KCMC Clinical Trials Unit	STANDARD OPERATING PROCEDURE	Effective Date	SOP-Number CTU 05-02
		Page 1 of 17	09 OCT 2006

Title: STUDY VISITS

SOP References: Source Documentation , Office Record, Data Management, Laboratory Tests and Procedures, and Pharmacy **Supersedes:** N/A

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	Review Date	Revision Date	Signature
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N/A	Initial	10 MAY 2005
CTU 00	Standardize format, clarify and add research procedures	09 OCT 2006

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PURPOSE: To establish procedures for performing clinical research evaluations.

POLICY: The Principal Investigator and research staff will coordinate and perform the required evaluations for assigned research protocols in accordance with the protocol, ICH guidelines, regulatory authorities, sponsor, and institutional review/ethics boards guidelines and regulations.

RESPONSIBILITY: Principal Investigator, Clinical Research Coordinator, Research Nurse, Research Pharmacist, Data Manager and designee.

A. DEFINITIONS:

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor or entered into the research database for each clinical trial participant.

Concomitant Medications: Any prescribed or over-the-counter medications, folk and herbal treatments, vitamin supplements, and drugs or agents used on the street to alter body or mind function.

Compliance: Adherence to protocol specifications, good clinical practice (GCP), and regulatory requirements.

Documentation: All records, in any form (including but not limited to written, electronic, magnetic and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a clinical trial, the factors affecting a clinical trial, and the actions taken.

Original Medical Record/Source Documents: Original documents, data, and records, including: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, laboratories, and at medico-technical departments involved in the conducting the clinical trial.

Patient Identification (PID) Code: A unique identifier code that is assigned by the investigator (or designee) to each research subject (participant) participating in a Network (or grouping) of projects by one Sponsor, such as AIDS Clinical Trials Group (ACTG), ISAAC (International Studies of AIDS Associated Co-infections), etc. A PID is used to protect the subject's identity and confidentiality in the research file. PID is used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data, and on all research documents that go to the sponsor, or outside of the Institution where the research is being conducted. A participant will only have one PID within the Network, but may participate in a number of research studies within that Network. SID is a study specific unique identifier, used together with PID to link the participant's status within the network. (See SID below.)

Source Data: All information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), and serve to verify the research record. (See Source Documentation SOP.)

Subject Identification (SID) Code: A unique identifier code that is assigned by the investigator (or designee) to each research subject (participant) to protect the subject's identity and confidentiality in the research file. SID is used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data, and on all research documents that go to the sponsor, or outside of the Institution where the research is being conducted. A SID code is subject specific for a specific study, whereas a patient identification (PID) code is subject and Network specific, but not study specific. (See PID above.)

B. PROCEDURES: Designed to educate, train, and be used as a reference for the clinical research coordinator and research team to perform required visit specific study evaluations for research protocols.

1. Screening and/or Pre-entry visits: The clinical research coordinator (or designee) will implement screening and/or pre-entry visits as directed by the assigned protocol including implementation of the informed consent process. (See Informed Consent Process and Recruitment SOPs.)

a. Informed Consent: The clinical research coordinator (and designee) will verify the completion of the informed consent document including correct date and signatures PRIOR to performing any screening procedures, including holding or stopping therapy ("washout") for anticipated entry. (Refer to Informed Consent Process SOP for details.)

b. Clinical Evaluations: The clinical research coordinator (or designee) will perform the required clinical evaluations for the assigned protocol including, but not limited to physical assessment, medical history, medication history, and laboratory tests and/or procedures.

c. Medications: The clinical research coordinator (or designee) will obtain a medication history as directed by the protocol, and for inclusion/exclusion eligibility for all study candidates. Medications may be documented on the visit specific flow sheet or on a subject specific medication log. If a medication log is used, original entries and changes should be reviewed, signed, and dated by the Principal Investigator. The medication history may include antiretroviral medications, preventative mother-to-child therapy (PMTCT), and/or concomitant medications. If the protocol requires documentation of concomitant medications, the agent (drug), start dates, dosage, route and frequency must be documented. If the date is unknown, all

attempts should be made to identify the year, and estimate start date as 01 JUL YEAR. The Principal Investigator and research team will verify that no study exclusionary medications are being used by the research subject. If the subject is on an exclusionary medication, the research team will query the participant's provider of the medication and research team to inquire whether an allowable non-exclusionary substitution exists.

