Westat

Division of AIDS
Clinical Research Operations and Monitoring Center

Site Visit Report

Pre-Inspection Audit

Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda

Conducted February 18, 2002 - February 28, 2002

Report Date: 8 March 2002

Contractor: We
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Authors: Jud
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Submission Date: Ma

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p. 53-56

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Not time - not
asked - to do entire
study record review

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SITE VISIT REPORT

Division of AIDS Clinical Research Operations and Monitoring Center

Contract Number:	N01-AI-15445
Dates Conducted:	February 18, 2002 - February 28, 2002
Location:	Kampala, Uganda
Contractor:	Westat 1650 Research Boulevard Rockville, MD 20850
Authors:	Judith Chamberlin, P.A., Dr. P.H. Steven A. Gustavson, D.V. M., RAC Michael Hensley, M.D. Susan Lander, B.S.N., M.P.H.
Submission Date:	March 8, 2002

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Background

On February 11, 2002 NIAID under contract N01-AI-15445, COA #4 authorized travel to Kampala Uganda for Westat to conduct a site visit and to assist staff in preparing for an upcoming FDA inspection for the HIVNET 012 clinical trial conducted under an NIAID-held IND. Westat was to conduct record reviews, assess human subjects/ regulatory compliance and inform staff regarding what to expect from the FDA inspection and how to prepare for it.

The site had been selected by FDA for an inspection as part of a Supplemental New Drug Application submitted to extend label indications to include the use of nevirapine in the prevention of mother to child transmission of HIV-1. This study was designated as pivotal and represented a critical subset of the overall data package supporting the label extension.

Inspection Approach

The FDA approach to a pre-approval inspection covers all of the major requirements, although typically the focus of a foreign inspection is on verification of safety data and data supporting primary efficacy endpoints. In assessing and preparing the site for the inspection Consent, IRB Approval, and Drug Accountability, were reviewed and additional emphasis was placed on the records which would have been examined as a part of the assessment of "establishment and maintenance of adequate and accurate case histories". An assessment of the site from this perspective provides a more accurate view of site's performance relative to FDA's focus and offers greater predictability as to the outcome of a FDA inspection.

Westat developed its review team to cover all operational areas of the site as well as review several areas that are often the focus of FDA on-site activities. To do this, Westat used pre-inspection trend analyses similar to those used by the Agency to identify problematic areas for further investigation. As the SNDA moves through the review cycle, various reviewers have the opportunity to look at the dataset and often identify concerns which become specific targets of inquiry when the FDA investigator is on site. While it may be impossible to anticipate all

Table 1 Requested Data Listings

Mother's Case Report Form	*Infant Case Report Form*
Participant Number	Participant Number
Mothers Demographic	Birthdate
Birthdate	Time of Birth
Dosing Information	AZT Dosing
Time Dose Taken	4a (# doses)
Dose # 1 (time)	4b (#ml remaining)
Dose # 4 (time)	Nevarapine Dosing
Dose # 8 (time)	6. (did infant require study drug from emergency supply, yes/no)
Delivery Information	Laboratory
Onset Labor (time)	HIV EIA
Membranes Ruptured (time)	Absolute CD4 Count
Physical Exam at Discharge	Hemoglobin
PE (normal or abnormal)	Follow-up
Laboratory	1.Current weight
HIV EIA	6. Illness or adverse event (yes/no)
Hgb	*Long Term Follow Up Form*
ALT (SGPT)	
Follow-up	Weight
Illness/adverse event (yes or no)	Height
	Hemoglobin
	Child's Termination (2a, 2b, 2c)

- **Data Patterns:** A general examination of the tables generated, in particular the table presenting information on labor and delivery from the Mothers' CRF, suggested that some of the data were non-random. This appeared to be true, for example of year of birth, in that clusters of patients with the same birth year were occasionally noted. As a starting point, a sample of the data was taken, based on birth year, with 1973 and 1974 being chosen. Ninety-three (93) patients were found with birthdates from these years. Of these, based on the entry in the Infant's CRF for AZT dosing, only 36 were AZT patients, raising some concern about patient selection and order of entry into the trial.

  Additionally, the data segregate into at least three parts, based on the use of numbers. These sections are bounded by patients 001-0230 (11/3/97-5/29/98), patients 0402-0751 (7/22/98-2/17/99), and patients 0765-0888 (2/22/99 – 5/29/99). In common were somewhat different patient profiles in each of these periods, as well as some apparent bias in the use of numbers entered into blanks such as "time of onset " (of labor), or "time of dose". The second period appeared to divide into two nearly discrete sections at patient 0623. Patients in the first block appeared to have often been complicated, with dosing often problematic. Patients in the second block (which followed an unexplained numerical gap of about 100 randomization slots), seemed to have been more in conformance with the protocol, but time entries not uncommonly appeared to represent estimates rather than actual data. Patients in the third set appeared to once again represent a more complicated population, but with some of the same data entry issues apparent in the second set. On its face, this pattern appeared to be consistent with a change in personnel completing forms or a change in work instructions. It was also thought to be compatible with getting a bit behind, then catching up, with completion of CRF's. The data tables were felt to suggest issues

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the potential or specific objectives of any inspection, clinical data trending techniques are an excellent mechanism to identify problems related to performance of the study team, problems which would be likely follow-up issues for FDA. In conjunction with the background documents provided, Westat reviewed the CRFs and requested data from several fields for infants and mothers (Table 1. Requested data listings). Based on that review, several areas of concern were identified which formed the basis of the initial site visit plan (Attachment 1):

- **Adequate and Accurate Case Histories:** To the extent the CRF is not the primary source document, entries on the CRF's will be supported by entries on other records, including but not limited to the patient records from the hospital and clinic. As a part of the inspection, it is not uncommon for the FDA auditor to arrive with data listings and then to compare those listings, by patient, to entries in patient charts. The default position is that the patient chart is assumed to be correct, in the event of a discrepancy. Because preliminary discussions with the site suggested that patient charts would be incomplete or not available, the potential importance of other source documents, and the role of the CRF or other records was apparent.

- **Data Patterns:** A general examination of the tables generated, in particular the table presenting information on labor and delivery from the Mothers' CRF, suggested that some of the data were non-random. This appeared to be true, for example of year of birth, in that clusters of patients with the same birth year were occasionally noted. As a starting point, a sample of the data was taken, based on birth year, with 1973 and 1974 being chosen. Ninety-three (93) patients were found with birthdates from these years. Of these, based on the entry in the Infant's CRF for AZT dosing, only 36 were AZT patients, raising some concern about patient selection and order of entry into the trial.

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with drug administration, with the collection of accurate clinical data on the CRF, and with the collection of safety data.

- **Maternal Drug Administration:** A comparison of the date/time of dosing for "Dose 1" to the date/time of onset of labor and to the date/time of birth, gave rise to some observations requiring follow-up:

  For 19 of 93 Patients (20%), the time of the first dose is at least 6 hours after onset of labor or its relationship to the onset of labor is unknown.

  For at least 2 of 36 (6%) apparent AZT patients, dosing does not appear to match the q3h schedule.

  For 7 of 93 (8%) patients, the time of Dose 1 and time of birth appear to overlap or very nearly so.

  In summary, based on the data from women with a birth year of 1973 or 1974, it was thought likely that more than 30% of the mothers would exhibit dosing errors of one sort or another.

- **Collection/Recording of Clinical Data:** Unusual clustering of numbers raised concern regarding the accuracy of some of the data collection or recording. For example, in the period between May 23, 1998 and September 9, 1998, there were fourteen (14) evaluable patient listings for this sample (birth years 1973 and 1974). Of these, and considering only time of first dose, nine (9) entries (64%) were accounted for by 0100, 0300, 0400, 0500, or 0600. Four (4) of these entries were 0600. Assuming no relationship between these patients, and assuming that only the hour was used (estimate), giving us 24 possible entries, the odds of this happening were roughly 1 in 2,000,000. This implied that these were probably, in fact, related events. Among the relationships possible was a problem with the person collecting or recording the events. The most common problem would be estimation of times rather than a recording of actual time. Since timing of dosing related to onset of labor was important, this was thought to be potentially an important finding. Similar patterning was seen in other areas, such as the period between February and May, 1999, for the field "time" for ruptured membranes, and was thought to be compatible with a reporting problem. Since it was apparent that one person had completed most CRF's, it seemed likely that the issues might relate to the performance of that individual or to a systemic problem with data collection.

- **Safety Reporting:** Looking first at the Examination at Discharge, for Mothers, more than 1/3 were marked "abnormal". These did not distribute randomly in that the three groupings referred to above showed different outcomes. For the group ending at Patient 230, there were 24 patients in the sample. Of these, 15 had "abnormal" exams, (63%). For the group ending at Patient 751, there were 48 patients. Of these, 18 had "abnormal" exams, (38%). For the group ending in Patient 888, there were 21 patients. Of these, 6 had "abnormal" exams, (29%). While the patterns were

interesting, the more interesting fact was that 39 of 93 mothers left the hospital with abnormal examinations, (42%). It was felt that the decline in reporting represented better patient selection, different site personnel, or perhaps the well known phenomenon of less complete reporting as a trial progresses.

On a similar note, looking at infant weights, it was apparent that a weight of less than 7Kg at 12-month follow-up was not an uncommon finding, despite the generally robust size of most infants at that visit. It was thought to be likely that some, perhaps many, of these infants had serious health problems. A sample of 43 such infants from the larger sample of 93, showed that all had adverse events at 12 months. Of these 43, only 11 were HIV positive, suggesting that upon audit of the site files, we would find more pathology than had been reported. More to the point, most of the SAE's reported for infants were in the newborn period, which was incompatible with the large number of infants with apparent Failure to Thrive past 6 months of age. Additionally, there was the matter of the Lancet paper, which mentioned 59 Serious Adverse Events in infants less than two months of age. Both the data sample described above, and the Lancet report, suggested more serious adverse events in infants than had been reported to FDA under the IND.

does the Lancet paper's data match yours

Taken together, it appeared likely in fact, that many adverse events and perhaps a significant number of serious adverse events, for both mother and infant, may not have been collected and reported in a timely manner to the FDA, under the IND.

Finally, the variability in recording of clinical information described above suggested, as did the limited BIPI audit in January, 2002, that comparison of CRF's or line listings to the patient records in Uganda might well result in discovery of additional AE's and SAE's, not present in either the IND reports or the SNDA. This would create two problems, the timeliness of IND reports, and the accuracy of the SNDA submission. Safety reporting therefore became a primary focus for the site audit team.

From this analysis, an inspection-plan was developed that would both assess the site for conformance to all rules and guidances and also would look at specific questions arising from the trend analysis of the data. For chart review a proposed patient list was developed from which to focus the in-depth review of subject charts, Attachment 2.

Westat staff were on site from February 18, 2002 through February 28, 2002. The initial effort focussed on the regulatory audit, chart review, pharmacy review and laboratory review. The second phase of the assessment added more detail to the review of accuracy of CRFs to source documents, SAE and AE reporting procedures and obtain more information with which to answer questions that arose in the initial data trending procedure.

Westat
Clinical Research Operations and Monitoring Center

PRE-INSPECTION VISIT REPORT
INTRODUCTION AND REGULATORY AUDIT

Name of Clinical Site:	**Makerere University-Johns Hopkins University Research Collaboration**
Address:	**Mulago Hospital, Kampala, Uganda**
Protocol Title:	**A Phase III Placebo-controlled Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates**
Enrollment Initiated:	**November 1997**
Program Officer:	**Samuel Adeniyi-Jones, M.D.**
Dates of Visit:	**18 February through 28 February 2002**

Westat Clinical Site Monitors:

Susan Lander, B.S.N., M.P.H. and

Judith Chamberlin, P.A., Dr.P.H. *(On site: 18-26 February 2002)*

Westat Regulatory Affairs Manager:

Steven Gustavson, D.V.M. *(On site: 25-28 February 2002)*

Biologics Consulting Group, Regulatory Consultant:

Michael Hensley, M.D. *(On site: 25-28 February 2002)*

Division of AIDS Project Officer for Westat Contract:

Jacquelyn Burns, M.P.A., *(On site: 22-26 February 2002)*

				in existence.

