

PRE-INITIATION REVIEW

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Address: University of Natal
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Grant Number: U19-AI517194

Protocol Title: 1. Implementing Antiretroviral Therapy in Resource Constrained Settings: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions and Survival in Participants Co-Infected with Tuberculosis and HIV (START)

2. The Viral Set Point In HIV-1 Subtype C Infection: Role Of Host And Viral Factors (Acute Infection) (AI)

Investigative site(s): CAPRISA START
Protocol: Prince Cyril
Zulu Communicable
Disease Centre and King
Edward VIII Hospital

CAPRISA AI Protocol:
CAPRISA Clinical
Research Unit/University
of Natal Medical School

Program Officer: START: Richard Hafner Location of Visit: Durban, South Africa
AI: Rod Hoff

Study sites See Appendix 1
visited:

Date(s) of Visit: 10-15 April 2003 Conducted by: Diane Pizzano, RN, CCRA
Robert Gramzinski, PhD

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SUMMARY OF SIGNIFICANT FINDINGS

This report of the Pre-Initiation Assessment Visit represents Westat's initial assessment of the CAPRISA site. The primary visit objectives included initial assessment of:

- The clinical research site's operations, regulatory and management practices;
- The study pharmacy's facilities and procedures;
- The clinical laboratory facilities and procedures; and
- The data management capabilities.

Specific visit findings are detailed in the attached "Pre-Initiation Review." The specific aim of this visit was to develop a site-specific site development plan in order to initiate the site establishment process and avoid potential barriers to study initiation.

I. OPERATIONS MANAGEMENT AND REGULATORY ASSESSMENT

The first component of the site-specific development plan is site management and operations. Assessments of clinical, administrative, and regulatory practices are described in this section. Specific comments are located in Sections II-IV of the attached "Pre-Initiation Review." CAPRISA personnel have had involvement in DAIDS-supported networks, including HPTN, ACTG, and HVTN. However, the non-network-supported CIPRA program will likely present challenges in areas that the networks did support, such as data management and analysis, regulatory support, and safety monitoring. Experience of existing study staff appears to meet the needs of the CIPRA program. Recruitment efforts are underway for a number of key positions, including the START Deputy Project Director. Filling this key position should be a priority, as this investigator will be responsible for day-to-day management of the START protocol and represent the Principal Investigator in his absence. Staffing within the Data Management Department is a concern which is addressed below. Site clinical and administrative facilities appear to meet the requirements of the CAPRISA studies. However, renovation of the clinical research facility at Prince Cyril Zulu Communicable Disease Centre (CDC) was not yet complete at the time of the visit and therefore could not be assessed. The Quality Management Plan will be developed as additional staff are appointed and protocol development proceeds.

Regulatory practices were reviewed during the visit. The CAPRISA Study Teams describe the planned informed consent process in accordance with U.S. and South African regulations (Title 21 US CFR Part 50, Title 45 US CFR Part 45, ICH E6 Guidelines, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa). Compliance with the requirements of Essential Regulatory Documents for the Conduct of a Clinical Trial (ICH E6) was observed during the visit, to the extent possible at this stage of protocol development.

Protocol development is the primary area of focus for CAPRISA at this time. It is anticipated that as the protocols are developed, many decisions that impact implementation will be required. Support should be provided to CAPRISA both in the areas of protocol development and identification of implementation issues, as needed. Basic preliminary Standard Operating Procedures (SOPs) are available at the various CAPRISA sites. Support should be provided in elaborating and finalizing SOPs and the study-specific Manual of Procedures (MOP), as requested by the site and noted in the Pre-Initiation Review.

Recommendations:

- **Complete recruitment and appointment of key study staff, specifically the Deputy Project Director for START and other key personnel;**
- **Provide a progress report regarding staffing and facilities, as directed by DAIDS;**
- **With the support of Westat, develop START Manual of Procedures (MOPs);**
- **With the support of Westat and DAIDS, develop a Safety Monitoring Plan;**
- **With support of Westat and DAIDS, develop CIPRA-specific regulatory procedures; and**
- **With Westat support, develop Quality Management Plan.**

II. DATA MANAGEMENT ASSESSMENT

Data management capacity is presently a concern for CAPRISA. The proposed structure of the Data Management Department includes a data manager, responsible for data management (including database design), quality control (QC), and quality assurance (QA); two data "capturers," responsible for data entry; and two QA clerks, responsible for prospective CRF review. Recruitment efforts are underway for two statisticians. Currently, the data manager is the only member of the data management department available to perform data management tasks. Data analysis plans were not addressed during this initial assessment. CAPRISA specifically requested assistance from Westat with CRF design. Support in developing a quality management plan and data quality management plan may also be necessary. Refinement of QA and data management procedures, such as transfer of data and prospective CRF review, may need to be considered prior to study start, depending on staffing needs and expected enrollment pattern. We anticipate significant data management support requests as CRF design and database design begin.

