 1 month of sending such memo to the PI.

- If response is not received within 30 days from the date initial memo was sent to PI, QAMC will submit study closure recommendation to the CIC and the study will be closed.

* Rare disease studies as well as Phase I and high priority Cooperative Group studies may receive a separate consideration due to the nature of such trials.

Study accrual status update for each disease category will be sent to the PI and Disease Specific Group on a periodic basis to assist the investigators with the accrual monitoring.

Appendix VI: Tissue Procurement Forms

VIa: Application for Tissue

☐ Approved
☐ Not Approved
☐ Priority Score

USC/NORRIS COMPREHENSIVE CANCER CENTER

Tissue Procurement Core Resource

Application for Tissue from the Fresh/Frozen Tissue Core

Application Date (mo/dy/yr)

Name of Principal Investigator	Contact person	Direct Telephone Number
		( )

Name of Institution, Department, and Mailing Address	Direct Fax Number
	( )
	E-Mail Address
	Fed Ex Account Number

If applicable: Funding Agency	Grant Number

	Type of tissue requested (Please fill in appropriate box with anatomical site.)			
	Fresh	Frozen	OCT Frozen	Other (Specify)
Representative Tumor				
Matched Normal Tissue				

Fluids requested (Please check box.)	Fresh	Frozen
Whole Blood		
Serum		
Urine		

Expected total number of cases required for study:	

Expected duration of study	Start date:	
	End date:	

Specific Aims of Study (Please include reason why fresh/frozen tissue is required.)			
Date of IRB Approval (mo/dy/yr)	IRB Number	Does this study require knowledge of patient ID? ☐ YES ☐ NO	Please attach a brief protocol with a copy of informed consent.
As Principal Investigator on this study, I hereby certify that the tissue/fluids requested for this study are to be used for the purposes of this IRB approved protocol only.	Signature of Principal Investigator:		

Is there a pathologist participating in your study?	If yes, name of collaborating pathologist:
☐ YES ☐ NO	

For USC/Norris Use	Date Shipped
Program committee assignment: ☐ GI ☐ GU ☐ Breast ☐ Heme/Onc ☐ Other_____	

Sue Ellen Martin, M.D., Ph.D.
Coordinator, Tissue Procurement Core

Andy E. Sherrod, M.D
Director, Adult Tissue Procurement Core

Mo-Li Chen
Project Specialist

VIb: Translational Pathology Core Facility Tissue Procurement Forms

VIb.1: FRESH/FROZEN SURGICAL OR BIOPSY SPECIMEN REQUEST

USC Norris Comprehensive Cancer Center
Translational Pathology Core Facility/Adult Tissue Arm
Fresh/Frozen surgical or biopsy specimen Request
Phone: 865-3374

Date Received _____

Ordered By : _____ Phone : _____

Principal Investigator : _____IRB # : _____

Protocol # : _____Billing Account : _____

Norris Hospital / University Hospital /LAC&USC (please circle one)

Patient Name: _____ MR # : _____ DOB : _____

CT or Ultrasound or others (please circle one)

Date _____Time _____Room No _____for the procedure

Site of the tissue _____

1. Need to have a signed inform consent on file prior all tissue/fluid collection

2. If the collection is from a resection case, need to have the name, PF#, date, time, site of the tissue and instruction sheet from the IRB protocol on how the tissue should be handled.

3. If the collection is from a biopsy case, for CT or ultrasound, need to have the name, PF#, date, time, site of the tissue and instruction sheet from the protocol on how the tissue should be handled. The research coordinator needs to schedule the bx with the cytology department to have a cytotech or cytology fellow present at the time of the collection, to confirm the tissue is tumor.

All paper should be scanned and sent to mhchen@usc.edu or delivered to Norris Room 2358.
Version September 12, 2011

VIb.2: RESEARCH PARAFFIN BLOCK SECTION REQUISITION

USC Norris Comprehensive Cancer Center
Translational Pathology Core Facility/Adult Tissue Arm
Research Paraffin Block Section Requisition
Phone: 865-3374

Date Received: _____ Contact: _____

Phone: _____ Email:_____

Principal Investigator : _____ Billing Account : _____

Protocol # : _____ IRB # : _____

Lab Agreement # :_____ Accession # :_____

Patient Name : _____MR # : _____ DOB : _____

Norris Hospital / University Hospital / LAC&USC (please circle one)

Tissue Type : _____ Pathologist : _____

# of H&E(5μm): _____ # Unstained Sections : _____ Thickness (μm) : ____

Charged slides / Glass slides (circle one)

Note: All above information is required

Please attach a copy of IRB approval letter and copy of the signed informed consent from the patient above. We also need to have copy of the protocol if there is a special instruction for processing the tissue.

