KILIMANJARO CHRISTIAN MEDICAL CENTRE (KCMC) AIDS CLINICAL RESEARCH SITE (CRS), IN COLLABORATION WITH DUKE UNIVERSITY MEDICAL CENTER (DUMC) CLINICAL TRIALS UNIT (CTU)
Clinical Research Site Quality Management Plan
Policies and Procedures

PURPOSE: The KCMC clinical research site (CRS) quality management (QM) plan outlines site specific internal measures to be used by the KCMC CRS, a collaborative partner of the Duke University Medical Center Clinical Trials Unit (CTU). The KCMC site QM plan includes quality control (QC) and quality assurance (QA) measures. QC will be continuous to identify problems and intervene with corrective actions. QA will be comprehensive and conducted on a periodic basis. A strong QM plan based on QC and QA assures that data are complete, accurate, and verifiable, and that clinical research participants' rights and safety are protected. The KCMC CRS QM plan has been developed to meet international, federal, sponsor and institutional regulations and guidelines, including Good Clinical Practice (GCP).

DEFINITIONS:

QM: The sum activities of QC and QA.

QC: Continuous assessment of work product produced to determine whether written standards are being adhered. Helps to immediately identify problems and intervene with corrective actions. An example includes 100% case report form (CRF) review prior to data entry for completion and accuracy.

QA: Periodic, comprehensive assessment of work product, and written standards and policies. Helps to identify problems, trends, additions or amendments to site-specific written standards, and teaching. An example is monthly internal audits of adherence to protocol.

SCOPE:

Applied to all clinical research being conducted at the KCMC CRS as a collaborative partner with the Duke University Medical Center (DUMC) CTU, under NIH funded grants.

RESPONSIBLE PERSONS:

1. Principal Investigators (PI):

John A. Bartlett, MD, DUMC CTU, Principal Investigator - Responsible for the overall conduct of clinical research under NIH funded grants at KCMC CRS. Dr. Bartlett delegates the day-to-day implementation and supervision of QM activities at the KCMC CRS to John Crump, MB, ChB, KCMC CRS Site Leader. Dr. Bartlett delegates the implementation and supervision of QM activities under NIH funded grants to personnel at DUMC CTU and KCMC CRS that are trained and qualified to perform these delegated tasks.

John A. Crump, MB, ChB, Clinical Site Leader, Principal Investigator – Responsible for the total conduct of NIH funded grants at KCMC CRS. Dr. Crump delegates the implementation and supervision of QM activities to KCMC CRS research personnel that are trained and qualified to perform these delegated tasks.

Both Drs. Bartlett and Crump are responsible for the conduct of all NIAIDS supported research studies conducted at the KCMC CRS, as well as the overall management of the research activities.

2. Site Coordinator (SC): The Site Coordinator is delegated the task of overall management of the QM plan.

Julieta Giner, RN, Site Study Coordinator - Responsible for development of the QM plan, including written standards, training, and ongoing assessment of use, need and validity. Ms. Giner, will work together with KCMC CRS study coordinators and other key research personnel to develop QM measures and activities specific to their area and need.

The study-specific coordinators will be responsible for the day-to-day implementation of the overall management of the KCMC QM plan, under the direct supervision of Julieta Giner, RN. This includes: coordination and application of all quality management measures and activities. Ms. Giner will oversee the QM plan for KCMC CRS personnel, including: health care workers (HCW), home based care workers (HBCW), data manager, laboratory data management system (LDMS) coordinator, laboratory staff, pharmacy, and CRS regulatory personnel. Ms. Giner, together with the study-specific coordinator will report QM findings (problems, trends, and corrective actions), as well as protocol implementation and regulatory compliance to Drs. Bartlett and Crump, DUMC CTU PI and KCMC CRS Site Leader.

Monthly and quarterly quality assurance reports will contain protocol-specific information and an overall summary of results. Report results will be disseminated to the CTU and CRS PI, Study PI, Site and Study Coordinator, Data Manager, and Clinical Research Nurses for appropriate review and response.