Recommendations:

- **Submit Data Management: "Preliminary Questionnaire" to Westat to initiate the CRF development process;**
- **With the support of Westat, initiate CRF design for START and Acute Infection protocols;**
- **In conjunction with the CRF design process, initiate database design for START and Acute Infection protocols;**
- **Examine Data Management staffing structure by reviewing job descriptions and evaluating feasibility. Provide results of internal evaluation to DAIDS, as directed by Program Officer;**
- **Complete recruitment and appointment of key data management staff; and**
- **With the support of Westat, develop Data Management and Analysis Plan.**

III. PHARMACY ASSESSMENT

The pharmacy at King Edward Hospital was assessed during the visit. Andy Gray, the Study Pharmacist is coordinating the procurement of investigational agents. Currently, procurement of generic drugs is being pursued. The site is awaiting bioavailability and bioequivalence data in order to pursue the Medicines Control Council (MCC)-required s21 license. These data are expected within three to six months. Pharmacy facilities appear to meet the needs of the START protocol. Recruitment efforts are underway for an associate study pharmacist to manage the day-to-day study pharmacy operations. Study SOPs and study-specific pharmacy procedures require development and finalization prior to study initiation.

Recommendations:

- **Provide drug procurement progress reports to DAIDS and START protocol team, as indicated;**
- **Complete recruitment and appointment of the Deputy Study Pharmacist position;**
- **Finalize study-specific SOPs; and**
- **Develop the Pharmacy Establishment Plan for START.**

IV. LABORATORY ASSESSMENT

The laboratories of CAPRISA consist of eight different labs, each performing a set of lab-based assays supporting the objectives of either the START or Acute Infection (AI) protocol. The CAPRISA labs are:

1. CAPRISA Lab, Durban[^];
2. Lancet Labs (BARC), Durban;
3. King Edward Hospital Microbiology Lab, Durban;
4. Africa Centre Lab, Durban[^];
5. Univ. Cape Town, Cape Town (UCT)*;
6. Cyril Zulu CDC, Durban;
7. Luthuli Hospital, Durban; and
8. National Institute for Communicable Diseases (NICD), Johannesburg.*

* Lab not visited.

[^] Lab under construction.

Appendix 2 details the set of assays that each lab will perform in the context of these clinical trials. The site-scheduled arrangement of our itinerary only allowed for a brief visit to only 6 of the 8 labs (UCT and NICD were not visited). Therefore, this report is primarily the result of verbal discussions of the current capabilities and GLP status of each lab, rather than a physical investigation of each lab. Based on these discussions, the following observations/recommendations are made.

Observations/Recommendations

- Individually, each visited lab appeared adequately staffed and personnel trained. Lab equipment appeared well maintained. In the two labs under construction (see notation above) this could not be, or was difficult to, assess.
- A challenge for the CAPRISA lab network may be in coordinating the work of all these laboratories with respect to the distribution of specimens, assay execution, data acquisition, and data analysis for each lab. **It is recommended that SOPs be developed that will facilitate and ensure good inter-lab communication. Additionally, incorporating into this SOP a written strategy that accommodates interim analysis of lab generated data will facilitate early observation of study objectives.**
- An experimental laboratory database is under development that will capture data generated from each laboratory and allow centralized archiving of lab data and comprehensive data analysis. This database, if developed, will greatly facilitate the timely analysis and reporting of study data.
- The CAPRISA lab (currently under construction) will perform specimen processing, tracking, and archiving. **It is recommended that this lab be fully functional prior to site initiation.**
- SOPs for the START protocol are written; however it appeared that common SOPs varied between labs in format and procedure and it is **recommended that all SOPs be standardized and harmonized between the labs.**

- Lab SOPs for the Acute Infection protocol have not been written and it is ***strongly recommended that a directed effort be made to complete these SOPs.***
- SOPs for specimen labeling and tracking would benefit from refinement of how, when, and where each specimen will be labeled and tracked. (for example, it is not clear whether specimens sent to Lancet labs will receive a second label from Lancet). ***It is recommended that specimen labeling and tracking details be discerned and incorporated into the appropriate SOP(s).***
- Lancet Labs use general lab SOPs for specimen processing and do not use protocol specific SOPs. ***It is recommended that either the Lancet Lab SOPs be reviewed by CAPRISA staff and incorporated into the CAPRISA site SOPs, or protocol specific SOPs be instituted by Lancet Labs.***
- From discussions it appears that adequate QA is followed in each lab, but due to time constraints, this could not be physically evaluated in each lab. ***It is requested that each lab manager fill out the Checklist left with them and return it to Westat for inclusion in the site visit records.***
- Staff are not formally trained in GLPs. ***It is recommend lab staff and lab-related staff attend a formal training course in GLPs prior to site initiation.***

LIST OF ATTENDEES

Study Personnel who met with the Westat Pre-Initiation Team during the Pre-Initiation Assessment

<i>NAME</i>	<i>TITLE/ROLE</i>
Salim S. Abdool Karim	Director/ Principal Investigator
Quarraisha Abdool Karim	START Project Director
Carolyn Williamson	Protocol Chair, AI
Joanne van Harmelen	Project Manager AI
Hirut Gebrekristos	Research Fellow
Nesri Padayatchi	CDC Site Manager
Koleka Mlisana	Acute Infection Study Manager
Marian Swart	Administrative Manager
Helen Kisbey-Green	Sr. Administrator
Des Sykes	Financial Manager
Kogie Naidoo	Clinical Manager-King Edward Hospital (KEH)
Irene von Middlekoop	Data Manager
Ayesha Kharsany	Lab Manager
Andy Gray	Study Pharmacist
Pearl Pillay	Clinical Regulatory Coordinator
Janet Frohlich	Vulindlela Site Manager Community Programme Manager
Rosalyn Hakin	University of Natal Accountant
Lee Sewnarain	Fogarty Training Administrator
Francois von Loggrenberg	Study Coordinator
Annette Badenhorst	Data Manager
Winston Hide	Director (?)
Greg Khoury	Manager, NICD
Sarah Cohen	Lab Manager, NICD
Lynn Morris	Lab Core C, NICD

PRE-INITIATION REVIEW

Reporting Instructions:

Indicate if the following topics were reviewed or addressed by checking "Y" if reviewed and the response was found to be adequate, or checking "N" if reviewed and the response was found to be inadequate. Check NA, if not applicable or not assessed. Provide comments as applicable.