d. Research Procedures and Laboratory Analysis: The clinical research coordinator (or designee) will assure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol AFTER the subject has provided written informed consent. No research procedures may be obtained prior written consent. The research coordinator (or designee) will coordinator with the receiving laboratories to assure that the correct procedures and specimens are labeled, collected, and that laboratory staff are available to receive and process research specimens. All research test results and procedures will be reviewed, signed and dated by the Principal Investigator. Abnormal results will be graded and if clinically significant must be documented, including action taken. The research team will verify protocol required action, and assure compliance. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

e. Eligibility Checklist: The clinical research coordinator (or designee) will use an eligibility checklist to verify that all inclusion criteria are met and that no exclusion criteria exist. Supportive documentation of all inclusion/exclusion criteria must be contained within the research record. The clinical research coordinator and Principal Investigator will confirm each subject's eligibility prior to the research subject's randomization and study entry.

f. Return Visits: The clinical research coordinator (or designee) will submit an appointment return with the appointment's coordinator for a return study visit as outlined in the protocol. The clinical research coordinator (or designee) will verify that visits occur within the protocol specified time frame (window). The clinical research coordinator (or designee) is responsible for notifying the study subject and research team, including, data management, receiving laboratories, and research pharmacy (if applicable) of the anticipated entry date. The research coordinator (or designee) will keep a schedule of anticipated study visits.

Missed study visits must be followed up and documented. (See Missed Study Visit SOP).

g. Source Documentation: The clinical research coordinator (or designee) will complete a protocol-specific flow sheet or other source documentation for the appropriate study visit and submit it to the Principal Investigator for review and signature. All signed source documentation must be filed in the office or medical records chart for the study patient. (See Office Record/Chart SOP.) Hard copy laboratory or procedure results may be filed in the office chart or subject research binder but should be consistent throughout the study. If filed in the subject research binder, only code identifiers should be used.

h. Case Report Forms (CRF): The clinical research coordinator (or designee) will complete CRFs as required by the assigned protocol and the data management center and submit them to site data management. (Refer to Data Management SOP for required timeline.)

i. Data Management: The clinical research coordinator (or designee) will collaborate with data management to schedule a new randomization/entry visit.

j. Pharmacy: The clinical research coordinator (or designee) will verify communication with the pharmacist when a randomization is scheduled for protocols that include study medications.

2. <u>Entry/Randomization Visit</u>: After eligibility has been confirmed by the PI and research coordinator, the clinical research coordinator (or designee) will schedule and implement the entry visit within the protocol specific timeline and conduct the entry/randomization visit as noted in the protocol.

a. Randomization: The clinical research coordinator (or designee) will collaborate with data management during the patient randomization process as necessary. Per protocol specifications, randomization may occur prior to Day 1/entry. (See protocol for timeline/restriction.)

b. Clinical Evaluation: The clinical research coordinator (or designee) will perform the required entry evaluations for the assigned protocol including, but not limited to physical assessment, review of signs/symptoms, diagnoses, medical and medication history, and

coordinate laboratory tests and/or procedures (see Standard Operating Procedures for Laboratory Tests/Procedures).

c. Medications: The clinical research coordinator (or designee) will record all study and concomitant medications in the flow sheet or medication log as required by the protocol at the entry visit. If the clinical research coordinator or nurse chooses to use a medication log, the visit flow sheet should document that a medication log is being used, and that it was reviewed and updated at this visit. (Example: "Medication log reviewed. No changes noted at today's visit." or, Medication log reviewed. Changes noted and documented on the medication log"). Original entries and changes to the medication log should be reviewed, signed and dated be the Principal Investigator.

d. Research Procedures and Laboratory Analysis: The clinical research coordinator (or designee) will assure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol AFTER the subject has provided written informed consent. No research procedures may be obtained prior written consent. The research coordinator (or designee) will coordinator with the receiving laboratories to assure that the correct procedures and specimens are collected, and that laboratory staff are available to receive and process research specimens. All research test results and procedures will be reviewed, signed and dated by the Principal Investigator. Abnormal results will be graded and if clinically significant must be documented, including action taken. The research team will verify protocol required action, and assure compliance. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

e. Pharmacy: The clinical research coordinator (or designee) will coordinator with the clinical research pharmacy and refer all subjects at study entry to the site research pharmacist for consultation/counseling regarding the initiation of study treatment and possible side effects for protocols that include study medication. The agent, route, dose and frequency of all study medications (or changes) must be recorded in the source documents flow sheet, record, or study medication log.

e. Return Visits: The clinical research coordinator will submit an appointment return with the appointments coordinator for a return study visit as dictated by protocol. The clinical research coordinator is responsible for notifying the study subject of the return date and keeping a

schedule of anticipated study visit returns in order to be aware of anticipated return study visits. Missed visits must be followed up and documented. (Refer to Missed Visit SOP).