It is anticipated that due to the relative immaturity of the CRS, potential obstacles in achieving a given component of this QM plan may occur at some time point over the course of this grant. Trends and root/cause analysis will be continuously assessed by the Site Coordinator and under the direction of the PIs, with input from the study staff. The QM plan and CRS research SOPs will continuously be reassessed, teaching reinforced, and when necessary, adapted as problems are identified.

3. KEY QUALITY CONTROL STAFF AND RESPONSIBILITIES

A. Quality Control (QC) Coordinators: The Data Manager is delegated the duty of QC Coordinator by the site PI.

Evaline Ndosi, KCMC CRS, Data Manager, Quality Control Coordinator - Responsible for NIH-funded data entry, data quality control measures, and data management issues at the KCMC CRS.

<u>Day-to-Day Data management activities will include</u>:

● 100% internal audit of all case report forms (CRF's) for accuracy and completeness prior to data entry. This includes proofreading:
- ▪ All case report forms
- ▪ Laboratory test values
- ▪ Numerical site
- ▪ Symptoms and diagnoses codes
- ▪ Mathematical calculations for accuracy.

● Timely entry of data, defined as no greater than 5 business days from a study visit or receipt.
● Follow through to receipt of all anticipated forms for data entry that are delinquent greater than 5 business days.
● Follow through to completion of all requested correction of errors on data to be entered.
● Assessment that all corrections on all data for entry have an audit trial, including dates, actions and person addressing the problem.
● Follow through on all queries to resolution of data to be entered, including queries generated by: internal audits, the sponsor, or supervisory study personnel.

Errors or problems identified by the Data Manager are returned to clinicians for correction. Notifications of errors or queries from the Network are immediately referred to the appropriate clinician for corrective action. Ms. Ndosi will discuss problems, trends, and issues with Dr. Habib Ramadhani, the Study Coordinator at the KCMC site weekly prior to the KCMC CTS research staff meeting. Findings and corrective actions will be discussed during weekly research meetings at KCMC, or more frequently if indicated. Laura Farrow and Evaline Ndosi will discuss problems, trends and issues occurring at the KCMC CRS monthly, at minimum, and report these findings to their site Study Coordinator.

Laura Farrow, DUMC CTU, Data Manager, Quality Control Coordinator – Responsible for providing adequate training and support in troubleshooting specific QC issues at the KCMC CRS.

B. Laboratory Data Management System (LDMS) Coordinator: The LDMS Coordinator is delegated the task of laboratory data entry, follow up and reporting to resolution of laboratory related queries, storage, shipment, and review and filing of all LDMS-related records.

Deborah Murray, DUMC CTU, LDMS Coordinator: Responsible for providing partial training and long-distance trouble-shooting support as possible via internet to the KCMC CTS LDMS Coordinator.

To be determined, KCMC CTS, LDMS Coordinator: - Responsible for ISAAC related laboratory data management system and data entry, data and specimen quality control measures, and data management issues at the KCMC CTS.

<u>Day-to-Day Data management activities will include</u>:

- Timely entry all laboratory data into LDMS, as defined as within 5 business days.

- Lead quarterly, at minimum, laboratory Quality Control assessment to confirm validity of ISAAC samples.
- Verify:
  - correct laboratory specimens obtained as protocol specified
  - patient and study identifiers on specimens collected
  - accuracy of data entered into the LDMS system
- Specimen storage and proper conditions maintained
- Prepare and manage specimen shipping
- Notify receiving laboratories and key supervisory ISAAC personnel of shipment.
- Follow through and respond to all laboratory-related queries within 5 business days
- Maintain valid certification and compliance with Tanzanian and International Air Transportation Association (IATA) Dangerous Goods Regulations
- Confirm validity of import permit for diagnostic/biologic specimens and report to supervisory research staff need for reapplication when necessary.
- Compile and maintain file of shipping reports to coincide with intensity of shipping.
- Maintain ongoing tally of laboratory and LDMS issues to be discussed every two weeks, minimum, during ISAAC staff meeting.
- Generate quarterly report for ISAAC laboratory and LDMS that identifies number and nature of problems, assessing for trends, needs and corrective actions to discuss with CTS SC and both PIs at minimum quarterly.