INTRODUCTIONS

I. GENERAL OVERVIEW	Y	N	NA	COMMENTS
1. Introductions	X			
2. Overview of Agenda	X			

I. PROTOCOL REVIEW

The status of protocol development was reviewed for both START and Acute Infection (AI) protocols.

II. CLINICAL SITE ADMINISTRATION

ITEMS REVIEWED	Y	N	NA	COMMENTS
Management of the clinical research site	X			
1. Do study-specific SOPs or Policy Manual(s) exist?	X			<p>Appendices 3-4 list SOPs developed for START and AI. For START, basic draft SOPs have been developed for the CDC and KEH clinical facilities, regulatory, pharmacy, community, data management, and administrative functions. Many of the SOPs for AI do require additional development. Most existing SOPs for both protocols require some refinement to ensure that scope, responsibility, and purpose of the procedures are defined. In some cases, the "Procedure" portion of the SOP needs to be revised to clearly provide a description of <i>how</i> the procedure will be completed.</p> <p>A START Manual of Procedures (MOP) has been drafted. This document will undergo revision upon further protocol development and definition of scope. This document may be combined with the study-specific SOPs.</p> <p>An AI MOP will be drafted upon further development of the protocol.</p>
2. Is the organizational structure of the clinical research site and affiliated sites, including job titles, clearly defined?	X			See Appendix 2
3. Do written job descriptions exist for all staff?	X			
4. Will subject screening logs, subject identification logbooks and subject enrollment logs be used in the trial?	X			

5. Are written procedures on file for internal staff communication as outlined below:	X			
- Conducting staff meetings on a regular basis?	X			CAPRISA-START conducts protocol teleconferences, ad hoc team meetings, and onsite study staff meetings. Written procedures are available for internal and external communication.
- Distributing QA/QC findings to staff members?	X			Procedure is available.
- Distributing monitoring site visit reports to staff members?			X	Not addressed
6. Are written procedures on file for external communication with:	X			An SOP for external communication is available, but was not reviewed during the visit.
- FDA?				
- DAIDS?				
- IRB/IEC?	X			
- Data management center?				
- Independent safety monitor, Independent Monitoring Committee, or DSMB?	X			
7. Describe the administrative facilities and services:				
- Proximity of offices to clinic, lab, pharmacy and data management center.	X			START: The CDC clinical study site is approximately 3 km (10 minutes) from the KEH clinical study site and pharmacy. The data management center at CAPRISA is approximately 8 km (20 minutes) from the clinical sites. AI: The AI clinical facility will be located at the Nelson Mandela School of Medicine. Laboratory sites include the on-site labs (HIV and HCG), KEH (STI), Lancet, Africa Centre, NICD, CAPRISA Laboratories, and Cape Town.
- Equipment (computer, internet access, copy machines) available to support trial procedures/needs	X			
- Presence of locked files for study records, regulatory documents and CRFs				KEH-Locked files are present. CDC-Locked files will be available for study records upon the completion of construction. CAPRISA Offices-Regulatory documents will be maintained at the CAPRISA offices, where sufficient secure space is available.
- Availability of mail or courier services and shipping services	X			
8. Preparedness and Adequacy of Staffing				

- Have key personnel been identified (study coordinator, pharmacist of record)?				The following positions are being recruited: –Deputy Director –Deputy Study Pharmacist –Nurse Counselors –Data Management/Quality Assurance manager –Statisticians (2) –Clinicians –Laboratory manger –Clinical trials coordinator –Training manager –Lab technician (AI)
- Are licenses and up-to-date CVs of professional staff on file?	X			
- What amount of time are key staff allocated to the study?	X			See Appendix 9
- Availability of PI				Professor Abdool-Karim is exceptionally committed and involved in many projects and research initiatives. Currently, the Project Director, Quarraisha Abdool Karim, is responsible for decision making in the absence of the PI. However, many decisions at this juncture in protocol development and site establishment do require Professor Abdool Karim's input. Recruitment efforts are underway for a Deputy Director responsible for making delegated study decisions. This position is critically needed.
- Is a Master Signature Log on file?	X			The Master Signature Log will need to be updated with each new staff appointment.
- Are other studies underway at the site?	X			Other studies underway at the site include: Acute Infection Pilot, ACTG 5175 (study start pending), and other HAART protocols. The PI also functions as a chair on HPTN and HVTN protocols. (note: An inclusive list of study involvement was not obtained during the visit).
9. Have staff received training in:				
- Protocol-Specific Procedures			X	Not applicable. Protocol Training will be scheduled upon finalization of the protocol.
- Required Education in the Protection of Human Research Participants	X			
- ICH/GCP	X			
- Certification to Ship Dangerous Goods	X			Adrian Asiria Lazarus received IATA certification for Shipping Dangerous Goods on 21 February 2003. See Appendix 5.
- Other training?				Not addressed
- How will training be documented?	X			Completion certificates are maintained for all study team members. A training tracking system was recommended to prevent expiration of certifications.
10. Quality Assurance/Quality Control				
- Have the person(s) responsible for QA and for QC been identified?	X			Irene von Middelkoop