Fee Schedule:
(Check All That Apply)

[ ] Paraffin sectioning 1st slide	$3.00 per slide
[ ] Paraffin sectioning additional slide	$1.50 per slide
[ ] H&E staining	$1.00 per slide
[ ] Procuring slides & blocks for reviewing	$20.00 per case
[ ] Pathologist review	$15.00 per 10 minutes

*--Office Use only--Date Completed:*_____

Version 9.12.11

VIc: PRICE LIST OF SERVICES

USC NORRIS COMPREHENSIVE CANCER CENTER
TRANSLATIONAL PATHOLOGY CORE FACILITY
NORRIS 2358 PHONE: 323-865-3374

	CC Member	Non Member
Tissue Procurement (frozen or fresh) (Norris) (Includes quality control, pathology report)	$20.00 per sample	$30.00 per sample
Serum/Fluid Procurement (Includes processing, for Norris)	$20.00 per sample	$30.00 per sample
BM/Blood Ficoll	$50.00 per sample	$75.00 per sample
Leukapharesis/Ascites Ficoll (50 vials)	$150.00 per sample	$215.00 per sample
Leukapharesis/Ascites Ficoll (25 vials)	$75.00 per sample	$110.00 per sample
Paraffin-Embedded Tissue		
-Pulling slides and pulling blocks (for 1 to 10 cases)	$20.00 per case	$30.00 per case
(for 11 to 30 cases)		$20.00 per case
(for 31 or more cases)		$10.00 per case
-Pulling blocks (for 1 to 10 cases)	$5.00 per case	$10.00 per case
(for 11 or more cases)		$5.00 per case
-Pulling slides only		$5.00 per case
-Tissue Prep w/ processing	$6.00 per block	$9.00 per block
-Re embed tissue block	$2.00 per block	$3.00 per block
-Sectioning 1st slide	$3.00 per slide	$4.00 per slide
-Sectioning additional slides	$1.50 per slide	$2.00 per slide
-Staining: H & E	$1.00 per slide	$1.50 per slide

Sectioning Frozen Tissue

-Sectioning 1st slide	$9.00 per slide	$13.00 per slide
-Sectioning additional slides	$1.50 per slide	$2.00 per slide
-Staining: H & E	$1.00 per slide	$1.50 per slide
-Stain with Histogene solution	$1.00 per slide	$1.50 per slide
Storage/Retrieving Specimens (up to 10 vials)	$10.00 per case	
-Each additional 10 vials	$5.00 / 10 vials	
Tissue/Fluid Procurement from UH or LAC/USC hospitals (Procurement Fee)	$20.00	
Courier Fee per trip to UH or County	$20.00	
Slides Storage containers		
Slides box (100 slides)	$10.00 each	$15.00 each
Slides container (10 slides)	$1.00 each	$1.50 each
Shipping and Handling (Include Styrofoam box)	$20.00	$30.00
Tissue Array	$250.00 per block	$310.00 per block

(120 holes – 1mm each, 60 holes – 2mm each)
(If precise site selection of tissue core is required additional fee of $30.00 per hour over 5 hours)

1. Sample Identification - Tech time total (-15 minutes each block @$25.00/hr, 40 blocks total = $250.00)
    a. Cutting and staining slide
    b. Staining H&E
2. Block construction
    a. Recipient block $50.00
    b. Array design, actual core manufacture And arrangement in recipient block ($25.00/hr) $175.00
    c. Processing of the TMA block, with cutting and Staining H&E $25.00

Version 9.12.11

Appendix VII: Template Language for Documenting Subject Consenting Process

Please ensure that language similar to the one provided below is included in your progress note documenting the consenting process.

Details of the study concept and treatment, as well as risks and benefits were discussed with the patient. Alternatives, including best supportive care, other treatment options and other clinical trials were discussed. The patient had an opportunity to ask questions. The patient expressed understanding of what was discussed and agreed to participate in the study. After this discussion the informed consent was signed, and the patient was given a copy of the signed Informed Consent Documents.