f. Source Documentation: The clinical research coordinator (or designee) will complete a protocol-specific flow sheet or other source documentation for the appropriate study visit, containing all protocol specified events occurring at that visit. The research coordinator (or designee) will submit the source document/flow sheet to the Principal Investigator for signature. All signed source documents must be filed in the office record. Protocols including study medications must contain a medication section where adherence, side effects and dosing are reviewed and documented. Hard copy lab or test results may be filed in the office record or subject research binder, file but must be consistent throughout the study. If filed in the subject research binder, code identifiers should be used.

i. Case Report Forms (CRF): The clinical research coordinator (or designee) will complete CRFs as required by the assigned protocol and the data management center and submit them to site data management within 5 business days of the actual study visit.

j. Data Management: The clinical research coordinator (or designee) will collaborate with data management during the randomization process. The clinical research coordinator (or designee) will complete CRFs as required per protocol and the data management center. Completed flow sheets and CRFs will be submitted to data management. (Refer to Data Management SOP for required timeline.)

3. <u>Evaluations During Treatment</u>: The clinical research coordinator (or designee) will implement the evaluations during treatment as directed by the assigned protocol.

a. Clinical Evaluation: The clinical research coordinator (or designee) will perform the required assigned protocol evaluations, which may include: physical assessment, review of signs and symptoms, new diagnoses, hospitalizations, medication changes, adherence to study medications, tolerability, side effects and laboratory tests and/or procedures.

b. Medications: For protocols requiring documentation of concomitant medications or using study medications, the clinical research coordinator (or designee) must record all study and concomitant medications on the flow sheet or appropriate medication logs as required by the protocol for every visit. All source visit flow sheets, notes, or medication logs must be queried and completed at each visit. Medications may be documented on the visit specific flow sheet or on a subject specific medication log. If a medication log is used, the study visit flow sheet should note that the medication log was reviewed and whether any changes were noted. (Example: "Medication log reviewed. No changes noted at today's visit." or, Medication log reviewed. Changes noted and documented on the medication log"). Any new entries or changes to the medication log should be reviewed, signed and dated be the Principal Investigator.

c. Research Procedures and Laboratory Analysis: The clinical research coordinator (or designee) will assure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol AFTER the subject has provided written informed consent. No research procedures may be obtained prior written consent. The research coordinator (or designee) will coordinator with the receiving laboratories to assure that the correct procedures and specimens are collected, and that laboratory staff are available to receive and process research specimens. All research test results and procedures will be reviewed, signed and dated by the Principal Investigator. Abnormal results will be graded and if clinically significant must be documented, including action taken. The research team will verify protocol required action, and assure compliance. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

d. Pharmacy: For protocols using study medications, the clinical research coordinator (or designee) will coordinate with the pharmacist regarding the dispensing of study medications, and refer patients as necessary for additional counseling/education. The clinical research coordinator (or designee) must document study drug adherence as well as the agent, route, dose and frequency. Current study medications, changes or discontinuations must also be documented in the source document or study medication log at every study visit for protocols including study medication(s).

e. Return Visits: The clinical research coordinator (or designee) will submit an appointment return with the appointments coordinator for a

return study visit as specified by the protocol. The clinical research coordinator (or designee) is responsible for notifying the study subject and research team of anticipated study return date and keeping a schedule of anticipated study visits. Missed visits must be followed up and documented. (Refer to Missed Visit SOP)

f. Source Documentation: The clinical research coordinator (or designee) will complete a protocol-specific flow sheet or source document for the appropriate study visit and submit it to the Principal Investigator for sign off. All signed source document notes must be filed in the office record for the study patient. For protocols using study medications, all source visit flow sheets will contain a Medication section which must be verified and updated at each study visit. Hard copy lab or test results may be filed in the office file or subject research binder, but must be consistent throughout the study. If filed in the subject research binder, code identifiers should be used.

g. Cases Report Forms (CRF): The clinical research coordinator (or designee) will complete CRFs as required by the assigned protocol and the data management center and submit them to site data management. (Refer to Data Management SOP for required timeline.)

h. Data Management: The clinical research coordinator (or designee) will collaborate with data management during the randomization process. The clinical research coordinator (or designee) will complete CRFs as required per protocol and the data management center. Completed flow sheets and CRFs will be submitted to data management. (Refer to Data Management SOP for required timeline.)