<p>- Describe of the process for conducting QC. (The process may include the use of QC reports, visit reminders, data entry and transmission reports, data queries, and delinquency lists)</p>	X			<p>The Quality Management Plan will be developed after the data management plan is finalized and roles and responsibilities of additional QA staff are defined.</p> <ul style="list-style-type: none"> • The data manager will use EpiData, the data management system, to generate QC reports, visit reminders, queries, and delinquency lists. • QA/QC findings will be distributed to study team via monthly meetings and electronic reports.
<p>- Describe the process for conducting QA audits. (The process may include audits of informed consent and subject education, eligibility criteria, scheduled laboratory tests and procedures, concomitant medications, drug dosing, AE identification and reporting, clinical endpoint identification, identifying trends in missed visits and follow-up visits.)</p>				<p>The preliminary plan is as follows:</p> <ul style="list-style-type: none"> • The on-site QA clerk will review CRFs against source documents at the clinical sites prior to data entry. • The study coordinator will verify the CRF on-site prior to data entry. • The QA/Data Manager will initiate any required data queries at the data management center. <p>Preliminary QA plans include monthly or quarterly review of 5% of CRFs on a set of pre-determined criteria (e.g. informed consent, adverse events, laboratory results). Results of the QA audits will be shared with the study team via monthly meetings and electronic reports. If necessary, corrective action will be initiated via training as needed.</p>

III. INFORMED CONSENT PROCEDURES

TOPIC REVIEWED	Y	N	NA	COMMENTS
11. Who is responsible for providing Informed Consent (IC) counseling?	X			Nurse counselors/Study Nurses at the CDC will be responsible for providing the initial Informed Consent (IC) counseling.
12. Will the subject be provided ample time and opportunity to ask questions and to decide whether or not to participate?	X			The informed consent process will occur over the course of 1-3 weeks, during which time the prospective participant is receiving daily Directly Observed Therapy (DOT). The potential participant has the opportunity to discuss participation with the study team during this time.
13. Who is responsible for providing a copy of the IC form to the subject?	X			Nurse Counselor
14. Are facilities adequate to assure subject privacy during counseling sessions?	X			<p>START-Upon the completion of construction, multiple private consultation rooms will be available at CDC.</p> <p>AI-Privacy is available within the clinical facilities that will be used for the AI protocol.</p>

15. How will subject confidentiality be maintained?	X			Separation of source documents and CRFs will be utilized. Participants will be identified by unique identifiers on all CRFs. All study-related information will be stored securely at the study site.
16. Who will document the IC process in the subject's medical record? (As required by 21 CFR 312.62b.)	X			The study team member who obtains informed consent will be responsible for documenting informed consent.

IV. REGULATORY COMPLIANCE

TOPIC REVIEWED	Y	N	NA	COMMENTS
17. Investigative Site				
- Have copies of documents outlining in-country, state and/or local regulations been obtained?	X			Medicines Control Council (MCC) regulations are on file at the site.
- Describe the levels of approval required for this study, including any collaborating U.S. institutions.	X			<u>START:</u> 1. IEC/IRB-Nelson R. Mandela School of Medicine, University of Natal, IRB #1 2. Medicines Control Council (MCC) 3. Ethekwini Health Department (for CDC) 4. KwaZulu Natal Department of Health (for KEH) <u>AI</u> 1. IEC/IRB- IEC/IRB-Nelson R. Mandela School of Medicine, University of Natal, IRB #1
- Have all approvals been obtained?			X	Not applicable-protocols are in development.
- Describe the regulatory files to be maintained at the investigative site.	X			The regulatory files maintained at the investigative site are presented in Appendix 6 and include the documents listed in the DAIDS SOP: Essential Documents (Version 2.0 8/1/02).
- Are files stored securely in an area with limited access?	X			Files are stored securely in a well-organized filing system that includes tabs for all DAIDS-required essential regulatory documents.
- Who is responsible for maintaining the files and ensuring the files are up-to-date?	X			Pearl Pillay, Regulatory Officer
- Has an in-country IRB/IEC reviewed and approved the protocol?			X	Not applicable-protocols are in development.
- Has an in-country IRB/IEC reviewed and approved the informed consent form(s)?			X	Not applicable-protocols are in development.
- What are the procedures for tracking and maintaining records of in-country IRB/IEC submissions and approvals?	X			The Regulatory Officer is responsible for tracking and maintaining records for IRB/IEC submissions and approvals. There is a SOP available describing this process.
18. Are the following Essential Documents available for review at the Investigator's site:				