Appendix VIII: Helpful Links

CAFE: http://cafe.usc.edu
CIC Schedule: http://uscnorriscancer.usc.edu/Core/CISO/ViewPending.aspx
CISO Web Site: http://uscnorriscancer.usc.edu/core/CISO/
Institutional Review Board: http://www.usc.edu/admin/provost/oprs/hsirb/
ICF Template: http://www.usc.edu/admin/provost/oprs/hsirb/forms/
FDA: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
HIPAA: http://ooc.usc.edu
Good Clinical Practice: http://www.citiprogram.org
Sample Protocol: http://www.usc.edu/admin/provost/oprs/hsirb/forms/

Appendix IX: CIC Protocol Submission Checklist

CIC Protocol Submission Checklist

Completion of the CIC protocol submission checklist is required in order to begin the process of study review and approval; the checklist serves as a single entry point into the protocol review process and contains the information needed for: 1) the disease specific clinical program review, 2) the scientific and operational review by CIC and CISO, and 3) the initiation of the budgeting and contract process. IRB submission will occur after final CIC approval.

Hello . Please use the Next & Previous buttons below to navigate and **click 'Submit'** when prompted. Submitting will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval. You may save your progress and come back later by clicking 'Save' below at any time.

Trial Title:

CIC Protocol Submission Checklist

CISO Number:

PI Name:

CO-PIs: (Select CO-PI) Add CO-PI to list ->

List of CO-PIs
(No co-PIs added yet)

Institution: USC Norris CHLA

Disease Specific Clinical Programs: (pick multiple if applicable)
Brain Breast & Breast Surgery Colorectal surgery GI oncology GU Oncology & Urological Surgical Oncology Gyn Oncology Head & Neck Hematology Lung Melanoma, Skin Cancer Phase 1 Radiation Oncology Radiology Sarcoma

Intervention Type:
1-Biological/Vaccine 1-Device 1-Drug 1-Genetic 1-Radiation 2-Behavioral 2-Nutrition 2-Other Intervention 3-Epidemiology/Observational 4-Correlative None

Purpose of Study:
Cancer Therapy Screening/Diagnostic Interventional Prevention Non-Cancer Related Ancillary Quality of Life Specimen Study Supportive Care All Diagnostic Early Detection Observational

Phase of Study:
Compassionate Not Applicable Observational Phase I Phase II Phase III Phase IV Phase I/II Phase II/III Pilot

Disease Site (gastric, bladder, etc...):

What is the Target Population for this Trial? (pick multiple if applicable)
Metastatic (specify line of therapy if applicable->)
Localized (if localized pick sub-options)
Adjuvant Neoadjuvant
N/A Other:

Is this a USC Initiated Study? Yes No

Is this a Multi-Center Trial? Yes No

If 'yes,' list sites only if investigator-initiated study:

Save Progress Previous Next

CIC Protocol Submission Checklist

Completion of the CIC protocol submission checklist is required in order to begin the process of study review and approval; the checklist serves as a single entry point into the protocol review process and contains the information needed for: 1) the disease specific clinical program review, 2) the scientific and operational review by CIC and CISO, and 3) the initiation of the budgeting and contract process. IRB submission will occur after final CIC approval.

Hello . Please use the Next & Previous buttons below to navigate and **click 'Submit'** when prompted. Submitting will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval. You may save your progress and come back later by clicking 'Save' below at any time.

Trial Title:

CIC Protocol Submission Checklist

Which USC hospitals and clinics or sites will be used? Please check all that apply:	☐ USC NCCC ☐ USC University Hospital ☐ Westside Prostate Cancer Center ☐ LAC ☐ HCC2 (USC Healthcare Consultation Center 2) ☐ USC Pasadena
Planned Accrual, USC	
Planned Accrual, Total	
What is the expected duration of the accrual period?	
Estimated number of patients seen at USC per year who will meet the eligibility criteria:	
How many cycles will the average patient undergo (i.e., average length on study)?	
Study fits within program scientific goals and priorities:	○ Yes ○ No
Is USC participating in all Phases or stages of the study/PK?	○ Yes ○ No ○ Not Applicable
Additional Comments:	
Does the study include serial pharmacokinetic and/or pharmacodynamic blood draws or does it require intensive safety monitoring (such as serial EKGs in one day)?	○ Yes ○ No
If you answered yes to the above question, we strongly recommend that the study uses the Clinical Trials Unit of USC; will the study use the CTU? (if not, please provide a justification in the comment box)	
Will the study require Radiation safety approval (Non-Standard scans, MUGA, PET CT etc)?	○ Yes ○ No

Save Progress Previous Next

CIC Protocol Submission Checklist

Completion of the CIC protocol submission checklist is required in order to begin the process of study review and approval; the checklist serves as a single entry point into the protocol review process and contains the information needed for: 1) the disease specific clinical program review, 2) the scientific and operational review by CIC and CISO, and 3) the initiation of the budgeting and contract process. IRB submission will occur after final CIC approval.