III. REGULATORY AUDIT

Indicate if the following topics were assessed. If satisfactory, check "Y". If not satisfactory check "N". Check "N/A" if not applicable or not assessed. Provide comments as applicable:

Table 4: Regulatory Audit

1. Current Investigator's Brochure	X			Three versions of the IB are on file: • 14-Dec-1995 version of the IB was included in the original IND application • 19-Nov-1997 version, and • 2000 version
- IND safety reports and IEC/IRB correspondence	X			Letters prior to January 2002 were on file advising the IRB of safety reports received. The letter dates and referenced safety report dates were: MU-JHU letter date: — Referenced safety report date: 25-May-98 — 8-May-98 26-Aug-98 — 2nd quarter, 1998 5-Jun-98 — date not referenced The reports were not attached and this monitor did not cross-reference these with the safety reports provided for verification by DAIDS. The following safety reports were recently submitted to the local IRB with a letter noting that some of them had previously been submitted. The staff was advised to file a copy of the letter with the reports, to record which ones were submitted. • 13 FDA IND safety reports from HIVNET 012 • Other Boerhinger safety reports the site had received from non-DAIDS source (including four of the five safety reports that had been provided to Westat by the Regulatory Operation Center (ROC) as DAIDS "Safety Memos" • A copy of the fifth safety report provided by the ROC (SM-646) was provided to Ms. Allen and was submitted to the local IRB during this visit.
2. Form FDA 1572 current	X			Forms FDA 1572 dated 3-Aug-1997 and 15-Jan-2002 were on file.

3.	Investigators' Curriculum vitae	X			CVs were on file for: • Jay Brooks Jackson (updated 10-Jan-2002) • Francis A. Mmiro • Laura Guay • Philippa Musoke Mudido • Florence M. Mirembe • Christopher M. Ndugwa • O. Margaret Achom • Clemensia Nakabito • Kenneth Kintu • Constance Ducar • Corey Duefield • Florence S. Kikonyogo • Michael C. Mubiru • Mary Musisi • And others…
4.	Copy of signed protocol and all amendments	X			• Version 1.0 of the protocol is on file and signed by Dr. Jackson (3-Aug-1999) and Dr. Mmiro (9-Jan-2002). • The first letter of amendment submission to the IND and a copy of "Amendment II" are on file.
5.	Sample case report form (CRF)	X			
6.	Human Subjects Protection Capabilities				Approvals are required at the following levels: <u>National Level</u> Uganda National Council for Science and Technology <u>Local Level</u> Uganda AIDS Research Subcommittee, of the STD/AIDS Control Program for the Ministry of Health, Uganda <u>U.S. Grant Investigator site</u> Johns Hopkins University School of Medicine, Joint Committee on Clinical Investigation (JCCI)
	FWA or other assurance number	X			Two SPA approvals and one CPA approval were observed to be on file: • Makerere University, SPA # S6233-11 • Mulago Hospital, SPA # S6234-03 • CPA # T-5124 (21-sep-2000 through 20-sep-2005) Ms Allen advised that there is also CPA # T-5125 on file, also with expiry of 20-Sep-2005. This was not verified by this monitor. The OHRP website was reviewed following the visit and the following CPA assurances are noted: • T5124 Makerere University Medical School • T5125 Mulago Hospital Both CPAs are noted to have "renew by" dates of 12/31/2003 (not 2005).

IEC/IRB Membership Roster	X			IRB rosters are on file for: The local IRB • 1996-1997 (Updated prior to SPA approvals, following request to comply with inclusion of community member). • There was also an updated IRB roster on file with an SPA # that did not match either of the ones assigned. (Number/date not recorded by this monitor. The last two numbers were different from either of the two SPAs). Johns Hopkins IRB • 1996-1997 • 2001-2002
IEC/IRB standard operating procedures (SOPs)		X		
7. Documented IEC/IRB approval of protocol and all amendments	X			National Approval: • 2-Oct-97: Approval (w/ clearance from the president pending) and request to allow study to proceed. Ms. Allen reports that written approval of the president is not issued to the investigative sites. Local Approvals: • 2-Jul-1997 Version 1.0 – first approval • 27-Oct-1997 Version 1.0 • 27-Mar-1998 Provisional approval to drop placebo arm • 14-Apr-1998 Amendment I • 2-Oct-2000 Amendment II Grant Investigator Site Approvals: • 23-Jul-97 Version 1.0 • 24-Feb-1998 – approval for interim change to the protocol for dropping the placebo arms of the trial. • 24-Mar-1998 – Amendment I • 27-Mar-2000 –Amendment II
8. Documented IEC/IRB-approved consent form and all revisions	X			Copies of informed consents, local language consents and back translations are on file for: • Version 1.0; • First letter of amendment; • Updated consent for First letter of amendment; and • Amendment II These are not signed/stamped/dated by either IRB. Neither certification of translation, nor identification of the translator is on file for the translated or back-translated informed consent documents. Documented approvals for the following consents are on file: Local Approvals: • Approval of English or Ugandan ICFs were not verified by this monitor. Grant Investigator Site Approvals: • 1-Jan-2000 –Amendment II with JHU IRB Stamp and date • 24-Mar-1998 – Letter of Amendment • 29-Sep-97 revised informed consent (not stamped/dated) • 11-Aug-1998 – with annual renewal

9. Documented IEC/IRB-approved assent form and all revisions			X	
10. Documented IEC/IRB approval of any other materials given to subjects. Specify. (e.g. written information, advertisements, compensation, other)			X	This requirement was discussed with Dr. Philippa Musoke and Ms. Allen who report that no written materials were used for recruitment or for patient education. Reimbursement was provided for transportation. Documentation of IRB approval for transportation expenses was not on file.
11. Documentation of financial aspects of trial (e.g. grant award, contract, subcontract)			X	The DAIDS project officer, Ms Burns, reviewed this requirement with the on-site investigators. Dr. Jackson was contacted and advised to bring documentation to the site prior to the inspection.
12. Annual summary of study progress submitted to IEC/IRB	X	X		Local IRB: There were no annual study progress submissions or protocol renewals on file prior to 11-Jan-2002. At this time a "2001 Progress Report" was submitted, including tables of SAEs reported during the 1st 18 months of subject's trial participation. Grant Investigator Site IRB: • 1st year annual report is not dated or signed and did not include the referenced attachment describing progress of the trial. This was stamped received by the JHU IRB on 6-Aug-1998 and approved 11-Aug-1998. • 2nd year annual report dated 20-Jul-1999. • 3rd year annual report dated 12-July-2000. • 4th year annual report dated 31-Jul-2001.
13. Documentation of annual IEC/IRB renewal of protocol and consent (and assent, if applicable).	X	X		Local Renewals: As above, there was no annual reports provided to the local IRB and subsequently no annual renewals were provided by the IRB. Grant Investigator Site Renewals: • 1st year continuing renewal dated 11-Aug-1998. • 2nd year continuing renewal dated 10-Aug-1999. • 3rd year continuing renewal on file (date not recorded by this monitor). • 4th year continuing renewal dated 9-Aug-2001.
14. Master Signature Log	X			A master signature log was recently created. Signatures are not on this list for the part time pharmacist, or the laboratory administrator. • The laboratory administrator's signature is on the laboratory signature log, as are other laboratory staff. The laboratory has maintained a signature log for several years. • The investigators were advised to make efforts to secure the pharmacist's signature prior to the inspection. Ms. Allen pointed out that the pharmacists signature is on his CV, so it may be possible to cross-reference the CV for his signature. • For future studies, the staff was advised to create a log to include a column for *initials*, in addition to name, title and signature.

15. Documentation of Laboratory Certification		X		The lab is not certified, but did participate in CDC-MPEP proficiency program during this trial. The lab has more recently participated in other proficiency programs, including CAP, UKNEQUAS, VQA, and QASI. The lab hopes to receive CAP or CLIA certification at such a time as these inspections are available in Uganda.
- If lab is not certified, review QC/QA procedures, inquire about validation methods used and obtain copy of lab director's CV (if not previously obtained).	X			See Laboratory audit report for additional details.
16. Copy of normal range values for each laboratory used and updates to normal ranges during the trial.	X			Normal range values have not been documented for the local population. • A list of textbook laboratory normal values was recently prepared and added to the file. A copy of the reference for this listing was included in the file. (Pediatric Reference Ranges, 2nd edition, Edited by Steven J. Soldin). • Also on file is a list of lab normal values for Johns Hopkins University laboratories. • The DAIDS grading of maternal hemoglobin was modified and a copy of the modified table was introduced to the monitors on Saturday, 23 February.
17. IATA Certification for Shipping Dangerous Goods		X		The laboratory administrator reports that she received training in dangerous goods shipping from Dr. Guay. Dr Guay reported that she is not IATA-certified and that she received training from Dr. Brooks Jackson. Dr. Jackson reported that he is not certified. Dr. Jackson was requested to retrieve and bring copies of IATA certification for whoever may have been certified during the time of the trial (possibly Estelle Piwowar).
18. Review documentation of stored laboratory specimens. - Determine location and storage condition of specimens on site. - Determine location of specimens, if shipped off site.	X			On-site specimens are presently stored in –70 freezer in the core lab. The freezer temperature is monitored daily and the core lab is equipped with two back-up generators. Some specimens have been shipped off-site to Johns Hopkins University. The computerized laboratory tracking system records storage location; dates of thaws, if any; and shipping information for study specimens. A copy of this information was provided to the clinical site for their laboratory binder.
19. Serious Adverse Event reports submitted to sponsor and IEC/IRB		X		<u>Local IRB:</u> Neither annual progress reports, nor reports of SAEs of study subjects were reported to the IRB until January 2002. <u>Grant Investigator Site IRB:</u> The annual reports to the JHU IRB were not reviewed for this requirement.

20. Subject Screening Record	X			Each antenatal clinic maintained a screening log. • The Old Mulago clinic maintained five logs, one for each clinic day. These are labeled with the days of the week and each woman was scheduled for her visits on the same day of the week. • The New Mulago screening log was maintained in the same notebook as the enrollment log. The screening log began at the first page of the book and the enrollment log began at the last page of the book. None of the participants provided written informed consent prior to collection of screening chemistry and hematology labs. These screening logs record information about women scheduled for enrollment visits *following* the screening. This monitor's initial understanding was that the logs recorded all women screened, but subsequent understanding was that they record only the women who agreed to attend the enrollment visit. The site staff reports that all women provided written informed consent for HIV testing, however, these records were not reviewed or verified by the monitors.
21. Subject Identification Logbook	X			There is one enrollment log for each antenatal clinic • The Old Mulago Log (also marked "Randomization log) • The New Mulago Log (lists enrollments in the back filling in from the last page forward, and in the front, lists women screened for the study.)
22. Subject Enrollment Log	X			
23. Are the research records stored in a secure area?	X	X		• The regulatory files are maintained on shelves in Dr. Guay's office. She was advised to place these in a locked cabinet. She said she will move them to the locked cabinet in the file room adjacent to the data processing room. • The CRFs are stored on shelves in the file room adjacent to the data processing room. • The hospital records are stored on shelves in the file room adjacent to the data processing room. • One half of the upper floor is secured at night with a locked steel door. Behind this door is the data processing area and file room. • The "source files" are stored in a file room on the ground floor.
24. Standard Operating Procedures (SOPS)	X	X		There were two procedure manuals used during the trial: 1) Study Specific Procedures (SSP) 2) HIVNET Manual of Operations There were no site-specific SOPs in place during the trial.
25. Staff Training Files		X		The staff is presently compiling available records to document training of staff before and during the trial. On hand is a copy of an agenda for a 3-day protocol training that was conducted prior to the trial, and this will be included in the training file.

26. Other Observations	X			• Permits for exporting specimens from Uganda and a CDC Import permit (valid 8-Jul-1999 through 8-Jul-2000) are on file.
				• Additional correspondence to the JHU IRBs on file include:
				  • 1-Feb-2002, IND Serial # 37 and 38 submitted
				  • 4-Feb-2002, IND Serial # 40 and 41 submitted

Additional Documents were provided to monitoring and auditing staff during the visit (or immediately prior to departure for visit), Attachment 3.