- The current Investigator's Brochure (IB), or other information describing clinical and non-clinical data regarding the investigational agent (e.g. package insert)		X		START-The need for an IB was raised during the visit, since the investigational agents are all licensed drugs in the U.S. However, the investigational regimen is not licensed in South Africa. This question will be referred to A. Martinez, Chief, DAIDS Pharmacy Affairs Branch. AI-Not applicable, no investigational agents will be used in the study.
- Provided to IRB/IEC (where required)?			X	Not applicable
- Form FDA 1572 (where required)			X	START-This protocol will not be conducted under an IND since it involves licensed agents. However, it is possible that this status could change. AI-Not applicable, no investigational agents will be used with the study.
- Investigator's Curriculum Vitae	X			
- Copy of signed protocol and any amendments			X	Not applicable-Protocols are in development.
- Sample case report forms (CRFs)			X	Not applicable-CRFs have not been developed yet.
- Human Subjects Protection Capabilities	X			
- FWA or other assurance numbers	X			FWA00000678 (exp. 7 May 04)
- IRB/IEC Membership Roster	X			
- Documentation of IRB/IEC approval of protocol and all amendments			X	Not applicable-protocols in development.
- Documented IRB/IEC approved consent forms and all revisions			X	Not applicable-protocols in development.
- Documented IRB/IEC-approved assent form and all revisions			X	Not applicable-protocols in development.
- Documented IRB/IEC approval of any other materials given to subjects. Specify (e.g., written information, advertisements, compensation, other).			X	Not applicable
- Regulatory authority (ies) authorization/approval/notification of protocol (where required)			X	Not applicable-MCC submission pending; protocols in development.
- Master Signature Log	X			
- Documentation of Laboratory Certification				Lancet Labs certified through SANAS, copies of accreditation for Lancet labs in Appendix 7. Cyril Zulu CDC and UCT labs not accredited. Other labs verbally confirmed they were accredited during discussions but copies of certification not provided.
- If lab is not certified, review QC/QA procedures, inquire about validation methods used and obtain copy of lab director's CV.				Cyril Zulu CDC: QA procedures are in place for sputum smears for acid fast bacilli. QA procedures not yet in place for on-site HIV rapid tests or urine-based pregnancy tests.

- Copy of normal range values for each laboratory used				Acute Infection: See Appendix 8 Lancet Labs: Present on-site, but copy not provided. Other Labs: Not provided.
- IATA Certification for Shipping Dangerous Goods (as required)	X			Adrian Asiria Lazarus received IATA certification for Shipping Dangerous Goods on 21 February 2003. See Appendix 5.
- Additional comments:	X			Please see Summary of Findings

V. PHARMACY PLAN

TOPIC REVIEWED	Y	N	NA	COMMENTS
19. Is a written Pharmacy Establishment Plan available for review? Review &/or discuss the following:		X		The Pharmacy Establishment Plan is in development pending finalization of drug procurement.
- If a <u>central</u> drug repository is to be used, are there documented instructions to ensure proper shipment, handling, storage, dispensing, and disposition of investigational product?		X		Antiretroviral investigational agents will be stored at KEH and dispensed to CDC for distribution to participants on the integrated arm. Shipping, handling, storage, dispensing, and disposition instructions have not yet been finalized.
- Where is the pharmacy located in relation to the primary research clinic?	X			The investigational drugs will be stored in the KEH Pharmacy. This is on the same campus as the KEH clinical site. KEH is approximately 3 km from the CDC clinical facility.
- What are the credentials of staff responsible for dispensing investigational product?	Y			Andy Gray, BPharm, MSc Pharm, is the Study Pharmacist for START. Recruitment efforts are underway for a designated pharmacist who will be responsible for the day to day operations. In addition, clinical pharmacists are in place at both CDC and KEH for non-study drug pharmacy needs.
- Describe the security of the overall pharmacy and of the areas utilized for the storage of study product and records.				Contains double-locked storage facilities. The pharmacy appears busy, with a large volume of pharmaceutical manufacturing and storage. Drug storage at the CDC needs to be clarified.
- Are refrigerators/freezers available, if required by the study?			NA	Not applicable
- What procedure will be used to ship investigational product to the clinical site?				Pending-to be finalized
- Is there a written procedure to ensure subjects have provided written informed consent prior to dispensing investigational product?	X			SOP010 entitled "Consent Check" specifies the procedure for verification of informed consent prior to dispensation of investigational product.
- How will accountability records be maintained?	X			Entries on accountability records will be recorded each time investigational product is dispensed, returned, or received from a supplier.
- What is the procedure for routine inventory?				CIPRA-specific routine inventory procedures will be finalized by the study pharmacist, but will involve a manual stock card system.

- Will daily temperature logs be kept, for investigational products requiring refrigeration, freezing, or for pharmacies located in tropical climates?	X			
- Name of in-country regulatory authority:	X			Medicines Control Council (MCC)
- Have in-country approvals for importing investigational products been obtained?		X		The Section 21 (s21) license is pending the results of bioavailability studies. These data should be available within approximately 3-6 months.
- Are in-country import permits required? If so, have they been obtained?			X	Not addressed
- Has a US export permit been obtained (if required by in-country regulations)? Note: usually not required if study is under FDA IND			X	Not addressed