Hello . Please use the Next & Previous buttons below to navigate and **click 'Submit'** when prompted. Submitting will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval. You may save your progress and come back later by clicking 'Save' below at any time.

Trial Title:

CIC Protocol Submission Checklist

Once you have completed the questions here, please click the 'Submit' button (this will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval).

Submit

Save Progress | Previous | Next

CIC Protocol Submission Checklist

Completion of the CIC protocol submission checklist is required in order to begin the process of study review and approval; the checklist serves as a single entry point into the protocol review process and contains the information needed for: 1) the disease specific clinical program review, 2) the scientific and operational review by CIC and CISO, and 3) the initiation of the budgeting and contract process. IRB submission will occur after final CIC approval.

Please use the Next & Previous buttons below to navigate and **click 'Submit'** when prompted. Submitting will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval. You may save your progress and come back later by clicking 'Save' below at any time.

Trial Title:

CIC Protocol Submission Checklist

Competing Trials

The following table lists potentially competing trials; please fill in the boxes in the last 3 columns in order to verify whether the trial is competing, to justify opening a competing trial and prioritize competing studies.

Protocol # & PI	Title	Accrual Info	Check if Competing	Comments (Justification for each yes/no)	Provide ranking/prioritization of this study in relationship to competing trials
		ACCRUAL STATUS:			

CIC Protocol Submission Checklist

Completion of the CIC protocol submission checklist is required in order to begin the process of study review and approval; the checklist serves as a single entry point into the protocol review process and contains the information needed for: 1) the disease specific clinical program review, 2) the scientific and operational review by CIC and CISO, and 3) the initiation of the budgeting and contract process. IRB submission will occur after final CIC approval.

Hello . Please use the Next & Previous buttons below to navigate and **click 'Submit'** when prompted. Submitting will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval. You may save your progress and come back later by clicking 'Save' below at any time.

Trial Title:

CIC Protocol Submission Checklist

Who is the sponsor?	
Sponsor's contact name, address, telephone, and e-mail address:	
Who will provide the case report forms?	
Who will do the study monitoring?	
List drugs supplied by the sponsor:	
List commercially approved drugs required for study which are not supplied by the sponsor:	
Will CISO assist the PI to complete/submit IND application and perform IND-holder task?	○ Yes ○ No
Additional Comments:	

Save Progress Previous Next

CIC Protocol Submission Checklist

Completion of the CIC protocol submission checklist is required in order to begin the process of study review and approval; the checklist serves as a single entry point into the protocol review process and contains the information needed for: 1) the disease specific clinical program review, 2) the scientific and operational review by CIC and CISO, and 3) the initiation of the budgeting and contract process. IRB submission will occur after final CIC approval.

Hello . Please use the Next & Previous buttons below to navigate and **click 'Submit'** when prompted. Submitting will send the form to the disease specific clinical program chair to provide verification of programmatic review and approval. You may save your progress and come back later by clicking 'Save' below at any time.

Trial Title:

CIC Protocol Submission Checklist

Does the protocol require any non-standard procedures/correlative studies?	○ Yes ○ No
Have the plans for safety monitoring, adverse event reporting been described in the protocol?	○ Yes ○ No
If 'yes,' in what section of the protocol?	
If 'no,' describe your plans for data and safety monitoring:	
Is Data safety monitoring plan adequately described in the protocol?	○ Yes ○ No
If 'yes,' in what section of the protocol?	
If 'no,' describe your plans for data and safety monitoring:	
Will the data/statistical analysis be done at USC?	○ Yes ○ No
Does the study have available funding?	○ Yes ○ No
If yes, please provide source of funding:	○ Industry Sponsored ○ Industry support of investigator initiated trial ○ Grant Support (specify ->) ○ COOP Group ○ NCI-CTEP sponsored ○ Other (specify ->) Other or Grant (specify):

Save Progress Previous Next