OPERATIONAL PROCEDURES AND GUIDELINES

- Adverse Experiences Reporting Requirements, (November 1997. Presumably Section 8 of the Study Specific Procedures Manual)
- Modification of Grading criteria for Maternal Hemoglobin
- Memo from Laura Guay: Procedures for Review of Laboratory Results (23-Feb-2002)
- "General Source documentation requirements relevant to HIVNET studies, including 012" (not dated. Faxed to Westat 15-Feb-2002 from FHI)

IRB CORRESPONDENCE

- Letter from Francis Mmiro & Brooks Jackson to JHU and Mugalo Hospital IRBs describing unblinding and requesting approval for continued open-label enrollment. (9-Mar-1998)
- Letter from Drs. Mmiro, Jackson, Musoke and Guay: Response to Queries of Dr. Sewankambo's Review Committee (13-Jun-2000)
- Letter from Prof. N. Sewankambo to Dr. Mmiro: Extended Mother-Child Followup in Nevirapine Trial recommendations with annotation by Dr. Guay that, "discussed with Dr. Sewankambo. Revised consent accepted. Full protocol approavl 4/10/2000 stands". (4-Oct-2000)

LABORATORY CORRESPONDENCE

- Laboratory Evaluation Report by Laboratory Consulting Services (1-Dec-1999)
- Memo to File from Constance Ducar: Re: CoreLab Accreditation (4-Jan-2002)

DATA MANAGEMENT CORRESPONDENCE

- Procedure Summary for On-site HIVNET 012 Data Processing Activities (22/02/2002)
- Procedures for Validating the CRF Relay System for HIVNET 012 Study Data (22/02/2002)
- Memo from P. Musoke: Study Numbers Without Delivery Hospital Records Available (22/02/2002)
- Memo from Corey Duefield: Infant Chemistry Test Results, prepared to describe source of chemistry and hematology data requested by Westat (26-Feb-2002)

OTHER

- "Summary of Site Monitoring Procedures and Findings: HIVNET 012", prepared by Melissa Allen (6-Sep-2001)

Prepared by: Date:

Susan Lander, B.S.N., M.P.H.

PRE-INSPECTION VISIT REPORT
SUMMARY OF RECORD REVIEWS

I. SOURCE DOCUMENTATION RECORDS

Various records were used to record case histories.

Hospital Records of Antenatal visits, Labor and Delivery, and Birth

- Formal obstetrical record, prepared by Mulago Hospital medical staff (not necessarily members of the research team).
- Initiated during first antenatal visit and records events of antenatal visits, events of L&D and immediate post partum/neonatal period. A discharge summary for the mother and infant(s) is also documented here.
- The record is specific to the individual pregnancy.
- New hospital records are created for earlier or subsequent pregnancies.
- Only reference to protocol participation is the label of the woman's study identification number.
  (This label is removed if the file is returned to the Hospital Medical Records file room, since the HIV status is considered confidential, and is not recorded in hospital charts.)
- Includes brief, one-line entry for each antenatal visit, to include date, estimated gestational age, Fetal heart ("heard"/"not heard", occasionally the actual rate is recorded), B/P, medications/indications.
- Antenatal ward notes record reasons for admission prior to labor.
- Operative notes are included for C-Section cases.
- Record of infant evaluation is sparse. Most infants had recorded Apgars of 10/10.

"Source File", aka "Patient Record"
(Referred to by monitoring/audit team as "Johns Hopkins file/forms")

- The shadow file in which clinic notes and abstractions from hospital charts are recorded.
- Study-specific clinic forms created by MU-JHU for recording study visits and other research-specific requirements.
- Includes original documentation for mother and infant(s) research clinic visits (scheduled and interim visits).
- Includes transcription of some laboratory data (on Eligibility Checklist form)
- Includes abstraction of on-study hospitalizations as captured by ward rounds nurse (Hospital Record Form)
- Not all forms include signature/date entries (e.g. Eligibility checklist form).

- Laboratory Requisition forms and forms returned from lab recording specimen storage are filed here.
- After about November 1998, original subject-specific laboratory reports, initialed by laboratory staff, are filed here.

Laboratory Source Documentation

- Beginning of study through approximately November 1998:
  - Four large (approx 3") binders contain line-listings of study data.
  - There are approximately 40-50 results, for various subjects and assays recorded on each page.
  - Pages are ordered by print date.
  - Results on each page are ordered by PID number and printed based on run date. If specimens are batched (e.g. HIV RNA PCR), then the source document may appear days or weeks after the specimen collection date.
  - Most of these are initialed by (reportedly) laboratory staff. The initials were not verified per the laboratory master signature log.
  - The monitors do not recall observing initials of either of the two on-site investigators on these line-listings.
  - The monitors recall observing, occasional initials of the data transcriptionist on these sheets.
  - Laboratory data from this time period was very difficult to locate and, in the interest of time, *for the most part, not verified* during record review.
- From approximately November 1998 through end of study individual laboratory reports are filed in "Source File".
  - Laboratory data from this time forward were verified during record review.

Hospital Records for non-obstetrical admissions

- New records are created for each individual non-obstetrical admission.
- These medical records are filed by the hospitalization number, not by client's name.
  - To identify hospitalization records, the fact that hospitalization occurred must be known.
  - Then, the hospitalization record number must be identified.
- During this visit, the MU-JHU staff reviewed their "source file" records for hospitalization numbers.
- During this visit, Dr. Philippa, on-site investigator, corresponded with the hospital medical director to request access to these records.
- Some non-obstetrical hospital records were secured for review by Tuesday, 26 February.

Additional Source Documents

Home Visit Logs

- Three Master Logs contain summaries of subject follow up. (Home visits are made if the patient fails to return to clinic for a scheduled visit.)
- Each home visitor has a logbook into which records of directions to the home and follow up visit details are recorded.

- Each home visitor also uses index cards (~ 5"x8") to record information prior to recording in her logbook.
- Used to document efforts made to track subjects lost to follow up.
- Reportedly reviewed at weekly Friday meeting of Visiting Nurses and Dr. guay. Served as bases for "Master Logs", which were intended as summary tabulations of ongoing follow-up attempts.
- One of two "Master Logs" was found to have been recently rewritten, reportedly because of the loss of the original in a "flood".
- Source used during the audit for identification of deaths not previously reported as SAEs.

"NVP Report" Books

- One book for each L&D ward
- Prepared by Midwifery staff (members of the research team)
  - Labor and Delivery and Immediate Post Partum Record
  - Birth and Newborn Record
  - Includes recording of study drug administration.

Ward Rounds Nurse Book

- One book used by the ward rounds nurse to record abstractions from in-patient hospital records and history obtained from subjects and/or family members.
- Source of hospital admission number (required for locating hospital charts)

II. RECORD REVIEWS

Records for 59 mother-infant pairs, including three sets of twins, were reviewed. Complete chart review, including verification of laboratory data recorded on the CRFs was attempted for four mother-infant pairs, however, verification of laboratory source documentation prior to late 1998 was not feasible due to the problematic organization of the four laboratory source binders (described, above). The remaining 55 subject records were reviewed to verify or identify: 1) eligibility for study entry and dosing; 2) clinical endpoints; 3) SAE and AE reporting errors; and 4) drug administration errors. Elements of eligibility verified for maternal enrollment included verification of informed consent, maternal age, gestational age, laboratory toxicities (as feasible), exclusionary co-morbid conditions and concomitant medications. Exclusion criteria for maternal and infant dosing were also verified.

Source document files that were used in the review included 1) the hospital record for antenatal visits, labor and delivery and birth and 2) the "Source File" (or "Johns Hopkins file"). Other hospitalization records for mother- and infant-illnesses were not available for review until the final day of the monitors' visit. The labor and delivery records recorded minimal information about the subjects and did not record reference to HIV status, protocol participation, or study drug administration.

The record of drug dispensed/returned as recorded on the JHU file was not verified using pharmacy logs. The calculations for infant dosing were not verified for all records reviewed.

Records for the following mother infant pairs were reviewed:

Table 5: Mother-Infant Pairs

Mother/Infant Pair ID Number		Mother/Infant Pair ID Number	
1	0010	31	0599
2	0020	32	0601
3	0023	33	0615
4	0024	34	0621
5	0042	35	0624
6	0046	36	0627
7	0054	37	0628
8	0057	38	0641
9	0071	39	0657
10	0100	40	0664
11	0164	41	0665
12	0175	42	0685
13	0191		0685-2 (twin)
14	0197	43	0691
15	0404	44	0695
16	0441	45	0696
17	0443	46	0711
18	0444	47	0730
19	0462	48	0740
20	0485	49	0751
21	0496	50	0770
	0496-2 (Twin)	51	0777
22	0501	52	0788
23	0514	53	0790
	0514-2 (Twin)	54	0834
24	0518	55	0842
25	0526	56	0850
26	0544	57	0867
27	0570	58	0887
28	0571	59	0888
29	0576		
30	0580		

III. SUMMARY OF FINDINGS

Table 6: Summary of Findings

	Number of mother/infant pairs examined	Number of pairs with findings (Percent)
Met eligibility criteria for enrollment &/or dosing[1]	59	52 (88%)
Dosing Error[2]	59	28 (47%)
Any of seven protocol-defined serious outcomes[3]	57	23 (40%)
	Number of mother/infant pairs examined	Number of pairs with finding (Percent)
Unable to verify HIV-1 endpoint due to stillbirth, neonatal death or lost to follow-up[4]	62	8 (13%)
HIV positive at end of follow-up[4]	54	18 (33%)

[1] All protocol-defined inclusion/exclusion criteria could not be verified using available source document files.

(e.g. Lab source documentation prior to late 1998. Eligibility checklist form included entries completed at various dates, none of which were signed or dated.)

[2] Delay in treatment, did not self-administer drug before presenting to labor ward, child received too many or too few doses of AZT, did not meet eligibility criteria to receive study medication.

Table 7. Summary of Findings by Subject ID Number
See Attachment 4 for detailed worksheets

Eligibility Violations	ID number	Total
• Did not meet eligibility requirements for enrollment (uncontrolled hypertension, 34 week gestation (twin pregnancy), Hgb 5.6)	0042-0 0685-0 0601-0	3
• Mother given Valium at enrollment visit for hypertension	0441-0	1
Dosing Error	**ID number**	**Total**
• Study baby died while sharing crib with non-study baby. Study drug administered to non-study baby following change in nursing shift.	0526-1	1
• Mother received Valium prior to receiving hospital-administered study drug	0580-0	1
• Mother dosed in 2nd stage of labor	0624-0	1
• Infant did not receive study drug	0730-1	1
• Subject didn't self-administer dose prior to presenting to labor ward	0691-0 0024-0 0020-0 0010-0 0614-0 0571-0 0624-0 0751-0 0071-0 0191-0 0621-0 0628-0	13

	0601-0	
• Dosing (initial and/or subsequent) delay while on L&D ward	0777-0 0621-0 0496-0 0444-0	4
• Too many doses AZT administered to infant	0462-1 0777-1 0023-1 0867-1	4
• Too few doses AZT administered to infant	0665-1 0711-1 0571-1 0571-1 0615-1	5
• Error in reporting/transcribing drug-administration data	0462-0 0462-1 0526-0 0614-0 0501-0	5
Unreported Serious Adverse Events (SAEs)	**ID number**	**Total**
• Congenital anomaly	0691-1 0526-1 0770-1	3
• Death after 18 month FU visit (infant) or 6 wk FU visit (Mother)	0518-1 0164-0	2
• Hospitalization	0834-1 0685-1 x 2 0685-2 0046-0	5
• Experienced potentially life-threatening event but because subject was not hospitalized or the event was not recognized (Grade 4 lab value), an SAE was not reported. (Hospitalizations were rare events due to local standard of care, lack of hospital beds or mother's unwillingness to accept admission for her infant.)	0054-1 0571-1 0685-2 x 3 0842-0 0867-1 0042-0	8
• Cancers listed in Ward Round Nurse's hospitalization summary were not mentioned in the hospitalization SAE report and not reported as separate SAEs	0164-1	1
Total Unreported SAEs		**19**
Unreported and Underreported Adverse Events (AEs) and SAEs	**ID number**	**Total**
• AE form (non-SAE) not completed during the 6 week follow-up period for AE reporting	0777-0 0197-1 0024-1 0164-1 0023-1 0730-0 0751-1 0867-0 0867-1 0191-0 0621-0 0628-0 0443-1	14

	0444-1	
• SAE/AE was graded less seriously than was indicated by reading the clinical description in the source document file (e.g. Grading of rashes did not follow DAIDS supplemental toxicity table for severity of cutaneous/skin rash/dermatitis AE's; or life-threatening events and Grade 4 lab toxicities were graded as mild to moderate)	0462-1 0850-0 0024-1 0570-1 0615-1 0628-1 0601-1	7
HIV status	***ID number***	***Total***
• Unable to verify due to intrauterine fetal demise, neonatal death or lost to follow up	0695-1 0691-1 0526-1 0441-1 0770-1 0641-1 0071-1 0042-1	8
Other Errors	***ID number***	***Total***
• Transcription error other than drug-related data	0580-0 0751-1 0696-1 0444-1 0501-0	5

[1] Two or more concordant results of HIV-1 RNA PCR assays drawn at separate visits.

III. HIV-1 RNA PCR ENDPOINT VERIFICATION

The following table documents additional subjects for whom positive or negative HIV-1 RNA PCR results were verified per laboratory source documentation.