VI. MANAGEMENT OF LABORATORY SPECIMENS

TOPIC REVIEWED	Y	N	NA	COMMENTS
20. Are written procedures available for the collection, processing, storage and transportation of laboratory specimens? Review &/or discuss the following:				START: Yes, SOPs are written. Recommended that SOPs be further detailed with respect to specimen labeling, collection, and transport. The specimen flow diagram is included in Appendix 10. AI: SOPs are not written yet. SOP Outline for Lab procedures are written and included as Appendix 11. The specimen flow diagram is included in Appendix 12.
- Are visits scheduled to ensure that specimens are obtained and processed based on protocol requirements?			NR	Future monitoring visits are planned but not scheduled.
- Who will oversee the completion of lab forms to assure they are completed accurately?				START: Cyril Zulu CDC; Study specific trained nurse. AI: To be designated.
- Who is responsible for processing specimens and shipping to outside laboratories?				START: Site Lab technician (to be designated) AI: To be designated.
- How will specimens be tracked?				Lancet Labs: This commercial lab uses a computer assisted program for labeling, tracking and reporting results. CAPRISA Lab: The central lab at CAPRISA will be responsible for specimen tracking and archiving. Plans are to use a computer labeling and retrieval system.

- What is the proximity of the laboratory to the clinic?				Lancet Labs: ~3 kilometers Cyril Zulu CDC: ~ 3 kilometers Luthuli Hospital: ~ 3 milimetes K. Edward Hospital: Africa Ctr: At site CAPRISA Lab: At site NICD: 1.5 hour flight to Johannesburg UCT: 1.5 hr flight to Cape Town
- Is the laboratory certified, licensed, or accredited?				Lancet Labs: SANAS See Appendix 7. Cyril Zulu CDC: No Luthuli Hospital: Verbal yes, requested documentation. K. Edward Hospital: Verbal yes, requested documentation Africa Ctr: Not Reviewed (NR) CAPRISA Lab: No (lab under construction) NICD: Verbal yes, requested documentation. UCT: No
- Does the laboratory participate in proficiency testing?				Cyril Zulu CDC: Yes, for sputum smears through the King George V Hospital laboratory proficiency testing program.
- Does the laboratory have written SOPs?				Lancet Labs: Yes Cyril Zulu CDC: NR Luthuli Hospital: Yes K. Edward Hospital: Yes Africa Ctr: NR CAPRISA Lab: NR NICD: NR UCT: NR
- Does the laboratory use QA procedures?				Cyril Zulu CDC: Yes, QA procedures are in place for sputum smears for acid fast bacilli. QA procedures are not yet in place for on-site HIV rapid tests or urine-based pregnancy tests.
- Does the laboratory record daily temperatures for refrigerators and/or freezers used to store reagents or specimens?				Lancet Labs: Yes Cyril Zulu CDC: NR Luthuli Hospital: Yes K. Edward Hospital: Yes Africa Ctr: NR CAPRISA Lab: NR NICD: NR UCT: NR

<p>- Describe the plan for hazardous waste disposal</p>			<p>NR Lancet Labs: NR Cyril Zulu CDC: All sputum specimens will be processed in a Class 11 Biohazard cabinet. On site and laboratory safety will follow recommendations of Biosafety in the Microbiological and Biomedical laboratories (3rd edition), Centre for Disease Control and Prevention and the National Institutes of Health. Sharp objects and needles will be placed in special "SHARP DISPOSAL CONTAINERS". The rest of the biohazard material will be disposed in special leak proof plastic bags, placed in appropriate containers, sealed and picked up by Medical Waste Systems who will incinerate the contents. Luthuli Hospital: NR K. Edward Hospital: NR Africa Ctr: NR CAPRISA Lab: NR NICD: NR UCT: NR</p>
<p>- How will test results be reported to clinicians, including panic values?</p>			<p>Lancet Labs: Electronic, Fax, telephone (urgent values). Cyril Zulu CDC: Reports will be generated on predesigned laboratory report forms, signed by the reporting laboratory technician. "Panic" results will be telephoned immediately or results reported verbally directly to the clinician supported with the laboratory report. Luthuli Hospital: NR K. Edward Hospital: NR Africa Ctr: NR CAPRISA Lab: NR NICD: NR UCT: NR</p>
<p>- How will errors detected/reported by the data center be corrected?</p>			<p>Lancet Labs: Through QA manager. Cyril Zulu CDC: NR Luthuli Hospital: NR K. Edward Hospital: NR Africa Ctr: NR CAPRISA Lab: NR NICD: NR UCT: NR</p>
<p>- Where will long-term storage of specimens occur?</p>			<p>CAPRISA Lab Archives</p>
<p>- Who will assess storage conditions to assure proper use of temperature, boxes and vials?</p>			<p>To be determined</p>
<p>21. Air Transportation of Specimens</p>			
<p>- Which staff members have received IATA training and have a current certification?</p>			<p>None; site will use Lancet Labs IATA certified personnel (Steve Pillay) until CAPRISA staff get certified. See Appendix 13.</p>

- Are there specific in-country regulations regarding the export or transport of specimens?			NR	
- If infectious substances are to be shipped outside the US, are the Department of Commerce export administration regulations (15 CFR 742,774) to be followed?			NA	
- Has the PI obtained an infectious substance import permit from the CDC?			NA	