The KCMC CRS, at this time, is not yet prepared to process PBMCs. The DUMC CTU will provide training to the identified KCMC CTS laboratory staff in order to build this capacity when the time comes. Once the KCMC site is adequately trained and prepared to process PBMCs, the responsible KCMC CTS Laboratory Technologist will participate in a quarterly Cryopreservation QC Program to evaluate the viability of cells from PBMCs processed at all sites.

4. KEY QUALITY ASSURANCE STAFF AND RESPONSIBLITIES

A. Study Coordinators: Responsible for the coordination and management of QA activities.

Julieta Giner, RN, DUMC CTU Study Coordinator: Responsible for the development of SOPs to address quality data and conduct of ISAAC trials. Ms. Giner will work collaboratively with Dr. Ramadhani, KCMC CRS Study Coordinator to develop QA activities, including the development of tools, review of their efficacy, and need for adaptation.

Habib Ramadhani, MD, KCMC CTS Study Coordinator: Responsible for the coordination and management of QA activities, under the ISAAC grant at the KCMC site. Dr. Ramadhani will report the overall QA findings for KCMC CTS to PIs Drs. John A. Bartlett and Prof. John Shao. Dr. Habib Ramadhani. Dr. Ramadhani collaboratively to develop, review, and revise QA activities, including QA measures and tools, together with Ms. Giner. Specific quality assurance activities include:

<u>QA duties will include</u>:

● 100% Informed consent verification and source document verification of entry criteria prior to randomization.
● Maintaining a screening/randomization log for each ISAAC protocol.
● 100% review prior to site action to confirm protocol step changes and endpoints.
● Conduct monthly summations to include: reports of internal audit results, and implementation and documentation of corrective actions, when necessary.
● Provide oversight and confirm receipt of reports of delegated QA activities, including responses/corrections by appropriate site personnel within one week to QA findings.
● Quarterly conduct analyses of QA data by compiling data, assessing for patterns and trends, and leading discussion with site staff, including both PIs, and DUMC CTU SC to identify corrective action.

The KCMC CTS Study Coordinator will delegate the task of monthly rotating source documentation review to the KCMC CTS Clinical Research Nurses.

B. Clinical Research Nurses: KCMC CRN are responsible for the QA activity of chart reviews.

Sister Bona Shirima
Sister Janet Kimaro
Sister Gertrude Kessy

Regular monthly ISAAC studies chart reviews at a rate of 10 patient charts for all active ISAAC protocols. This must be at minimum no less than 30% of all ISAAC study visits per month. Therefore, this rate may be increased depending on accrual rates. Included in this number will be:

- the first two charts of all new protocols
- the first two charts of all new staff to be reviewed

Priority of charts to be reviewed will be as followed:

- new staff: 100% of all visits until competency proven
- new protocols: first 3 participants until protocol compliance established
- high risk or high enrolling protocol (e.g., investigative drug studies, protocols enrolling pregnant women, pediatric subjects or other vulnerable subjects)

Chart audit QA duties include:

● verify source document to research file for:
- All data entered, verifiable and attributable
- Study specific evaluations completed
- Proper procedure used in corrections

The following is a list of specific areas to be included in ISAAC chart audits at KCMC:

- Study visits:
  - proper study subject identification
  - proper identification of visit # and date
  - proper timing (interval between visits) as specified in each specific ISAAC protocol
  - proper evaluations completed:
    - test and procedures
- Study specified evaluations have results present
- Toxicities: reporting, grading, action, including laboratory textiles
- new events or ongoing diagnoses
- Any serious adverse events (SAE) necessitating immediate action, including death, hospitalizations, and documentation reporting and follow through to resolution
- Clinical endpoint(s) reached as described in each ISAAC specific protocol, including actions and reporting
- Adherence to KCMC SOPs and GCO
- Monthly participation in QA Committee
- Participation in QA in-services

In studies were investigational study medication is being used, or when protocol specified, the following additional list should be added:

- Concomitant medications
- Prohibited medications
- Dispensation and return and return record in study note, including:
  - dosing
  - administration
  - indication
  - adherence

Dr. Habib Ramadhani will provide clinical oversight and review all internal audit findings. The CRN will report a compilation of internal findings to the KCMC Site Coordinator, who will then review and present together with the CRN findings and recommendations to KCMC CTS personnel during monthly meetings.

All corrective actions to internal audit findings will be supplied to the responsible study personnel on a form that allows for tracking of problem, person, action taking and time of action. These forms will be resupplied to the CRN within 5 business days with response or resolution. The SC, PIs, IRB/IEC will be notified of significant audit findings such as entry violations or unreported SAE's.

In addition to chart audits, the **CRN will develop study specific flow sheets and eligibility checklist for all ISAAC clinical research studies.** Prior to their usage, Dr. Ramadhani will review the product for accuracy.

C. Clinical Regulatory Coordinator: Responsible for the coordination of regulatory submissions, compliance and management of their QA activities. Each site's Clinical Regulatory Coordinator (CRC) will oversee all aspects of protocol submission and approval for his/her perspective site through the ACTG and through the local Institutional Review Board (IRB). Each site's CRC will manage safety reports, investigator brochures and package inserts, consent forms, annual progress reports, IRB communications, FDA form 1572, and other regulatory information, as well as Network communication.

Janet Mueller, DUMC CTU, Clinical Regulatory Coordinator – Responsibilities as noted above. The following QM activities are to ensure that the regulatory files are complete and up to date:

- monthly audits of the protocol registration checklist to ensure protocol approval accuracy
- monthly audits of safety reports submitted to the local and federal regulatory bodies
- monthly assessment to ensure CVs, licenses and ethic training modules are completed and current
- monthly query audit of protocol renewal to ensure timely submission of continuing reviews
- monthly audit of secured shared virtual space for date, completeness, and accuracy.

Ahaz Kulanga, KCMC CTS, Clinical Regulatory Coordinator - Responsibilities as noted above. The following QM activities are to ensure that the regulatory files are complete and up to date:

- monthly audits of the protocol registration checklist to ensure protocol approval accuracy
- monthly audits of safety reports submitted to the local and federal regulatory bodies
- monthly assessment to ensure CVs, licenses and ethic training modules are completed and current
- monthly query audit of protocol renewal to ensure timely submission of continuing reviews
- monthly audit of secured shared virtual space for date, completeness, and accuracy.

Both Clinical Regulatory Coordinators will present weekly to ISAAC staff a regulatory update to include: submission status, version dates, and any regulatory matters.

5. QUALITY MANAGEMENT TOOLS

Tools to document the KCMC CRS QM review and track corrections will be utilized and maintained for all ISAAC related QM. Tools include:

A. Data Management Tools:

The Data Manager will utilize the following QC tools to assist in Quality Assurance:

- Daily Keying and Transmission Reports
- Update Reports
- Error Identification, Correction and Tracking Reports
- Delinquency Lists
- Queries
- Edit Failure Lists

- Data Retrieval Programs
- Reference guides provided by Sponsor
- Summaries of reports to be used for intervention purposes

B. Laboratory Data Management System (LDMS) Tools:

The LDMS Coordinator: will utilize the following QC tools to assist with Quality Assurance:

- LDMS for data entries
- LDMS for shipping
- Shipping reports
- Quarterly reports
- Redundancy system to check and recheck data before entry, including:
    - Patient Identifiers prior to specimen labeling
- IATA Certification
- Notice of shipment to receiving laboratory

C. Quality Assurance Tools:

- Randomization Logs and Screening Logs
- Eligibility checklist
- Protocol specific schedule of events checklist
- Protocol specific flow sheets, including:
    - Study visits
    - Adverse Events
    - Concomitant Medications, if applicable
    - Pharmacy drug dispensation log

These tools are designed to provide adequate source documentation as well as to reflect eligibility criteria, which include: informed consent, screening, randomization process, medical and medication history, physical examination, signs and symptoms, laboratory tests and values and the dispensing study drug(s) for each protocol. In addition, protocol-specific flow sheets help clinical research nurses with day-to-day quality assurance measures for all clinic visits. Completion of these flow sheets documents laboratory tests and procedures, specimen collection, questionnaire completion, physical examination, signs and symptoms, medication dosing/changes, hospitalizations, adverse events and clinical endpoints. Missed study visits, procedures and/or tests and the reasons for them are documented. Missed visits may be documented as such on the schedule visit number flow sheet.

- **Audit Tools:**

Protocol audit tools are designed to document a formal review of designated records, charts, and source documents. The following items are included on all audit tools/reports: Records,

Time Period, Date of Audit, Name of Reviewer, Problems Identified, Comments, Corrections, and Clinician Signature. Protocol deviations and violations are immediately reported to the Network, IRB/Ethics Committee, CRS and CTU Study Coordinators, and CTU and CRS PI's.

- Generic verification checklist
- Monthly reports
- Quarterly reports

The generic verification checklist is a KCMC site developed step-by-step checklist for reviewing: informed consent process and life throughout study, eligibility criteria, laboratory procedures, other procedures, results of procedures, including toxicities, grading, actions, and and reporting, medical history collection, concomitant medications, including dosing, indication, and duration (if applicable), study visit schedule, including protocol specified windows (if applicable), missed study visits and action, study medications, including dispensation, return, dosing, adherence, and counseling, adverse event/serious adverse event reporting, causality, action, and reporting, and clinical/laboratory endpoints identification and reporting. Additional protocol-specific categories may be added as necessary.

- Sponsor provided handbooks or “virtual” handbooks

- **Reports**

Reports are a useful QA tool for identifying, tracking and improving CRS performance. All CTU/CRS research staff will receive a synopsis QM reports at monthly ISAAC meetings, at minimum. A synopsis of reports categorized will aid in the tracking of patterns and trends in order to initiate corrective action(s).

- **Quality** Assurance References And Resources

Quality management measures are guided by KCMC CRS SOP, Good Clinical Practice (GCP), and NIH Guidelines, including Pharmacy Manual, Site Registration Guidelines, and Forms Manuals.

8. RESULTS

A. Problems And Trends: Problems and trends identified by the implementation of the KCMC QM plan will be promptly addressed in a variety of ways. Constant communication between the Data Manager, Clinical Research Nurses and the CRS Study Coordinator will assist in the early recognition of problems to avoid the development of trends. However, all audit results will be shared, documented and compiled into reportable formats (as specified in earlier sections) to increase awareness of problems and trends and to assist in the development of responsive corrective action.

B. Corrective Actions: Early recognition of problems and all audit results will be proactively addressed through communication, review and analysis. Each ISAAC Study Coordinator will work closely with the appropriate key personnel as well as all members of the ISAAC team to identify and implement appropriate corrective measures.

10. EVALUATION

The KCMC CTS Quality Management Plan will be reviewed annually by all responsible persons. Basic revisions and revisions to reflect changes in staff will be made at that time.

Reviewed by: _____Date: _____
Prof. John Shao, MD, KCMC ISAAC CTS Principal Investigator

Reviewed by: _____Date: _____
John A. Bartlett, MD, DUMC ISAAC CTU Principal Investigator