Table 8. HIV RNA PCR Assay Results Verified with Corresponding CRF

ID Number	Visit Type
0005-1	Fourteen week
0007-1	Fourteen week
0008-1	Six week
0008-2	Six week
0009-1	Fourteen week
0013-1	Fourteen week
0020-1	Fourteen week
0023-1	Birth
0023-1	Six week
0027-1	Fourteen week
0029-0	Six week
0032-1	Birth
0032-1	Six week
0038-0	Six week
0038-1	Six week
0041-1	Six week
0050-0	Delivery
0061-0	Delivery
0062-0	Delivery
0062-1	Birth
0062-1	Fourteen week
0065-0	Delivery
0069-0	Seven day
0070-1	Fourteen week
0072-0	Six week
0073-0	7-day
0074-0	Delivery

ID Number	Visit Type
0086-0	Delivery
0093-0	Six week
0093-1	Six week
0103-0	Delivery
0158-1	Six week
0170-0	Eligibility
0176-0	Eligibility
0178-0	Eligibility
0182-0	Six week
0185-0	Eligibility

0189-0	Six week
0189-1	Six week
0192-1	Six week
0194-1	Six week
0195-0	Six week
0195-1	Six week
0212-0	Six week
0212-1	Six week
0215-1	Seven day
0217-1	Six week
0227-0	Eligibility
0231-0	Eligibility
0237-0	Six week
0237-1	Six week
0241-0	Delivery
1110-1	Fourteen week

Adverse Events: Routine Identification and Reporting

The process for reporting AEs to the database was explored with, and described by, the lead data manager, Ms. Musisi, who was the lead data transcriptionist through much of the trial. This process was not documented and had inherent flaws including the level of accountability for identification of events, absence of shared accountability and absence of quality control measures to ensure completeness of reporting. Responsibility for initiating the AE form completion lay with the data transcriptionist, not the clinicians.

- The source documentation form completed by the clinician during the clinic visit included "yes" and "no" check boxes for whether there had been any illness or adverse events.
- If this was checked, "yes", the data transcriptionist would forward the source file to one of the on-site investigators for completion of the AE form.
- If the AE was determined to be serious, the investigators would secure the signature of the Ugandan PI. On occasion, one of the on-site investigators would sign the PI signature line.
- The process appeared to be driven by the transcriptionist's recognition of an AE and there did not appear to be any quality control mechanisms in place.
- For the most part, neither the Principle Investigator nor any sub-investigator actually saw the patient experiencing an AE or SAE. Completion of the form, as well as decisions on seriousness, causality, relation to study drug and severity were made on the basis of second hand information.
- Unreported AEs were identified in which the illness/AE check box had been checked, "yes", but where no AE form was completed.
- AEs (non-SAEs) were not reported after six weeks for mothers or infants.

Serious Adverse Event Reporting

The procedure for reporting SAEs was not included in the study-specific procedures manual provided by FHI prior to the visit. There was a copy of AE Reporting Procedures in the SSP binder and this was made available to the monitors upon arrival.

The procedures were discussed with the staff and are described as follows:

- Only hospitalizations and deaths were reported as SAEs before or after six weeks of life.
- Grade 4 AEs were reported as SAE's only if they resulted in a hospitalization.
- After six weeks of follow up, infant-adverse events and illnesses appear only as an 'indication' on the concomitant medication CRF, and are thus recorded only if the child received treatment for the illness. The indications on the concomitant medication sheets are not graded. (Thus it would not possible to know if 'malaria' meant cerebral malaria or slide-negative malaria.);
- Deaths were not reported after 18 months of age for infants or after six weeks for mothers, even if the death was the result of an ongoing medical problem experienced during the study's 18-month follow-up period. AEs experienced during the 18-month follow up period were not always followed to resolution;
- A stillbirth was reported as a Grade 3 serious adverse event for the mother;
- Adult severity grading criteria for adult hemoglobin values were modified from the DAIDS toxicity table as follows:

- 7.0-7.5 g/dl Grade 1
- 6.0-6.9 g/dl Grade 2
- 5.0-5.9 g/dl Grade 3
- <5.0 g/dl Grade 4

- Drs. Guay or Musoke based the grading of the SAEs primarily on the transcribed hospitalization summary. The clinician treating the child was consulted if necessary;

Serious Adverse Event Documentation, Grading and Clinical Follow-up

- The grading assigned on the SAE reports were not well documented in the John Hopkins files. There were several instances in which a grade 2 or 3 was assigned to a hospitalization that appeared to be life threatening from the clinical description;
- Very few events were ever assigned a grade 4- life threatening (2 or 3 out of the 60 records reviewed);
- The grades assigned to the adverse events were usually based on clinical impression and often did not correlate with the corresponding laboratory marker (i.e., anemia would be assigned a 'moderate' severity rating based on a clinical description of 'moderate pallor', regardless of the true hemoglobin value); and
- There was no source documentation that the physician/investigators reviewed or graded lab results. Accordingly, it is possible that laboratory abnormalities went unnoticed and AE forms may have been missed.

HIV RNA PCR Endpoint Verification

As previously described, laboratory source documents through late 1998 were presented as line listings printed by report date, including results for multiple subjects per page and filed in four large binders. The results are difficult and time consuming to locate, and many entries could not be verified.

- By the end of 1998, subject-specific laboratory reports were printed and filed in the "Johns Hopkins File." These were used to verify the 12 and18 month HIV RNA PCR endpoints recorded on CRFs;
- Additionally, the results of 53 HIV RNA PCR assays from the line listing of laboratory results (see table, above) were compared to the CRF entries. All were entered correctly.
- Laboratory documentation of assay results and package inserts for assays used were not reviewed.

Compliance with Protocol Schedule of Evaluations

The blood collected during the study did not always follow the schedule of evaluations outlined in the protocol. For example:

- 12 month HIV-1 RNA PCR and 12 month HIV ELISA assays were added later in the study;
- CD4 counts were done on all children at 12 and 18 months, even if they were HIV negative;

- The laboratory stored samples of plasma and serum at each blood collection (if there was remaining specimen after testing) rather than following the schedule of evaluations;
- There is poor documentation that blood was collected on filter paper at each blood draw. Records documenting filter paper collection during the first year or so of the study are not on site, and the filter paper samples have reportedly been sent to JHU, although this was not verified at this visit.

Other General Observations

- There were few non-drug related transcription errors (i.e. from JHU files to CRFs) identified during the thorough review of four records. Five such errors were identified and they were minor errors. However, in comparing the information that was summarized on the John Hopkins files with the labor and delivery source document file, several significant discrepancies were noted;
- There were very few children lost to follow-up (2) and very few missed visits.

Prepared by: Date:

Judith Chamberlin, P.A., Dr.P.H. and
Susan Lander, B.S.N., M.P.H.

V. GENERAL OBSERVATIONS

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Prepared by: Date:

Judith Chamberlin, P.A., Dr.P.H. and
Susan Lander, B.S.N., M.P.H.

PRE-INSPECTION VISIT REPORT
PHARMACY AUDIT REPORT

Name of Clinical Site: **Makerere University- Johns Hopkins University Research Collaboration**

Protocol Title: **A Phase III Placebo-controlled Trial to Determine the Efficacy of Oral Nevirapine and the Efficacy of Oral AZT in Prevention of Vertical HIV-1 Transmission**

Name and Address of Pharmacy: **Kampala, Uganda**

Date of Audit: **20-26 February 2002** Conducted by: **Susan Lander, B.S.N., M.P.H.**

Table 9: Investigational Pharmacy Personnel

Sematiko Gordon Katende	Pharmacist	No (The part time pharmacist is no longer employed by the MU-JHU Research Collaboration.
Laura Guay, M.D.	Co-Investigator	Y

I. MAINTENANCE OF RECORDS

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No). Provide comments whenever necessary or helpful.

Table 10: Pharmacy Records

[illegible]	[illegible]	[illegible]	[illegible]
A. Are the following protocol-specific documents present?			
1. Form FDA 1572	X		The 1572s are on file with the site regulatory documents.
2. Prescriber signature list		X	Prescriptions are not used in this study.
3. Most recent version of the protocol for which the site has IEC/IRB approval	X		On file with site regulatory documents.
4. Subject study assignment list		X	A study subject assignment list was not used for this study. The subjects are assigned to the next consecutive study number and the treatment assignment is identified by the labeling of pre-prepared study drug bottles. The treatment arm noted on the bottle is transcribed into the enrollment log and recorded on the enrollment form in the source file, as well as the CRF.
5. Drug ordering instructions		X	Ordering instructions were not observed by this monitor.
B. Are the following records accessible only to the site pharmacist or his/her designee?			
1. Study assignment lists			N/A. The treatment assignment is not documented on a list at the site. When the individual patient kits were opened, the treatment assignment was identified on the bottle and then recorded on the enrollment visit source document.
2. Investigational agent accountability/inventory records		X	The inventory records are currently stored in the clinical research offices. Dr. Guay was advised to store the regulatory and other records in a locked steel file cabinet in the file room.
3. Order forms/shipping receipts	X		Four of five shipping invoices are on file. There is no invoice for the first shipment, which was hand delivered by the U.S. PI to the site. There is, however, documentation, itemizing contents of this shipment recorded on the National Drug Authority Import/Export application, prepared by Dr. Guay.
4. Subject-specific profiles, if used			N/A

Table 11: SECURITY AND STORAGE OF THE INVESTIGATIONAL DRUGS

A. Inspect the investigational drug storage area.			
1. Are the investigational drugs stored under double lock or in a limited access area within the pharmacy?		X	The drug was stored in various locations: • Bulk supply was stored in a locked cabinet in the apartment of Dr. Guay. • Individual bottles of supply were transported from the bulk supply to a locked room in the Old Mulago antenatal clinic area (no longer in existence), from where the study drug was dispensed into the individual bottles. • The study drug kit was opened upon enrollment / randomization of the woman and she is provided with a bottle containing medication for her first dose, to be taken upon onset of labor. • The remaining supply in the kit includes a bottle of maternal drug and two bottles each of AZT or NVP. These are then taken to the Labor and Delivery ward of the hospital where the woman intends to deliver. Old Mulago has a locked room in which the kits and the patient's records are stored. New Mulago has a locked cabinet for storing the patient's drugs. • Both wards also keep replacement supplies in case the subjects require additional medication.
2. Are the investigational drugs stored according to the manufacturer's specifications?	X		Drug was stored at room temperature. However, the temperature conditions of the storage areas were not monitored during the trial.
3. Outdated drugs are not mixed with the supply.			Not assessed. Drug is no longer on hand.
4. Is refrigerator and/or freezer storage available?			Not applicable
a. Refrigerator			
b. Freezer			
c. If yes, describe location of refrigerator and/or freezer and method of monitoring temperature. Note: It is recommended that if refrigerator and freezer are similar in appearance and within close proximity to one another they should be clearly marked to prevent errors in drug storage.			

Table 12: DRUG ACCOUNTABILITY, PREPARATION AND DISPENSATION

A. Accountability:			
1. Do the inventory additions listed on the investigational account-ability records agree with the shipment receipts?	X		There is a record of bulk drug received from the CRPMC and stored in Dr. Guay's apartment. This record notes dates that supply was removed and taken to the Old Mulago ANC pharmacy. These entries were not all made at the time of transfer, they are not dated or initialed, nor is this record an original copy. The staff was advised to secure and file the original copy within the study drug binder. NOTE: There are no shipping or accountability records for the supply received in the first two shipments received from Johns Hopkins.
2. Are the accountability records legible and complete with each entry initialed by the pharmacists of record or other authorized personnel?	X		The site pharmacy plan noted that the pharmacist and the on-site investigators would dispense drug. But there is evidence that other staff also dispensed study drug on occasion. Other staff who dispensed study drug include: • Margaret Achom, Study coordinator • Wasana Aida, , (Role undetermined) • Kabasonga, (Role undetermined) When Dr. Guay was asked about these, she noted that there is a list of all staff who dispensed study drug. It was not clear to this monitor that all of these staff members were on this list. A copy of the list was not made during the site visit.
Note: Computerized inventory and accountability logs are acceptable; however, they must include entry codes or initials of authorized personnel for each entry and must be reproducible in hardcopy if requested.			
3. Are there any entries in the accountability records which indicate dispensing of investi-gational agents to persons other than subjects enrolled in this/ these studies?	X		Following death of study baby 0526-1, the non-study baby who shared the same crib was administered study drug.
4. If study drug is commercially available, are procedures in place so that the study drug is not mixed with the general supply?			Not applicable
5. Compare the inventory balance documented on the accountability records with the actual physical inventory.			
a. Is the inventory correct?			Drug is no longer on site. Destruction records are on site and document destruction of remaining study drug on 4-Jan-2002.
b. If No, provide actual numbers of the agent counted as well as the amount recorded on the accountability record for each discrepancy noted. Indicate either the reason for the discrepancy or whether the reason remains unclear after discussion with the pharmacist. If the reason remains unclear, discuss possible actions or procedures which might be developed to prevent recurrence, if appropriate.			