VII. PLANS FOR DATA AND SAFETY MONITORING and MONITORING OF CLINICAL STUDY SITE, PHARMACY AND LABORATORY

TOPIC REVIEWED	Y	N	NA	COMMENTS
22. Are there documented plans for Data and Safety Monitoring, if required by DAIDS? If so, do they include one of the following?		X		The current version of the protocol includes language describing the use of a non-DAIDS affiliated DSMB. The protocol team has decided to use a DAIDS-affiliated DSMB with 3 local members. The language in the protocol needs to be changed to reflect the DAIDS-affiliated DSMB. Additionally, the protocol needs to specify the operating procedures of this DSMB.
- Independent safety monitor?			X	Not applicable
- Independent Monitoring Committee or Safety Monitoring Committee?			X	Not applicable
- Data and Safety Monitoring Board?		X		This language needs to be drafted (see above)
- If a non-DAIDS affiliated DSMB has been organized, have the charter, operating procedures, proposed roster and CVs been submitted to the PO?			X	Not applicable
23. Describe the final decisions made jointly by the PO and PI regarding ongoing safety reporting requirements for research not performed under an IND/IDE.			X	Not addressed
24. Will monitoring of the study site, pharmacy and laboratory be required? If so, describe.				Clinical Monitoring by the Westat Monitoring Group is expected for these trials. A detailed monitoring plan has not yet been developed.

VIII. PLANS FOR ASSESSING, MANAGING AND REPORTING ADVERSE EVENTS

TOPIC REVIEWED	Y	N	NA	COMMENTS
25. Are documented procedures available for assessing, managing and reporting adverse events (AEs) and serious adverse events (SAEs)? Review &/or discuss the following:	X			Draft language regarding toxicity management and serious adverse events is included in the current version of the protocol. The preliminary plan includes: <ul style="list-style-type: none"> • Participants will be provided with training in symptom recognition for expected toxicities; • The study team will be trained to recognize and manage toxicities; and • Management of AEs will be based on WHO guidelines. Adverse event management and reporting procedures will require further refinement as the protocol and database management systems are developed.
- How are AEs graded? How is "serious" evaluated and by whom?	X			The DAIDS Toxicity Table will be used for severity grading. The clinician, lab manager and study coordinator will monitor study participants for toxicities. The PI will be notified in the event of a toxicity. The PI will report the SAE to the IEC/IRB and DAIDS as required.
- Who will complete the AE-related CRFs, and how will they be reviewed for accuracy?			X	Not addressed-AE procedures will be further defined as the protocol is developed.
- Describe the plan for reporting SAEs to the designated safety monitor, safety monitoring committee, or DSMB (where required).	X			The tentative plan involves the PI reporting SAEs to the program/medical officer and IEC/IRB. Plans for reporting to the DSMB are not finalized.
- Will life-threatening or fatal SAEs be immediately reported to the IRB/IEC and to the sponsor?	X			
- Will IND expedited safety reports submitted to the FDA be reported to the IRB/IEC and to the PO within 24 hours? (Where required)	X			
- Will there be timely reporting of all AEs to the database?				Pending-The safety database has not yet been developed. However, timely reporting of all AEs to the database will be a requirement of the data management plan.
- Will there be annual reporting of AEs to the IRB/IEC and to the PO?	X			
- Will AEs be followed/tracked to clinical resolution, and then reported appropriately?	X			
- Are the procedures in compliance with GCP and 21 CFR 312, or has the PI obtained a waiver from the FDA (for trials with INDs/IDUs)?				Pending-Unable to answer since the adverse event reporting procedures are not finalized.

- Are there documented procedures for the management of side effects and for dealing with medical emergencies within the resource constraints of the host country?				Both CDC and KEH clinical facilities have the ability to manage medical emergencies. Documented procedures should be reviewed prior to study initiation.
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IX. INVESTIGATIONAL NEW DRUG/INVESTIGATIONAL DEVICE EXEMPTION (IND/IDE)

TOPIC REVIEWED	Y	N	NA	COMMENTS
26. Is documentation related to clinical trials with INDs/IDEs available for review? Record the following (as required):			X	The protocol will not be conducted under an IND.
- Name, institution and address of IND/IDE sponsor			X	Not applicable
- FDA IND/IDE Number			X	Not applicable
- Procedures for required time-sensitive notifications, to include:			X	Not applicable
- Seven-day IND Safety Reports			X	Not applicable
- Fifteen-day IND Safety Reports			X	Not applicable
- IDE Reports of Unanticipated Adverse Device Effect			X	Not applicable
- Annual IND reports			X	Not applicable
27. Are copies of all written correspondence with the FDA available for review? (Copies should be submitted to the PO.)			X	Not applicable

X. DATA QUALITY MANAGEMENT PLAN

TOPIC REVIEWED	Y	N	NA	COMMENTS
28. Are documented procedures for a data quality management plan available for review? Review &/or discuss the following:		X		The data management plan is in the early stages of development. The site has requested Westat support for CRF development. The site plans to use EpiData as a data management system and requests an evaluation of this system from the Westat Data Management Department. The CRA requested the completion of the data management "Preliminary Questionnaire."
- Source documentation requirements (Source documents should be signed and dated, legible, contain current information, original and accurate with no conflicting data recorded elsewhere)	X			A SOP describing source documentation procedures does exist. Existing records were reviewed during the visit, which demonstrated practices consistent with GCP/ICH E9 and the DAIDS source documentation SOP.
- Study initiation components, including:			X	Not addressed
- training site staff			X	Not addressed
- establishing schedules for receipt of forms, specimens and electronic data			X	Not addressed