4. <u>On-Study/Off-Treatment Evaluations</u>: For protocols using study medications, the protocol may require subjects who have stopped study medication to be followed as, "On-Study/Off-Treatment." On-Study/Off Treatment evaluation must be followed as directed by the assigned protocol.

a. Clinical Evaluation: The clinical research coordinator (or designee) will perform the required evaluations for the assigned protocol, which may include: physical assessment, review of signs and symptoms, new diagnoses, hospitalizations, medication changes, adherence to study medications and laboratory tests and/or procedures.

b. Medications: For protocols requiring follow up on concomitant medications or using study medications, the clinical research coordinator (or designee) must record all study and concomitant medications in the source document flow sheet, study/clinic note, or appropriate medication logs for every on-study/off-treatment visit, including date subject stopped study medication, reason, and if another medication has been substituted. If the clinical research coordinator (or designee) chooses to use the medication log, documentation must confirm that the medication log was reviewed and updated if any changes occurred. The Principal Investigator will review, sign and date any new entries or changes. The study agent, route, dose and frequency, start & stop dates, return of the discontinued study medications, and reason for stop will be documented on the source document flow sheet, clinic/study note, or study medication log for every on-study/off-treatment visit

c. Research Procedures and Laboratory Analysis: The clinical research coordinator (or designee) will assure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol AFTER the subject has provided written informed consent. No research procedures may be obtained prior written consent. The research coordinator (or designee) will coordinator with the receiving laboratories to assure that the correct procedures and specimens are collected, and that laboratory staff are available to receive and process research specimens. All research test results and procedures will be reviewed, signed and dated by the Principal Investigator. Abnormal results will be graded and if clinically significant must be documented, including action taken. The research team will verify protocol required action, and assure compliance. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

d. Pharmacy: The clinical research coordinator (or designee) will notify and regularly update the research pharmacist of the study subjects' On-Study/Off-Treatment status.

e. Return Visit: The clinical research coordinator (of designee) will submit an appointment return with the appointments coordinator for a return study visit as dictated by protocol. The clinical research coordinator (or designee) is responsible for notifying the study subject and research team of the return date and keeping a schedule of anticipated

study visits. Missed study visits must be followed up and documented even for study subjects who are On study/Off Treatment.

f. Source Documentation: The clinical research coordinator will complete a protocol-specific flow sheet or other source documentation note for the appropriate study visit and submit it to the principal investigator for signature. All signed source document notes must be filed in the office or medical records chart for the study patient. Hard copy lab or test results may be filed in the office file or research file but must be consistent throughout the study. If filed in the research file, code identifiers should be used.

g. Case Report Forms (CRF): The clinical research coordinator will complete CRFs as required by the assigned protocol and the data management center and submit them to site data management. (Refer to Data Management SOP for required timeline.)

h. Data Management: The clinical research coordinator will collaborate with data management during the randomization process. The clinical research coordinator will complete CRFs as required per protocol and the data management center. Completed flow sheets and CRFs will be submitted to data management. (Refer to Data Management SOP for required timeline.)

5. <u>Study Discontinuation</u>: In anticipation of study discontinuation, the clinical research coordinator (or designee) will notify the team of upcoming study discontinuation to aid in transition to health management follow up and commercial medication (if applicable). The clinical research (or designee) will implement the study discontinuation evaluation as directed by the assigned protocol.

a. Clinical Evaluation: The clinical research coordinator (or designee) will perform the required evaluations for the assigned protocol including but not limited to physical assessments, review of signs and symptoms, new diagnoses, hospitalizations, medication changes, adherence to study medications and laboratory tests and/or procedures.

b. Medications: For protocols requiring follow up on concomitant medications or using study medications, the clinical research coordinator (or designee) must record all study and concomitant medications in the

source document flow sheet, study/clinic note, or appropriate medication log.

c. Research Procedures and Laboratory Analysis: The clinical research coordinator (or designee) will assure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol. The research coordinator (or designee) will coordinator with the receiving laboratories to assure that the correct procedures and specimens are collected, and that laboratory staff are available to receive and process research specimens.

All research test results and procedures will be reviewed, signed and dated by the Principal Investigator. Abnormal results will be graded and if clinically significant must be documented, including action taken. The research team will verify protocol required action, and assure compliance. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

d. Discontinuation: The clinical research coordinator will verify communication with research pharmacist regarding the discontinuation of study treatment and collaborate with primary care providers for continued health care management.

e. Study Medications: For protocols that are using investigational agents or dispensing study product, the clinical research coordinator must record the return of all study medications in the source document flow sheet, clinic/study visit note, or appropriate medication log at the discontinuation visit. Documentation must include: agent, route, dose and frequency, stop date, return of all study medication/product, and if the research subject is transitioned to commercial drug supply. The Principal Investigator will review, sign and date any new entries or changes.