Drug	Accountability Record	Inventory Amount

Explanation/Discussion:			
6. Check the investigational agent supply. Determine if the amount on hand seems reasonable taking into consideration the following criteria: number of participants enrolled at this site; the treatment arms to which the participants are assigned; whether or not study accrual is active; and the amount of drug routinely dispensed to a participant at each visit.			
a. Is the amount of drug supply on hand reasonable?			Drug is no longer on site.
[redacted]			
B. Drug Preparation and Dispensing			
Review a sampling of prescription records for a minimum of ten subjects and assess the following items. List prescriptions reviewed: • Prescriptions and dosage calculations were verified for a number of the charts reviewed. No problems were identified in these subjects (*not recorded.*)			
a. Has the site pharmacist prepared protocol-specific written instructions or a synopsis of the protocol that provides pharmacy personnel with information on proper dispensing and preparation procedures?		X	
b. Are the prescriptions signed by an authorized prescriber whose name appears on the Form FDA 1572?			N/A
c. Do the study treatments dispensed match those indicated on the treatment assignment list?			There is no study treatment list to verify this information. The treatment assignment was documented on the bottle itself and transcribed to the enrollment book, the source file and the CRF.
d. If the dose must be calculated based on weight or body surface, has the dose been calculated correctly?	X		For those infants checked, yes.
e. If the investigational agent is a liquid or injectable solution, is the dose volume accurate for the dose?	X		As above, yes
f. If the study agent requires compounding/admixing by the pharmacist, is there a clear record of the agents and quantities used and the calculations involved?			Not applicable.
g. Was the quantity of drug dispensed sufficient for the protocol-prescribed dispensing interval? (The amount dispensed may be in excess as determined by site policy.)	X		Generally, yes. In cases of extended labor, the L&D staff would use the replacement stock on hand.
h. Do the pharmacist's notations on the prescriptions regarding the dispensed investigational			Not applicable.

agent and the quantity dispensed have a corresponding entry in the accountability log?			
2. Is it routine practice at this site for prescriptions to be prepared in advance of scheduled protocol visits? If yes, describe the routine dispensing practice:	X		The coordinator reviews the daily clinic schedules to determine the number of women scheduled for enrollment at each antenatal clinic. She left a note to the part time pharmacist who would prepare enough kits for both clinics. After the women arrived to the clinic, signed consent and had seen the clinic physician for verification of eligibility (gestational age, etc.), the staff would notify the coordinator who would return to the pharmacy supply room to retrieve the next sequential kit. She would then return to the clinic "Enrollment Room" where the box would be opened.
3. How does the investigational pharmacist usually receive study drug prescriptions? Describe:			As noted above, the coordinator provides a note that a given number of kits are required that day.
4. To whom does the investigational pharmacist dispense study drugs? Describe:			The drug is collected by the study coordinator.
5. Does the site have a routine procedure to account for participant drug returns, broken vials, etc.? Explain:			Drug returns are reported in the source file for all infants in the AZT arm at study week 6, as is the maternal report of home dosing of the infant. There is a return log for all subjects, which documents the dose taken, and the amount returned unused.

Table 13: QUALITY ASSURANCE AND COMMUNICATION

A. Quality Assurance			
1. Does the institutional pharmacy have written general policies and procedures for handling investigational drugs?		X	The HIVNET Manual of Operations (February 28, 1997) has a section tabbed for "Investigational Product Inventory and Storage" but the page included notes that, "This section is being written by PRAB. When finalized, it will be incorporated into the HIVNET MOP". The FHI Protocol Manager reported that this document was never provided for the manual.
2. Has the pharmacist of record developed special policies and procedures relevant to the conduct of the investigational drug studies?		X	
3. Are routine physical inventories performed at regular intervals and documented?		X	Intermittent inventories were conducted and documented by Dr. Guay who reported that these were not conducted routinely. The record reflects that they were conducted at a frequency of about once each month.
a. If yes, date last performed:			
4. In cases of absence of the pharmacist of record, have provisions been established for back-up coverage?	X		The on-site investigators, Drs Guay and Musoke also dispensed study drug into the kits. For the most part, Dr. Guay provided this coverage. There was also evidence of dispensations by three other staff, as noted in Section III, above. During a period of about two months during the fall of 1998, there was documentation of another staff member, Vidya Gopal, transporting bottles of study drug from the bulk supply to the pharmacy. Dr. Guay said that she had a key to her apartment and to the locked cabinet within where study drug was stored, and that there was a supply of extra keys for all offices and for this cabinet maintained by the secretary.
B. Communication			
1. Is there a method in place for informing the investigational pharmacist of a subject's treatment assignment at randomization?	X		The labeling of the bottles in the kits notify the pharmacist of the treatment assignment.
2. Is there a method for assuring the investigational pharmacist that research subjects have given informed consent prior to dispensation of the study treatment?		X	The pharmacist is not aware of the informed consent process, but the patient ID is not assigned until enrollment. The coordinator who dispenses the kit to the patient assigns the patient id based upon the number on the box. The informed consent process takes place directly prior to the dispensation and several staff members involved discuss the study and provide opportunities for questioning.
3. Is there a standard procedure by which the site pharmacist of record routinely receives pertinent communication from other site personnel? (In particular, IEC/IRB approvals, protocol modifications or clarifications, dispensing considerations,	X		The pharmacist received information about how many kits to dispense each day. No regulatory documents were retained in the pharmacy storage room. There was a note within the pharmacy log from the coordinator requesting that the pharmacist dispense 5 tablets of AZT, instead of 3, due to shortage. (This note is not dated.) There is a note from 17-Feb-99 within the pharmacy log from the L&D staff requesting dispensation of additional replacement

handling instructions)			AZT.
4. Does the pharmacist maintain a file of protocol-specific correspondence?		X	
5. Is the pharmacist routinely notified when participant study medication is modified between scheduled protocol visits?			Not applicable.
6. Does the pharmacist have a method for documenting modifications of investigational drug treatment which occur between clinic visits?			Not applicable.
7. Does the investigational pharmacist participate in regular meetings with the clinical research staff?			The part-time pharmacist does not participate in the staff meetings, but Dr. Guay reports that meetings were held with him to provide initial orientation of training for the protocol requirements and that they would meet to discuss changes in the study (e.g. the decision to reduce the volume dispensed).

8. Other Observations?	X		• Remaining drug supply was destroyed on 4-Jan-2002. There are four gold NCR sheets on file documenting the destruction of the drug.
			• A final accountability record, signed and dated 4-Jan-2002 by Dr. Guay is on file.
			• Source files and home visit logs were reviewed for seven subjects who were assigned to placebo, but not yet delivered, at the time of unblinding in February 1998. There was no documentation that placebo was replaced with active product prior to delivery.
			  • There was a note in the home visit log for subject 071 noting, "mother collected to get AZT rather than placebo." This note appeared to be added later to the record, was added to a portion of space between two longer notes, was made with different ink and was not signed or dated.
			  • There was no documentation regarding unblinding of the following subjects: 047, 050, 051, 060, 061, and 069
			  • It is not clear when the site staff received the unblinding list.

Prepared by: Date:

Susan Lander, B.S.N., M.P.H.

Westat
Clinical Research Operations and Monitoring Center

PRE-INSPECTION VISIT REPORT
LABORATORY AUDIT REPORT

Name of Laboratory	**Core Laboratory, Makerere University-Johns Hopkins University Research Collaboration**
Address:	**Kampala, Uganda**
Date(s) of Visit:	**23-February 2002**
Conducted by:	**Susan Lander, B.S.N., M.P.H. and Jacquelyn Burns, M.P.A.**

Laboratory Personnel Involved with the Study:

NAME	TITLE
Constance Ducar	Laboratory Administrator

Background Information

The Core Lab provides services to MU-JHU research projects and also some private payment services. The laboratory does not provide services for routine clinic or inpatient care. Due to time constraints and staff availability, a detailed laboratory audit could not be performed.

Other laboratories used during the course of the trial include:
1) Lymphoma Lab at the Hospital – for back up during hospitalizations
2) Microbiology Lab at the Hospital
3) Stat Lab in research clinic, where Hgb and Malaria Smears are performed

These other labs were not audited.

Indicate if the following topics were addressed (check N/A, if not applicable) and provide comments as applicable:

Table 14: Laboratory

TOPIC	YES	NO	N/A	COMMENTS
1. Introductions	X			
2. Overview of Agenda	X			
3. Sign lab monitoring visit log		X		
4. Laboratory director's CV (secure copy), publications, relevant experience	X			Ms. Ducar is a Medical Technologist with US laboratory experience and industry experience. This was a limited visit. The CVs were not reviewed. The qualifications of Ms. Ducar appear to appropriate if she is provided appropriate oversight by a Laboratory Director.

5. Discussion of qualifications, ongoing training, roles and responsibilities of individual laboratory staff	X			There are seven Ugandan technologists, one laboratory assistant, one messenger, two data entry staff and two cleaning staff.
6. Laboratory workload	X			The workload appeared appropriate at the present time, but this was not reviewed for time period of study accrual. Studies that were conducted concurrently with HIVNET 012 were not reviewed during this visit.
7. Hours of operation			X	
8. Describe after-hours, holiday and weekend staffing schedule for receiving and processing specimens			X	This was not discussed in detail, although we did learn that there were at least three other laboratories that provided back-up service for some study required laboratory assays.
Quality Assurance				
9. Does the laboratory have documented Quality Assurance (QA) procedures?	X	X		Prior to 1998, there was not an active QA program. Since Ms. Ducar took over the administration of the laboratory there have been ongoing QA programs and the activities are documented in annual summaries. The laboratory does a daily QA run for many of its laboratory tests, although a report of these activities was not reviewed during this visit.
- Are these procedures signed by the Laboratory Director and available for laboratory staff?		X		These are not signed by Dr. Jackson, the Laboratory Director. They are signed by Ms. Ducar.
- Is documentation available to verify QA procedures are implemented to ensure study data quality and integrity?			X	Not assessed.
10. Does the laboratory have Standard Operating Procedures (SOPs) procedures?	X			Ms Ducar was advised that SOPs were in place prior to her arrival, but she was never able to locate documentation of these SOPs. Following her arrival, SOPs were developed and implemented.
- Are these procedures signed by the Laboratory Director and available for laboratory staff?		X		These are not signed by Dr. Jackson, the Laboratory Director. They are signed by Ms. Ducar. The SOPs are in binders in the office. Presence of SOP manuals in other work areas was not verified.
Tour of Facilities				
11. Laboratory Facilities	X			
- Proximity to Clinic	X			The laboratory is housed in a free-standing building on the grounds of Mulago hospital. It is across the street from the research clinic.
12. Office Space	X			Ample desk and shelf space, and locked steel file cabinets are available.
13. Record Security and Storage	X			Regulatory documents, procedures manuals and documentation of QA activities are stored in the office of the administrator. Records of specimen testing runs are stored in a locked file room on the lower floor of the lab.

