CTSC Clinical Research Quality Assurance Program
for Investigator-Initiated Interventional Trials

1. Overview
Typically used in tandem throughout the current healthcare industry, “auditing” and “monitoring” do not represent a single concept. The primary defining characteristics distinguishing auditing and monitoring are independence, objectivity and frequency. Auditing represents evaluation activities completed by individuals independent of the process on a periodic basis and monitoring represents evaluation activities completed by individuals who may not be independent of the process on a routine or continuous basis. Therefore, auditing provides for a more objective assessment. Both processes are desirable to assure that the rights and safety of the study subjects are protected, and that the study is conducted, in accordance with the protocol, SOPs, ICH GCP guidelines, and the applicable regulatory requirements.

2. Definitions
- Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and the applicable regulatory agency requirements.
- Auditing is a systematic and independent examination of trial-related activities and documents to evaluate whether the trial-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's SOP, GCP and other applicable regulatory requirements. Auditors collect evidence and compare against standards, review documents, assess deviation and non-compliance and recommend actions.

3. Scope
The CTSC Clinical Research Quality Assurance Program (CCRQA) is comprised of both auditing and monitoring elements implemented as needed, based on the scope of the clinical research project. This service is offered for all Investigator-Initiated studies that otherwise are not audited/monitored by another entity. The activities aim to provide a proactive (as opposed to “for cause”) regulatory assessment of the studies in order to preclude the development of non-compliance situations. The program is provided at no cost for unfunded studies. The recharge rate for funded studies will be negotiated on an individual basis.

Principal Investigators (PIs) carry the ultimate responsibility for the conduct of the research study, for the safety of the human subjects, for the data quality and for regulatory compliance. The CCRQA Program is meant to assist in supporting the overall quality of the study, but it is ultimately the PI’s responsibility to conduct the study according to the Federal, State, and local regulations and UC Davis SOPs and policies.

The CCRQA team will provide periodic metrics reports to TRICC and the HSOC with summary analysis of the program performance (not specific Investigator or protocol performance).

The CCRQA Program consists of five stages:

i. Study Protocol Determination
   a. In collaboration with the IRB and using internally generated databases, all new Full Committee approvals are identified.
   b. The QA effort for studies is prioritized by:
     * Level of risk to subjects (surgical procedure; investigational drug/device; condition/indication-patient vs. out-patient procedures);
     * Complexity of the protocol (type of procedure; number of procedures; proposed enrollment; number of study visits; etc.); and
     * Experience of the PI/study team.
c. The team sends notification to the Principal Investigator on the study, describing the CCRQA program and offering to set up the initiation visit. If the PI is interested, the CCRQA team will proceed with the program.

ii. **Initiation Visit**

During the initiation visit, the CCRQA team will meet with the Principal Investigator and key study personnel to analyze the potential QA needs for the study. The CCRQA will provide study binders that contain an overview of investigators and staff responsibilities, web- and print-based resources, and sections for organizing study documents.

The visit also includes the discussion of the quality assurance needs for the duration of the study. Two levels of the oversight are available depending on the risk level:

- **Investigator-Initiated Studies (not including investigational drug/device)**
  
  This type of study is eligible for Level I, limited QA Reviews, principally including regulatory compliance, such as Informed Consent documentation and process, Adverse Events reporting, and Protocol Deviation reporting.

- **Investigator-Initiated Studies with Investigational (new or approved) Drug/Device where UC Davis or Researcher is the Sponsor-Investigator**

  These studies would qualify for Level II, comprehensive QA Review, including all elements of the limited QA Review and also Data Quality review. Studies of this nature must comply with 21 CFR 312 (Investigational Drugs) and/or 21 CFR 812 (Investigational Devices).

During the Initiation visit the CCRQA reviewer(s) will:

1. Ensure that the investigator and staff are adequately informed about the trial
2. Explain the organization and use of the study binders
3. Distribute the QA plan to the PI and coordinator
4. Discuss with the PI and study team the QA visit schedule
5. Instruct the study team to notify the CCRQA when the first and second subjects are enrolled
6. Schedule the QA visit meeting

iii. **Quality Assurance Review**

QA review begins after the first 2 subjects are enrolled in the trial (or within 6 months of first subject enrolled, whichever comes first) [protocol complexity dependent].

**Level I - Limited Quality Assurance Review**

1. Verify that investigator follows the approved protocol and all approved amendments.
2. Verify and review that study site is maintaining all essential documents.
3. Verify that written informed consent was obtained before each subject’s participation in the trial. [100% of study subjects]
4. Verify that the investigator is enrolling only eligible subjects.
5. Verify that source documents and other trial records are accurate, complete, current, and maintained. [100% first 2 subjects; then 10% random sample remaining subjects]
6. Verify investigational product disposition and documentation (including but not limited to receipt, storage, supply, dispensing, and returns as applies) and compare administration records with dispensing and shipment records with IDS Pharmacy. [100% first 2 subjects; then 10% random sample remaining subjects]
7. Check for documentation of dosing and/or therapy (including but not limited to study article/product/drug/therapy administration information, including start and stop dates of treatment). [100% first 2 subjects; then 10% random sample remaining subjects]

8. Check for documentation and timely reporting of adverse events.

9. Check for documentation and reporting of protocol deviations (including but not limited to: subject eligibility, missed study visits, study visits conducted outside of visit window as prescribed by protocol, tests/exams/procedures not performed, etc.).

10. Verify that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, and dated.

11. Check for documentation of screen failures, subject withdrawals, exited subjects, etc.

12. Inform the investigator of any deviations from the protocol, SOPs, GCP, and applicable regulatory requirements. The investigator is responsible for taking appropriate action designed to prevent recurrence of the detected deviations.

Level II - Comprehensive Quality Assurance Review

Includes all activities for Level I QA Review, PLUS:

1. Verify the accuracy and completeness of the Case Report Form (CRF) data entries against source documents and other trial-related records to ensure accuracy and consistency.

2. Inform the investigator of any CRF data entry errors, omissions, or illegibility and ensure that appropriate corrections, additions or deletions are made, explained, initialed, and dated by study authorized staff.

3. Verify resolution of any queries from previous monitoring visits.

iv. Quality Assurance Report and Follow-Up

1. CCRQA team will prepare the QA report and send to PI and Study Coordinator.

   The QA team will compile and submit a written report to the investigator after each QA visit. The report will contain the date of the visit, a summary of what was reviewed, and statements concerning the findings, deviations, deficiencies, conclusions, actions taken (or to be taken) and/or recommendations to secure compliance.

   It will be the obligation of the Investigator to address the issues listed in the report and provide resolution. The CCRQA team may be asked to assist with questions regarding resolution of the issues identified in the report.

   The reports generated by the CCRQA Program are the property of the Principal Investigator.

   The CCRQA team will not be specifically conducting a review for clinical research billing compliance; however, if obvious discrepancies are noted, the HS Compliance Billing Analyst will be notified.

   2. Determine timing of next visit.

   3. Continue with the QA review plan until human subject participation is concluded and PHI documentation is no longer accessed.

v. Study Close-Out Consultation

   The final consultation will be conducted to assure that all study activity has been recorded and finalized, and that all reports have been filed according to study requirements. A final report will be issued to the PI once the QA activities are complete for a study.

   Disclaimer: While this service is intended to augment the maintenance of compliance with regard to conducting the research study according to the protocol, the federal, state, and local regulations, ICH GCP guidelines, and institutional policies, ultimately the Principal
Investigator remains responsible for the conduct of all research project activities. The CTSC and its QA reviewers shall be held harmless in the event that any errors, omissions, or other deficiencies are left unresolved or undetected.