If the study participant does not return all previously dispensed study product, the clinical research coordinator (or designee) must attempt to determine if the participant has any study product in his/her possession or if this was discarded, and document these findings. For research subjects who admit to having additional study product(s), the clinical research coordinator (or designee) must counsel and document attempts to have that remaining study product returned. The research coordinator (or designee) will notify the research pharmacy of study product disposition.

Per protocol specifications, protocols using investigational agents or study product may require follow up 4 weeks after end of study product, regardless if the study participant has transitioned to commercial supply of medication or not.

f. Concomitant Medications: The clinical research coordinator must document the agent, dose, route and frequency for current concomitant medications, changes or discontinuations (including antiretroviral medications) in the source document flow sheet, clinic/study note, or concomitant medication log at the discontinuation visit. At the end of study visit, concomitant medications that continue will be noted as continuing on the date of end of study visit. The Principal Investigator will review, sign and date the final entries.

g. Source Documentation: The clinical research coordinator will complete a protocol-specific flow sheet for the appropriate patient visit and submit it to the Principal Investigator for signature. All signed source document notes must be filed in the office or medical records chart for the study patient. Hard copy lab or test results may be filed in the office file or research file but must be consistent throughout the study. If filed in the research file, code identifiers should be used.

h. Case Report Forms (CRF): The clinical research coordinator will complete CRFs as required by the assigned protocol and the data management center and submit them to site data management. (Refer to Data Management SOP for required timeline.)

i. Data Management: The clinical research coordinator will collaborate with data management during the randomization process. The clinical research coordinator will complete CRFs as required per protocol and the data management center. Completed flow sheets and CRFs will be submitted to data management. (Refer to Data Management SOP for required timeline.)

6. Follow-Up Visit(s): Protocols using investigational agents or dispensing study product, may require a follow-up visit 4 weeks after study product is discontinued. Additionally, subjects with ongoing adverse events (AE) at study discontinuation may need to be followed under study until the event has resolved, if causality of the AE to study participation is suspected. Protocol may allow for some of these follow up visits to occur through telephone contact as long as no additional study or laboratory evaluations are required.

a. Clinical Evaluation: The clinical research coordinator (or designee) will perform and document the required follow up evaluations for the assigned protocol, including, but not limited to physical assessments, review of signs and symptoms, new diagnoses, hospitalizations, SAE, medication changes, status of ongoing AE, and laboratory tests and/or procedures. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

b. Research Procedures and Laboratory Analysis: The clinical research coordinator (or designee) will assure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol. The research coordinator (or designee) will coordinator with the receiving laboratories to assure that the correct procedures and specimens are collected, and that laboratory staff are available to receive and process research specimens.

All research test results and procedures will be reviewed, signed and dated by the Principal Investigator. Abnormal results will be graded and if clinically significant must be documented, including action taken. The research team will verify protocol required action, and assure compliance. (Refer to Toxicity Management, AE/SAE Reporting, and Healthcare Management SOPs.)

c. Medications: The clinical research coordinator (or designee) will query and document any changes in end of study medications. The Principal Investigator will review, sign and date the entries.

d. Source Documentation: The clinical research coordinator will complete a source clinic note or protocol-specific flow sheet for the follow up visit or telephone call and submit it to the Principal Investigator for review and signature. The signed source document will be filed in the office or medical records chart for the study patient.

e. Case Report Forms (CRF): If a study follow up CRF exists, the clinical research coordinator (or designee) will complete the CRF as required by the assigned protocol and the data management center and submit them to site data management. (Refer to Data Management SOP for required timeline.)

f. Data Management: The clinical research coordinator (or designee) will complete the CRF as required per protocol and submit to the data

management center. (Refer to Data Management SOP for required timeline.)

7. <u>Missed Study Visits</u>: Anticipated study visits that are missed or out of the protocol specified time-frame (window) must be documented as missed study visits. The clinical research coordinator (or designee), together with research team will attempt to contact/locate the study participant and bring the study subject back into care. If the study participant wishes to discontinue study prematurely, then a discontinuation visit will be scheduled. (See Study Discontinuation Visit for details.) Subjects that choose to discontinue should be referred for primary health care management. All attempts and action to locate and bring the study participant back into care or for study discontinuation must be documented and filed as source documentation. If the study subject chooses to discontinue prematurely, the study team, including data management and pharmacy, and the sponsor must be notified of the premature discontinuation visit. If the study participant has missed two consecutive study visits and all attempts to locate the study subject are unsuccessful, the study participant may be prematurely discontinued as lost to follow-up. (Refer to protocol for specifics on premature discontinuation.) Subjects should not be discontinued as lost to follow-up until all efforts to locate and bring the subject back into care have been exhausted.

This SOP has been read and understood by:

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