REVIEW OF REGULATORY DOCUMENTS

14. Is there a copy of the approved protocol and all pertinent amendments?	X			
15. Is there a copy of current protocol procedure manual and procedure updates?		X		The assays run for the study were also run by the lab for other studies, so no protocol-specific procedures were in place during the study.
16. Is there a protocol-specific correspondence file?	X			
17. Is there a copy of current laboratory certification, licensure or accreditation?		X		
18. Does the laboratory participate in proficiency testing?	X			During the study, the laboratory participated in the CDC-MPEP program for HIV rapid testing and Western blot. In 2001, the lab began partipating inproficiency testing with 1) CAP for hematology, chemistry and malaria smears, urinalysis and HIV RNA quantitative testing; 2) UK-NEQAS for CD4/CD8; and 3) QASI for CD4/CD8 testing. A sample exchange program between the lab and the local Joint Commission on but the two labs utilize different equipment, so adequate comparison of results was not possible.
19. Is documentation available for actions taken if proficiency testing indicates there is a problem with an assay?			X	
20. Is there a copy of normal lab values?		X		Normal laboratory values for the study population are not available. The possibility of deriving normal values from available study data was explored by Dr. Hensley and Ms. Ducar.
21. Do the appropriate laboratory personnel have certification to ship dangerous goods?		X		Ms. Ducar was trained by Dr. Guay, who is not IATA certified. Dr. Guay reported that she was trained by Dr. Jackson. Dr. Jackson reported that he did not receive IATA certification. Subsequent to this visit, Dr. Jackson reports that the CD-ROM for IATA certification was provided to Ms. Ducar and that she is now certified. Documentation of this was not reviewed.
22. Does the laboratory have certification for containment equipment?			X	Not assessed.
23. Does the laboratory have an Exposure Control Plan?	X			Ms. Ducar reports that there is post exposure plan in place, however, this is not always implemented as many of the Ugandan staff do not wish to have HIV testing performed.
24. Is there a current copy of the laboratory signature sheet?	X			This is reinitiated every year and there are several copies of this on file going back to about 1997. Dr. Jackson had not signed signature log for past several years, although his signature was on the 1997 list. Ms. Ducar was advised to secure his signature on the more recently prepared logs.
25. Other Observations?		X		

LABORATORY CAPABILITIES

26. Is the Specimen processing area clean and well organized?	X			
27. Is there adequate storage space for document retention?	X			
28. Other Observations?		X		
29. Are facilities, equipment and resources adequate to meet the Bio-safety level requirements for the study?	X			*Record Biosafety level of the lab*: BL-2
30. Are appropriate and labeled containers available for disposal of hazardous waste?	X			
31. Other Observations?		X		
32. Is the laboratory equipment acceptable and sufficient for the purposes of the study?	X			
33. Does the laboratory have back-up procedures in place for equipment failure or malfunction?	X			Specimens are sent to another local lab (Name not obtained) should equipment fail. Some older equipment (e.g. coulter counter) has been retained in the lab and could be used for back-up.
34. Does the laboratory keep an updated log of all routine, daily QC parameters monitored for each instrument?			X	Not assessed.
35. Are maintenance records maintained for equipment?			X	Maintenance records were not reviewed or verified during this audit. Ms. Ducar reports that the lab had a Servicing contract with Techmed Nairobi and equipment is calibrated every 6 months.
36. Are there certification documents for protocol required equipment? List equipment and certification expiration dates.			X	Not assessed.
37. Other Observations?		X		
38. Is there a reagent log to document receipt, preparation and expiration dates?			X	Not assessed.
39. Other Observations?		X		

SPECIMEN MANAGEMENT

The monitor will review records to assess specimen management procedures.

Specimen Receipt	Y	N	NA	COMMENTS
40. Is there a documentation and inventory of specimens received?	X			
Specimen Processing	**Y**	**N**	**NA**	**COMMENTS**
41. Is there documentation of specimen processing related parameters (reagent lot #, kit #, reaction times, reaction temperatures, etc.)?			X	Not assessed.
42. Are appropriate positive and negative controls being used with each run?	X			Ms. Ducar reports that controls are run daily.
43. Is there documentation of actions taken when controls fall outside of the acceptable range?			X	Not assessed.
44. Is there documentation of actions taken when study samples are used but the study procedure fails?			X	Not assessed.
45. Are appropriate biosafety procedures being followed when processing specimen and discarding hazardous waste?	X			
Reporting of Results	**Y**	**N**	**NA**	**COMMENTS**
46. Are the test reports communicated to the physician/clinician in a timely manner as per the study operating procedures?			X	Not assessed. From the documentation available in the clinical area, it appeared that reports were printed regularly. However, there was no documentation that suggested lab abnormalities were being reviewed or graded by the clinicians. From late 1998 onward, lab results were filed in the subject's "source file" so that clinicians seeing the subjects could review these results. Prior to that, line listings were printed out and these were observed to be initialed in the lower right hand corner, presumably by laboratory staff.
47. Have there been any life threatening or "panic values"? If so, were these documented and reported promptly?			X	Not assessed.
Specimen Storage	**Y**	**N**	**NA**	**COMMENTS**
48. Is a specimen storage log available to document specimen type, subject, date of collection and location?	X			Computerized records of specimen storage are available. This system records location of the specimens, occurrences of thaws and shipment of specimens. A printout of stored and shipped specimens was recently provided to the clinical research center. A record of filter paper specimen storage was not provided and the documentation of this protocol requirement could not be thoroughly assessed during this visit.
49. Are the specimens being stored as per the protocol specifications?	X			Specimens are stored in a -70 freezer.
50. Are the specimens for storage being appropriately labeled as per the			X	Not assessed.

protocol specifications?				
51. Is there a daily log of temperatures for the refrigerators and freezers?	X			There is a log on the outside of the freezer and this records daily temperatures. The lab administrator says that there are files of freezer logs from at least 1998 onward. There may be logs for 1997. Logs used during the trial were not reviewed during this audit.
Shipping			N/A	COMMENTS
52. Is there documentation of specimens shipped out of the laboratory	X			As noted, there is a computer record of shipments of specimens which have been sent to Johns Hopkins University.
53. Are specimens shipped per protocol requirements?			X	Not assessed.
Additional Comments				COMMENTS
54. Describe specimen-tracking procedures employed during specimen collection, processing, testing, transport and storage	X			Specimens are first assessed to determine if acceptance criteria are met. Then an accession number is assigned and the specimen is recorded in the computer system. After the specimens are processed, aliquots are distributed to the technicians, and work orders are generated from the computer. These work orders remain outstanding until the results are entered into the system. Prior to distributing lab reports to the clinic, a series of five checks is documented between the original run records, assay controls and data entry. The final lab report is initialed by Ms. Ducar or her designee and sent to the clinic. Prior to November 1998, laboratory staff initialed the lab line listings before being sent to the clinic staff.
55. Other Observations?		X		

DATA MANAGEMENT

TOPICS ASSESSED				COMMENTS
56. Are data reports generated (or case report forms completed) and submitted to the study data center in a timely manner?			X	Not assessed.
57. Has the laboratory received requests for data clarification? If so, are responses documented with the CRFs?			X	Not assessed.
58. Other Observations?		X		

ADDITIONAL COMMENTS:

- **Run records and package inserts for HIV-1 RNA PCR test kits were not reviewed.**
- **Documentation of presence and location of stored filter paper specimens were not reviewed. These records are reportedly not computerized and the presence of such records was not verified.**

Prepared by: Date:

(Signature)

Discussion and additional observations, (Including Review by Dr. Hensley)

Reviewing Records of Patient Participation:

Although access to hospital records for subjects admitted during the course of the trial had been sought by the Boehringer team in January and requested on several occasions prior to our visit, no hospital charts other than the obstetrical records had been provided to WESTAT by the time of our arrival on 2/25/02. Moreover, only repeated requests and very frank conversations with the sub-investigators ultimately resulted in some progress, with the first such records arriving for review by the third day of our visit.

Problems accessing hospital charts had been previously (January) noted by BI, and had been described verbally by the sub-investigators during pre-audit telephone calls. The reason was said to be both the system for storage and the personnel responsible for storage.

System: Inpatient charts for the hospital are said to be maintained in a room of approximately fifteen by twenty (15x20) feet. A new file is prepared for every patient, for every submission. Each infant can be theoretically be identified uniquely by two means, an admission number from the birth record, and by his/her name. The admission number is also referred to as a registration number and is provided to mothers as a card given at discharge. In order for the record of a hospitalization to bear the same number previously associated with the infant or mother's name, the mother must reportedly bring the card with her when she brings the baby to the hospital or clinic. If the mother has lost the card, or forgets it, a new number is assigned for the new hospitalization. Identification would then rest on name, and since each child may have an English name and a Lugandan or Swahili name, and since more than one child may have the same name, identification by name is not foolproof.

Finally, hospital records are established in paper folders made of material similar to construction paper, with loose documents inside, usually without clip, tie, or other means to secure them. Labs are rarely present. These folded construction paper files, each containing a few sheets of paper of various kinds and sizes, are reportedly stacked on the floor of the document room. The stacks are said to correspond roughly to time periods. The concept of a chronological inpatient chart for each patient, bearing a unique identifying number, appears not to have been implemented at this institution.

Personnel: In order to find all possible records for any one patient over the 18 month study, period, it is reportedly necessary to look at every record in that section of the document room corresponding roughly to that period of time. While this is not impossible, it is time consuming and rather difficult. Moreover, with dozens of admissions every night, and with a very limited staff to prepare and track records, responses are problematic. The study staff appeared to be somewhat

intimidated by the person responsible for the record rooms, a man reported to be very difficult to deal with.

In our case, the matter was finally solved by a written request by the hospital administration, together with a cash bounty for every chart found, paid by the JHU team (reportedly) to the manager of the record room, ultimately, approximately ten (10) records were found per day. In no case where multiple admissions were known to exist were all records for any one patient located, however. Under these circumstances, the ordinary test of comparison of a chronologically ordered CRF to a chronologically ordered hospital chart, proved impossible during the period the audit team was on site.

In summary, therefore, the audit team was afforded very limited access to records of hospitalization for illnesses, full access to obstetrical records, and full access to CRFs and shadow charts.

The CRF's were maintained in good order in a locked room on the second floor of the clinic building. Shadow charts for the HIVNET 012 trial, as well as the long term followup to the 012 trial, were stored in equally good order in another locked file room on the first floor of the clinic building. CRFs and shadow charts for other trials were observed in the same two site rooms.

Review of CRF's and Shadow Charts: After initial discussions related to FDA inspectional procedures, and a renewal of our request for hospital records, a sample of CRF's and Shadow Charts, together with obstetrical charts, were reviewed. Margaret Achomnes, the study coordinator who led us as an initial tour of the facility, as well as Dr. Guay, responded to questions and produced more records, as required. No restrictions were imposed on access to these records, and copying was permitted wherever requested.

Several points of significance became apparent during the first two days of reviews and discussion:

- **Standards for Seriousness and Severity**.

Although initially Dr. Guay described strict adherence to protocol specified endpoints for collection of safety data, interpretations of seriousness and severity were not actually made according to the protocol or according to 21CRF.

For mothers, only adverse events and SAE's through 6-8 weeks post delivery were captured. Deaths were likewise captured routinely only through 6-8 weeks post delivery. For infants, all adverse events through 6-8 weeks, and all SAE's through 18months of age were to be captured. Deaths prior to 18 months of age were to be captured, but not later. An absolute cut off for follow up was, in fact, imposed at 6-8 weeks post delivery for mothers and 18 months of age for infants.

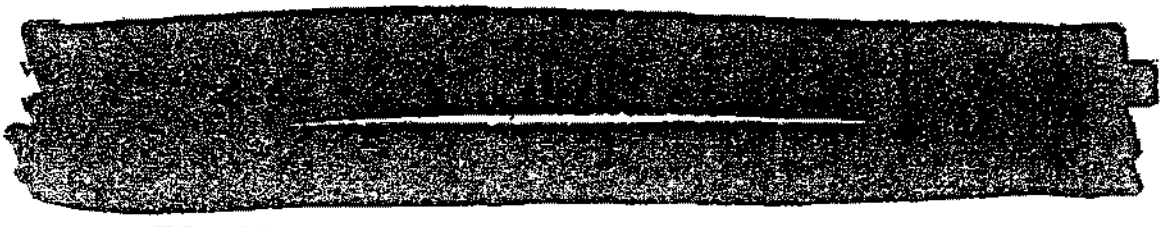
Strict cut off dates for follow up were compounded by exceptions to ordinary reporting rules, justified on the bases of local standards of medical care. Moreover, the original version of the protocol carried a pre-1997 definition of "Serious". A later, April, 2000 version, included the 1997 rule expanding the CFR definition of "Serious", but this had apparently not been noticed by the study team.

Regarding local, Mulago, standards, an adverse event had to be life-threatening in order to justify hospitalization. An infant with malaria or pneumonia, for example, who would in a western environment be hospitalized, perhaps even in critical care, might well be treated in Kampala as an outpatient. As a second example, an infant with Failure to Thrive, even progressing to Marasmus or Kwahiorkor, would not have been reported to have experienced an SAE unless admitted for rehydration or nutritional supplementation, a very late stage event.

Missing from the protocol definition of "Serious" was the 1997 addition of events wherein intervention was required in order to prevent a worse outcome, such as hospitalization or death. Since patients were kept out of hospital by very aggressive therapeutic approaches, many events are recorded in the CRFs or shadow charts as adverse events rather than SAE's. Since the events thought of by the study team as only being "AE's", as opposed to "SAE's", were not routinely captured for infants after 6-8 weeks, many events that would have fallen within this definition were missed, resulting in an under-reporting of SAE's.