- Data collection procedures	X			A SOP entitled "Completion of CRFs" is available, but may need to be modified when the study-specific data management plan and protocol are finalized.
- Standards for CRF completion	X			A SOP entitled "Completion of CRFs" is available. However, this SOP was not reviewed in detail during the visit. Westat can provide guidance regarding the additional data management SOPs required for study initiation.
- Eligibility confirmation and randomization (as required)	X			SOPs entitled "Establishing Participant Eligibility" and "Randomisation Procedures" are available. However, there was insufficient time to review these SOPs during the visit.
- Data system description	X			EpiData 2.1b is a stand-alone, password protected system that provides exports available to statistical analysis programs. The system also provides routine reports generated in Access. The site has experience with this system and would prefer to use it because it is easy to use. Westat referred the description of the system to the Westat data management group for a feasibility evaluation.
- Data system validation				Unknown-referred to Westat data management group.
- Procedures for addressing data queries	X			A SOP entitled "Resolving Data Queries" is available. However, there was insufficient time to review this SOP during the visit.
- Data entry procedures		X		Double data entry will be used. SOPs describing data entry should be developed as the data management plan is developed.
- Data cleaning and data edits			X	Not assessed
- Data QC techniques (e.g., manual review of CRFs, establish text coding procedure, establish frequency of delinquency reports and report review, schedule and conduct periodic review of database data to CRF data, develop a schedule for interim data analysis)	Y			Quality Control-Visit schedules and reminders, on-site prospective CRF review, validation of data entry, double data entry, generation of data queries, electronic generation of reports.

XII. DATA ANALYSIS PLANS

TOPIC REVIEWED	Y	N	NA	COMMENTS
29. Are data analysis plans available for review? Review &/or discuss the following (where required):			X	Not addressed
- A plan for early stopping			X	Not addressed
- A plan for unmasking of study treatment assignment medication due to patient health concerns, and for unmasking for interim analyses and final analysis			X	Not addressed

XIII. ADDITIONAL COMMENTS- Please see Summary of Findings

TOPIC REVIEWED	Y	N	NA	COMMENTS
1.				
2.				
3.				
4.				

XIV. CLINICAL TERMS OF AWARD SUBMISSIONS

TOPIC REVIEWED	Y	N	NA	COMMENTS
Has the PI met all submission requirements under the NIAID Clinical Terms of Award, to include the following for each investigative site/IRB:				The appropriate documents are on file at the site. However, a listing of submissions was not available at the time of the visit.
- IRB/IEC's name	X			
- IRB/IEC Office of Human Research Protections (OHRP) registration number	X			
- FWA (Federal Wide Assurance) number for institution/site	X			
- IRB/IEC notification of protocol approval			X	Not applicable
- IRB/IEC approved protocol, identified by version number and/or date			X	Not applicable
- IRB/IEC approved consent forms identified by dates during which they are valid			X	Not applicable
- ISM, SMC, or DSMB information, if applicable, to include:			X	Not applicable
- Charter			X	Not applicable
- Operating procedures			X	Not applicable
- Proposed roster			X	Not applicable
- CVs			X	Not applicable
- IND/IDE Information, if applicable, to include:			X	Not applicable
- Name, Institution, and Address of IND/IDE Sponsor			X	Not applicable
- FDA IND/IDE Number (copy of letter from FDA)			X	Not applicable
- FDA Correspondence, (copies of all written communication with the FDA)			X	Not applicable
- Risk Information (e. g., IB, or information obtained through published literature review or other venue)			X	Not applicable

- Safety reporting procedures for research not performed under an IND/IDE			X	Not applicable-Not finalized
- NIH Recombinant DNA Advisory Committee (RAC) Approval (if required)			X	Not applicable
- Institutional Biosafety Committee (IBC) Approval (if required)			X	Not applicable
- Documentation of Training in Human Subjects Protections (for all study staff responsible for design/conduct of the research)	X			Not applicable
Note that for the duration of the award it is the responsibility of the PI to submit to DAIDS documentation of IRB/IEC continuing reviews, DSMB reviews/summaries, IND/IDE Safety Reports, continuing RAC & IBC approval, training in the protection of human subjects for new study staff, and inclusion enrollment reports. Notify DAIDS of subsequent protocol amendments or changes in IRB/IEC approval status within 3 days of the IRB/IEC decision.	X			

SIGNATURE PAGE

Reviewed by:

Date:

(Signature of DAIDS Program Officer)

Prepared by:

Date:

(Signature of Clinical Research Associate)

The signed copy of this report will be maintained in the Clinical Research Operations Monitoring Center Project Files at Westat.

LIST OF APPENDICES

1. List of Study Sites Visited
2. Organization Structure Diagrams
3. SOP Table of Contents, START Protocol
4. SOP Table of Contents, Acute Infection Protocol
5. IATA Certificate
6. Essential Regulatory Documents List
7. Accreditation Documents, Lancet Labs
8. Lab Normal Range Values, Acute Infection Protocol
9. Staff Allocations
10. Specimen Flow Diagram, START Protocol
11. Lab SOP Outline; Acute Infection Protocol
12. Specimen Flow Diagram, Acute Infection Protocol
13. Transport of Dangerous Goods Certificate, Lancet Labs