After 6 weeks of age, for infants, site-declared "AE's" are mentioned only as reasons for concurrent medications. "NonSerious" adverse events (in Ugandan terms) that were picked up on unscheduled "sick" visits after 6 weeks, were not included at all. To the extent these were actually SAE's, these SAE's were not recorded. On several occasions Dr. Guay stated that there were probably "thousands" of such missing events. Some are missing because they were not captured after six weeks and some are missing because the unscheduled visit forms were not transcribed to the CRF's.

Adding to the complexity of this matter is the misuse of the Severity Scoring System. For clinical events generally, a hospitalization was required for a "3" or occasionally a "4". This means that not uncommonly, medically severe events that were treated aggressively on an outpatient basis were scored as a "1" or "2". Severity Scales for hemoglobin were ignored because of the prevalence of anemia in the population. Severity scores for other labs may also be questioned in the absence of local normal ranges for common laboratory determinations.



•<u>Review based on Second hand descriptions of events</u>: Patient care at Kampala, whether in Old Mulago, New Mulago, on the clinics, is provided by local physicians. Although some of these are employed by the study team (apparently) none participated in preparation of the CRF pages, including those describing AE's or SAE's. Information of such pages was for the most part, transcribed by Maria Musisi (Transcriptionist) working either from what we have, by convention, referred to as "Shadow Charts", containing the MU/JHU study specific forms, or from summaries by hospitalizations written by another nurse, "Matilda", who upon learning of an admission of a study patient, would review the hospital chart and sometimes interview the doctor caring for the patient, and/or the patient or patient's mother. Matilda and perhaps others, maintained their notes in personal notebooks.

The page of the "Shadow Chart" from which adverse events (including those which should have been serious adverse events) were the "Infants Follow-up" and "Unscheduled Visit" forms. Like all other pages in the loose leaf notebook referred to as the shadow chart, these pages were forms created by the MU/JHU Study Team for the purpose of capturing data that would have been not ordinarily have been written down in the medical records, or would have been lost.

While having Maria and Matilda copy over and summarize clinical data is an idea with some merit, as is the shadow chart used to buttress the weak records system, the concept of the principle Investigator or sub-investigator making determinations of such critical matters as seriousness, severity, and causality for Serious Adverse Events on the bases of second-hand or third-hand accounts of these events is highly problematic.

Taking into consideration the decision by Dr. Jackson, Dr. Guay, et al, to coin their own local definitions of seriousness and severity , and keeping in mind the under-reporting of SAEs which resulted from that, ("thousands") then the entire safety reporting system can be seen to have been significantly different from that expected in an IND study.

In explanation, Dr. Jackson and Dr. Guay cited a need for consistency in a somewhat chaotic and very busy clinic system. Regarding the definition of "Serious" they cited ignorance of the 1997 safety reporting regulation, although the protocol, as amended in 2000, included a clear statement of the new rule. They also reported that they had never had "GCP" training, and had never attempted a Phase III trial.

Finally, it should be noted that the Boehringer Auditors in January and on this visit, as well as the WESTAT auditors, noted that transcription errors were not uncommon within this system.

•**Follow-up of SAE's As a Confounding issue**: Further complicating the problems with the safety reporting system was an apparent failure to implement follow-up of SAE"s *to clinical resolution*, a requirement long published by FDA. Specifically, an SAE that had not resolved at 6 weeks. (mothers) or 18 months (infant) was listed as "ongoing" in the CRF and in the database. With no further follow-up for purposes of the HIVNET 012 study. For example, an infant with failure to thrive, marasmus, kwashiorkor, or tuberculosis, (all of which were reported SAE's, who later died as a consequence, was never reported with a fatal outcome if the death came after 18 months of age.

As a consequence of these observations the BIPI database submitted to FDA is incomplete, in that events which should have been SAE's were often not reported as such, and if reported were typically not followed to resolution. Total outcomes were clearly under-reported. Adverse events captured on unscheduled visit forms were also not reported adding generally to an under-reporting of safety data.

•**Review of Secondary Source Records**: All of the above described information was apparent upon review of CRF's Shadow Charts, and Obstetrical Records. (See BIPI Audit report and findings by WESTAT auditors for examples). While continuing to await the advent of hospital charts for the study patients, the audit team began a search for other forms of source documentation. Because of earlier mention of visiting nurses notes, we asked to see these.

What was provided initially was a set of these (3) blue notebooks, hardbound and approximately A-4 paper in size. Each bore many dated notations by visiting nurses, with each entry including the patient name and identifiers, as well as the study number and address. The initial entry in each case was typically a detailed set of directions to the patients dwelling, sometimes including a map, as well as notes regarding visits. Sometimes AE's or apparent SAEs were maintained as well. Since the nurses initiated visits after a series of scheduled clinic visits were missed, it is not surprising that deaths not previously reported to FDA were found in these records.

As the audit team reviewed these blue logs, a number of deaths not previously listed in the BIPI database, the 2001 annual report, or any other source known to us came to light. As we sought information on these deaths, we learned that the blue logs were actually summaries prepared from stacks of index cards (pink and green) containing similar but more detailed notations. These pink and green cards

were then reviewed, yielding still more deaths, some of which had not been transcribed into the blue logs.

Discussions with the lead visiting nurse (Agnes) led to the understanding that the nurses, as a group, would record information in a fairly consistent manner. Each, when visiting in a home, would do nothing more than jot a few notes in a small black notebook. In her car or in the office the nurse would then fill out the pink or green cards, from memory. The cards were not completed in the home because the other family members (husband included) usually did not know the mother was HIV(+).

At a Friday meeting every week, the nurse reportedly reviewed the visits, shared information, and discussed the patients. At some later point in time, the cards were then transcribed (or summarized) into the blue logs. The purpose for this was never explained although the question was asked several times. A master log was also completed for patients from each of the two hospitals. These were later checked against the cards and other sources, and like the blue logs, and to have notable inaccuracies. One of the two "master logs" was discovered by one of the BI auditors (Pauline Carr) to be a recent transcription, based on the newness of the paper. The lead nurse acknowledged this, explaining that the original had been lost in a "flood".

In summary, the best source record for deaths appeared to be the visiting nurses pink/green cards. Others (blue books and master log) were inaccurate by comparison.

The discovery of "new" deaths and the resulting focus on tabulations and cross referencing occupied most of 3 audit team members time for more than two days. The resulting tables are attached (Attachment 5). Dr. Guay will review these and will comment. She was surprised however, that any death might have been missed, since Maria Musisi was to have created a death form for each Shadow chart, for each death learned of by the visiting nurses. In our review such forms were often, but not consistently found. Nevertheless, some deaths did not surface in the reporting system.

•Relationship of absent follow-up of SAE's, underreporting of SAE's, and discovery of "new" deaths: In order to gain insight into the reasons some deaths were not in various databases, a series of four (4) cases where the deaths were not in the BIPI database, were chosen at random. A review of these deaths provided new insight into the consequences of the issues described in this report. Two additional cases of patients with obvious health issues not included in the BIPI SAE listing were then checked as well.

These cases are discussed below and are represented by attachments 6 - 11. In brief however, the deaths checked were rather dramatic cases of "FTT", or Failure To Thrive, usually accompanied by marasmus, and/or kwashiorkor,

and/or malaria, and/or tuberculosis, and/or the poor appetite and chronic vomiting and diarrhea associated with AIDS. In each case the diagnosis was made early, the infant dropped off the growth chart, and eventually died. In only one case was an SAE noted, and that with an outcome of "continuing", at 18 months.

Dr. Guay explained again that unless the baby was hospitalized the event was not "serious", within the Mulago definition, and that only "serious" events were reported after 6 weeks. Again, since even "Serious" events were followed to only 18 months, even if worsening, even the one FTT that was an SAE was not reported as "fatal".

In each of these cases, the BIPI or FDA reviewer, working from SAE and AE listings, or from death lists on expedited safety reports would have no way of knowing that these infants were seriously ill and died a wasting death, described by the terms FTT, marasmus, and kwashiorkor, complicated at times by malaria and repeated episodes of infectious disease.

Two other obvious FTT cases sampled who were not deaths were equally problematic, with one (0178) showing up in the BIPI database as "bullous impetigo" despite flat-lining of the growth curve at 6 months of age.

Before presenting the documentation related to individual cases, it is important to identify the kinds of documents that are included:

Growth Charts These were located in the Shadow Chart, (also referred to by site personnel as the "source documents"). Some were found in the Shadow Chart for the HIVNET012 study described by the original protocol, and some were found in the "Long Term Follow-up" Shadow chart. They are not part of the CRF.

HIVNET 012 data listing These pages were provided by Pauline Carr, a BI auditor, from a copy of the database the BI team brought with them for the audit. Since the copy was incomplete, pages were not available for each patient. In that situation, the Illness pages from the CRF were relied on for a list of reported AE's and SAE's.

Long-term Follow-up, Child's Serious Illness/AE This is a page from the long term follow up CRF, not a part of the data included for the BIPI SNDA. These were found in the CRF notebooks, however. They are blue in color in the original, and so they copy darkly.

HOSPITAL ADMISSION FORM This is an MU/JHU form, included in the Shadow Chart to document a hospital admission. It was completed by a study team nurse and is the source for SAE data transcribed into the CRF by Maria Musisi and others. It is not part of the CRF.

INFANT'S FOLLOW-UP This is an MU/JHU form, in cluded in the Shadow Chart as a place to record information collected during a scheduled clinic follow up visit. It was completed by a study team physician or nurse, and was the source for transcription of information entered into the CRF by Maria Musisi and others. It is not part of the CRF.

FACE SHEET This is a form used in the hospital as the cover page for a hospital admission chart. It is yellow, and copies darkly as a result. Because the paper is very thin, writing on the back side of this form also shows through with copying.

CLINIC NOTES This form occurs in some hospital admission records, as a manila or grey sheet of paper that copies very darkly. It appears to be the form or paper actually used in the clinics when am MU/JHU form is not provided.

Death Report of Baby (handwritten) This is an example of a hand-created form, written by a nurse, such as Maria Musisi, to describe an infant death. This would have been prepared on the basis of notes from a visiting health nurse.

Infant's Illness/AE This is a CRF page used for recording adverse events, including serious adverse events. This form was completed by Maria Musisi, or another transcriptionist, working from MU/JHU forms, hospital records, or visiting nurse records.

Concomitant Medications Log This form is from the CRF and was used to capture concomitant medications. It was typically completed by Maria Musisi or other transcriptionists, working from MU/JHU forms, nurses notes, or other records.

HIVNET 012 (Infant 030) Infant's Follow-up This is a CRF page corresponding to the MU/JHU INFANT"S FOLLOW-UP form, described above, and represents the page to which information from the MU/JHU form was transcribed. Maria Musisi or another transcriptionist would have completed this form.

Infant's Status Change Notice This is a CRF page used for any status change, including exiting the study at the 18 month visit. Maria Musisi or another transcriptionist would have completed this form.

Note that whenever a transcriptionist completed a CRF page, the transcriptionist's Staff ID number was recorded in the lower right hand corner of the page. Staff ID 05 was Maria Musisi.

Case Synopses:

512-0062 - 1-6 (attachment 5). This infant is shown in the BIPI database as having experienced only facial swelling and bruising (an SAE, resolved) a common cold, scabies, and severe anemia (not an SAE). The 18 month Exit visit form describes no pathology, (9/24/99). By that time, however, the baby was critically ill.

The growth chart and shadow chart showed that. At 15 months the baby had fallen off the growth chart and never recovered.

A long term follow-up form, 3/19/00, and not a part of the 012 data provided for BIPI, describes the FTT and other health issues.

On 4/10/00 the baby was admitted for nutrition, persistent and acute diarrhea and vomiting, and FTT. The baby died the same day.

512-0728-1-7 (attachment 6). This infant, in the BIPI database, has 9 events listed, only three of which were described as "serious". There was pneumonia (resolved), diarrhea (resolved), and pulmonary Tuberculosis (ongoing).

The 12 month on-study visit shows a weight of only 7.8 kg, and a diagnosis of FTT, not captured in the CRF.

An 18 month followup form shows a weight of 6.1 KG, and the comment of "wasted" and "FTT".

An unscheduled visit form at 18 1/2 months shows a weight of 5.9 kg, marasmus (FTT), diarrhea, etc. More marasmus (FTT), diarrhea, etc. More details are provided in clinical notes, attached.

A death note indicates death about 2 months later.

The growth chart graphically depicts the baby's decline, beginning 12 months, well within the 18 month study period.

512-0518-1-8: (attachment 7). For this infant the BIPI database page was missing. The CRF pages, however, show Bronchopneumonia, (resolved) marasmus (ongoing), LOM (resolved), Tuberculosis (resolved), and FTT (ongoing). This case therefore represents one where these issues were picked up and described as SAE's apparently because of a hospitalization at about 12 months of age. The fatal outcome, was not, however, reported. The date of the 12 month visit report (9/20/99) indicates onset at 9/20/99 whereas the growth chart shows precipitous decline by 9 months.

Note that the 18 month exit form from the CRF, dated 3/3/00, does not comment on the baby's terminal state. Three months later the infant was dead.

Note that this infant was also on the CHS high dose Vitamin A protocol.

512-0827- 1-5: (attachment 8): The BIPI database for this infant shows four SAE's , all related to a single episode of infectious disease, all resolved. FTT, marasmus, and kwashiorkor are not mentioned.

The 18 month Exit Form is without comment, although a followup form the same date, 9/27/00 notes weight loss due to diarrhea plus poor appetite. This is based on a shadow chart form from 17 month/26 days.

The baby died 4/9/01 of marasmus and kwashiorkor. The cause of death rather nicely outlines the terminal course in this infant:

Electrolytes imbalance
Persistent diarrhea
Underlying ISS (AIDS) +
Kwashiorkor

The growth chart documents the decline from 18 months. Again the fatal outcome is not shown in the CRF.

512-0764-1-06: (attachment 9). Here again, there is not BIPI page listing events for this patient. The CRF, however does not list FTT as an SAE.

FTT is mentioned as a reason for a multivitamin or 2/17/99 is without comment.

A shadow chart form dated 8/19/99, lists FTT with an onset of 8/17/99, the same date as the 6 month visit.

The 18 month exit form 8/15/00 is without comment.

An MU/JHU form, from 18 months, shows a weight of 7.5 kg. FTT, and "gross wasting".

The growth chart well documents the entire history.

In this case a severely debilitating, obviously serious AE, is not described beyond a notation in reference to a con med.

512-0178-1-4: (attachment 10). This infant appears in the BIPI database with a single, mild, AE, bullous impetigo.

Instead, the growth chart documents a dramatic Failure To Thrive apparent at 8 months of age. A clinic note from 12 months, 5/28/99, shows a weight of only 5.9 kg, and a diagnosis of FTT.

The 18 month Exit form is dated 12/13/99, and does not comment on the wasting illness.

At 29.3 months the baby weighs only 7.2 kg.

Clearly the BIPI database does not describe, even approximately, the devastating decline of this infant during the study.

These examples demonstrate somewhat graphically the incomplete nature of the safety data developed by HIVNETO12 and provided to BIPI for submission to FDA. Clearly, one lesson learned from the audit team's exploration of missed deaths was that any SAE listed in the BIPI database as "ongoing" must be followed up. Many likely had a fatal outcome.

- Hospital Records: Although much time was spent waiting for records of hospitalizations of study patients, only about 20 were found in time for review. An additional number were found on the last day the team was on site, but too late to be reviewed. In total, only 13 were examined and compared to CRFs and Shadow Charts.

  In each case, like the Obstetrical records seen before, each chart described a single hospitalization. A single scrap of paper in one chart outlined another hospitalization a few weeks earlier.

  In no case (as was also true of the Obstetrical records) did the chart describe the HIV status or the fact the patient was on a trial.

  In every case, the illness was accurately depicted in the CRF.

  In 11/13 cases, errors were made in reporting concurrent meds in the CRF. These observations are outlined in the following table.

Table 15: Review of Hospital Records, Compared to CRF's and Shadow Charts

Patient Identification	Serious Adverse Events	Observations
0632	Admitted 3/6/00-3/8/00, pneumonia, treated with chloramphenicol and salambutol primarily	CRF also records as con meds prednisolone, Panadol, and amoxicillin, which are not in chart but are in shadow record.
0776	Admitted 8/2/99 with severe anemia, CHF, sepsis, pneumonia, and malaria	CRF con meds does not list Lasix and blood transfusion, although these are mentioned in "illness" section of the illness report.
0705	Admitted 6/21-25/99, with fever, seizures X 2, cough, conjunctivitis, meningitis (R/O measles).	CRF con meds does not include paracetamol.
0853	Admitted 1/12-13/00, with fever, convulsion, cough, malaria, and anemia	CRF con meds lists ranferon, nizoral, ferrous sulfate, and multivitamins which are not in chart, and fails to list X-pen. Ranferon is mentioned in the shadow record.
0674	Admitted 12/24-27/99, with fever of sudden onset, cough, wheezing, and rash.	CRF agrees with chart

0710	Admitted 5/28/99 – 6/1/99, with hypopigmented rash, hepatomegally, and pneumonia.	CRF con meds do not list Genatmycin, but does list cotrimoxazole, pyramethamine & sulfadoxine, and ranferon, not in chart.
0573	Admitted 12/6-9/99, with fever, cough, vomiting, hemoglobin 3.6	CRF con meds list cotrimoxazole, pyramethamine&sulfadoxine, not in chart.
0534	Admitted 2/27/99-3/1/99, with anemia, bronchopneumonia, thrush, "severely wasted", R/O sepsis, multiple abscesses	CRF con meds does not list X-pen, septrim, and paracetamol.
0693	Admitted 3/27/00-4/3/00, with convulsion, "wasted", fever, "on TB drugs"	CRF is accurate.
0852	Admitted 2/16-19/00, with malaria, severe anemia, fever, diarrhea, cough	CRF con meds does not list pyramethamine & sulfadoxine, and ceftriaxone, not in chart.
0612	Admitted 5/22-25/99 for severe pneumonia, and 6/2-6/99, with bronchopneumonia, fever, and convulsions	CRF does not include 5/22 chloramphenicol or 6/2 Vitamin A.
0253	Admitted 6/18-21/99 with malaria, severe anemia	CRF con meds does not list folic acid, ferrous sulfate, or cotrimazole for this period.
0588	Admitted 11/15-30/99, with pneumonia, possibly TB or Staph.	CRF con meds can only be partially checked because of hand writing. Ceftraxone and chloramphenicol are not in CRF. Nizoral is in CRF but not in chart.

- **Summary of Discussions with PI and Sub-investigators:** Daily discussions with Dr. Guay and usually Dr. Musoka occurred each of the last 5 days of the audit. Dr. Jackson participated the last two days.

All acknowledged the findings as generally correct. Dr. Guay and Dr. Jackson noted that many ("thousands") of unreported AE's and SAE's occurred. Dr. Guay thought it unlikely that any deaths on the visiting nurses notes were unknown to the study team, however, given their weekly review. If the death had followed 6-8 weeks post partum in the mother, or had occurred after 18 months of age, she agreed that it would not have been in the database.

They acknowledged their use of their own interpretation of "serious" and of severity. Both denied being aware of the 1997 definition of serious, which included events wherein intervention prevented a worse outcome, such as hospitalization or death. All agreed that this meant that there had been a sizeable under-reporting according to this definition.

All denied understanding that SAEs must be followed to clinical resolution. All acknowledged that any event that had a fatal outcome after 18 months would therefore have been listed as "ongoing" rather than fatal.

All agreed that they (PI and subinvestigators) had generally not seen the trial patients, and had as a rule, not reviewed the CRF's prepared by Ms Musisi, et al, for accuracy at any time, before or after entry into the Data Fax system for SCHARP.

All agreed that in evaluating AE's or SAE's, they had relied almost entirely on second or third hand summaries by the study staff, without attempting to verify accuracy.

All expressed great concern and an intention to take corrective for the next trial.

In one interview, when confronted with findings in source records of references to an apparent concurrent study (Attachment 11), Dr. Guay acknowledged that 1/2 of the HIV positive infants in the 012 trial were entered into a CHS trial. This double blind trial evaluated the therapeutic potential of high dose vitamin A, compared to placebo. A recent unblinding was described by Dr. Guay as showing a positive result. Dr. Jackson proposed acknowledging this in his publications of the 012 data, since half of the infants who were HIV positive would have gotten this additional therapeutic intervention,

Both Dr. Guay and Dr. Jackson expressed concern regarding statements made regarding safety and efficacy in the Lancet paper, and resolved to review the data.

It appears that the entire study team is eager to re-evaluate (re-monitor) the database, to correct inaccuracies.

At the heart of these issues, however, are four (4) problems that must be corrected. First, as noted above, neither Dr. Guay or any sub-investigators, or Dr. Jackson ever reviewed CRFs for accuracy. They depended on the nurse midwives to accurately transcribe data. A QC process must be implemented immediately, preferably by a physician.

Third, as noted in other portions of this report, the site is without standard operating procedures and relies heavily on word of mouth, tradition, and the work of the nurse-midwife teams to assure consistency.

[redacted] a remarkable lack of understanding of Good Clinical Practices, as applied to a Phase III, IND trial was apparent. Re-training of these personnel, based on a site-specific set of SOP's is likewise a high priority.

Finally, it was not at all clear, even in the last hours of the last day of the audit, that the PI and Sub-investigators fully understood or appreciated the significance of the observations. Their assessment appeared to be that they had attempted to do too much with too few resources. The issues of oversite, management, and personal responsibility within a highly regulated environment did not yet seem to have been appreciated.

Proposed Corrective Actions, HIVNET 012

Safety Data for HIVNET 012: Information describing adverse events was most thoroughly collected during the first eight weeks after delivery, for both mothers and infants. These data are recorded in either MU/JHU forms (shadow charts), in hospital records, or in the CRF's. The primary difficulty with these data are the arbitrary definitions of seriousness and severity that were employed. After eight weeks, it appears likely that the date and cause of most deaths can be determined. Other safety data are incomplete, and any attempt to reconstruct these data would apparently be characterized by incomplete reports and lost events.

Accordingly, a re-monitoring or data recovery operation directed only at the first eight weeks and at survival data would seem feasible. In order to make this meaningful, ordinary conventions regarding Seriousness would have to be applied, and at least some severity scoring for laboratories would have to be waived.

Such a process should be conducted under a protocol, with associated procedures developed for data management and subsequent statistical analyses.

Claims regarding safety in either FDA submissions or published reports, should be re-considered after review of the revised data.

Safety Reporting (future): Central to the safety reporting issues from Mulago are four themes. First, no waiver was apparently sought to broaden the definition of "expectedness" for the trial. This could be easily dealt with in the future. Second, the site must conform to CFR definitions of Seriousness if the data are to comparable to those collected by anyone else. Third, the prospect of the sub-investigators and PI not actually

seeing the patients whose events they are evaluating should be addressed. If they cannot see them, the clinic and hospital physicians ought to be trained and given responsibility for completing the initial version of the safety reporting form. Fourth, the sub-investigators or PI ought to review MedDRA or COSTART coding of terms.

Process and Procedure: A core issue for the Mulago site is an absence of documented internal procedures. Reliance on memory and precedent is useful but likely to be associated with inconsistencies in data collection.

Accordingly, development of a set of Mulago-specific SOP's, together with associated training is a second critical issue. These should extend to the laboratories and data management group at Mulago.

Provision for periodic internal audit and review of the procedures should be included (annual).

Quality Assurance and Quality Control: Absence of investigator supervision is another core issue at Mulago. In part this could be addressed by implementation of two functions, QC and QA. QC is essentially a periodic check for the completeness of data collection. (Are the forms being filled out appropriately? Is information being captured as planned?) A part of this is comparison of a sample of CRF's to source documents. This might be anything from 25% to 100%. QA is a periodic audit function, carried out by a different individual with a different perspective. For example, in Mulago, the sub-investigators could have established a QC function as the study progressed, with periodic audit being carried out by someone officially responsible for Quality Assurance. In setting up the SOP's for the site, both functions need to be considered and responsibilites assigned.

Records of Hospitalization: In the absence of an attempt to reconfigure the hospital medical records system, a simple (albeit partial) solution, would have been to have a Xerox copy made of the medical record of any study patient admitted to hospital. This could then be included in the "shadow chart".

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ATTACHMENTS

Attachment 1	Mike Hensley 12-February 2002 memo, "Observations, HIVNET 012 Data and Documentation
Attachment 2	Proposed Patient Audit List
Attachment 3	Additional Documents Provided During the Visit
Attachment 4	Table of Subject-Specific Record Review Findings
Attachment 5	Deaths not included in IND Annual Report # 034 BI Data SNDA Submission Lancet Paper (September 1999)
Attachment 6	Patient Record, Sample 1
Attachment 7	Patient Record, Sample 2
Attachment 8	Patient Record, Sample 3
Attachment 9	Patient Record, Sample 4
Attachment 10	Patient Record, Sample 5
Attachment 11	Patient Record, Sample 6
Attachment 12	Health Visitor Job Description with reference to Child Health Study (CHS)