Data management plan

Protocol Title: Impact of HIV Status on Hepatitis B Vaccine Response.

Protocol number: 10452

Protocol version and date	Version 1.0 02 Mar 2016
Funding Sponsor	Kenyatta National Hospital (KNH)
Study Principal investigator	Lawrence Mwaniki
Study Site	Partners in Health Research and Development- Thika, Kenya
Users/Audience	Data management team and Principal Investigator

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1. Synopsis of research project

This data management plan will be used and must be adhered to by all clinical trial staff members. SOPs for data management must be in line with this plan. Trainings conducted in the course of the study must be in line with this plan.

Study Design: Prospective interventional study of HIV infected preadolescent boys and girls.

The primary objective of this study will be to identify factors which impact HBV vaccine response and durability in HIV positive pre-adolescent boys and girls in sub Saharan Africa. One to one randomization will be done based on ART status. One group will be on ARVs while the other will be on multivitamins and septrin. Up to 200 preadolescent HIV positive boys and girls will be enrolled into the study.

Secondary objective:

1. To determine predictors of response to Hep B vaccination series in HIV positive, HBV susceptible individuals.
2. To determine the efficacy of Hep B vaccination series in HIV positive and CMV negative individuals, susceptible to HBV.

Study duration: A total of 12 months with possible additional 3 months.

Mode of data collection: RedCap will be used to capture study data. The data manager will be responsible for creating the RedCap database where he/she will incorporate branching logics and also create validation rules. Reports will also be created in RedCap as directed by the principal investigator. Case report forms (CRFs) will be used during normal clinic visit, then data will be transcribed into RedCap.

2. Data Management Goals

Principles of highest value include: Data accuracy and completeness, flexibility, and confidentiality.

2.1.Data Accuracy and completeness

Accuracy of data that is being reported is critical since HIV positive patients may be resistant to treatment and it's important to have accurate reports to avoid misclassification. It is also of at most importance to know their response to Hepatitis B vaccine since they are immune compromised. It is also important that results are not delayed from the lab due to their importance in management of patients

2.2. Flexibility

National guidelines on management of HIV positive pre-adolescents may change during the course of the study, and it is important for the study to accommodate possible changes in guidelines. Patients who may become eligible to initiate HAART due to change in national guidelines will be initiated ARVs despite the eligibility status in the study or whichever study arm they are in.

2.3. Confidentiality

Patient records must be confidential. The only identifier between a name and participant id will be the link log. Electronic records must be password protected, and all staff members must be GCP trained before handling research data.

3. Description of procedures

3.1.Screening

Once HIV positive preadolescent boys and girls have been referred to the research clinic through the set referral system, registration will be done at the reception. The next available counselor will take a pre-assembled screening folder from data department and initiate the screening process. Assenting must be done before any study procedures have been performed. The guardian must provide parental permission. Demographics will be recorded on the SDEM CRF. This will include DOB, age, gender, years in school, HIV care program, ART status, and if on HAART, current regimen.

3.2. Enrolment

At the enrolment visit, eligibility of the patient will be confirmed. Enrolment consent form will be administered before any other procedures are performed. Blood draws will done for CD4 and viral load testing. Patient identifiers will be allocated in a sequential order. Hep B vaccine will be administered and a vaccine report card (VRC) issued to the patient to feel safety information at home for the next 14 days. Thermometer use training will be done. Guardians will be issued with thermometers to monitor temperature of the patients at home. This will also be recorded at home.

3.3. Safety visit

After every vaccination visit, patients will be schedule to return for a safety visit 7 days after vaccination. VRC retraining will be done and any AEs recorded and reported. Replacement of lost supplies will be done at this visit.

3.4. Follow up

There will be a maximum of 4 follow up visits in this study. The second and the third visits will be vaccination visits, while the fourth visit will be at one year post vaccination to check for response and toleration of vaccine. CD4 testing and viral load will be done at this visits. A samples will also be drawn for HBV serology testing. Patients who are still susceptible will be given a booster vaccine at this visit.

3.5. Exit

An exit visit may occur at one year post vaccination for those whose HBV antigen result is immune. Those who test susceptible will be advised to return after 3 months to access safety and response to the booster. A disposition form must be filled at the exit visit, and locator information collected for future contact.

3.6. Archive

Study documents will be archive for 10 years after completion of the study. This will be as per the local IRBs guidelines. Before records have been archived, data completeness must be confirmed through data cleaning. A database lock must have occurred.

4. Completeness

4.1. Likely causes of missing data

Missed appointments: Data team will generate report on late for follow up on a daily basis. This report will be sent to the retention officers. A phone call will be made a day after missing the target date, and there after a home visit will be planned. Participants whose visit window closes will have a missed visit CRF completed and an update made into RedCap.

Delayed results: Lab results will be done at the CTRL lab which is based in Nairobi. This may cause a delay in the turnaround time. Reports will be run from RedCap on a weekly basis detailing pending results and the report forwarded to the lab manager.

Missing data points: Situations may occur where some items are missed during regular visit. Staff trainings will be done before the study commences and refreshers on a quarterly basis thereafter. CMEs will also be done on a regular basis. A training file will be kept by the training coordinator. RedCap will also have reports on missing data points.

5. Accuracy/correctness

Human error in this study may include wrong completion of the VRC cards and wrong readings of temperatures by the guardians and the participants. Retraining's will be done before issuing, and during the safety visit. Calls will also be made on a regular basis to remind them to fill the card. Any participant who reports challenges will be invited to visit the clinic for retraining immediately. Data entry errors into RedCap may occur. Procedures to detect errors will be ranges and branching logic. Any measure out of range will have an alert. Example is a high temperature above 38.7 will have a messaging prompting AE form completion.

6. Verification

Three levels of QC will be put into place. A data officer will enter data into RedCap and update the form status as verified. He/She will update an excel worksheet that data was entered into RedCap. A second data officer will then review the entries into RedCap against the source document checking for completeness and accuracy. The data manager will be the final level of QC where he/she will also verify entries into RedCap are complete and accurate, then change the form status to complete. The site coordinator will also request for 10% of the files and review them against RedCap to confirm accuracy and consistency.

A site monitor will review all files specifically the regulatory binders, consents, screening visits, enrolment visits and closure out visits. This will be intended to confirm GCP compliance. Backup of data captured by local databases will be backed up weekly in an external location. No data will be transferred through emails.

7. Security/Confidentiality

Database password protection: Each RedCap user will have a unique user account and password. This will be set to expire after two weeks and no password can be repeated once used. None activity for five minutes will prompt a timeout. Computers in the site will contain a password which will also expire after 3 months. None activity will prompt computer locking. Participant CRFs will only contain PTIDs and no names will be printed on them. All documents with names will be stored together under lock and key in the site coordinators office. Binders will be stored in data storage room in bulk filers that are file proof. Access to this room will be limited to authorized personnel only. A file movement log will be maintained in data to record movements of patient records.

8. Data availability and access

RedCap data will be accessible to statisticians through approval from the Study principal investigators. Stata 13 and R codes will be maintained in RedCap for easy retrieval of data. Reports will be generated every biweekly from RedCap and sent to the Principal Investigator highlighting study progress. Data on safety of the HBV vaccine will also be availed to the Principal investigator and study statistician during scheduled safety review meetings. Once publication of results have been done, findings will be uploaded in the site website and published in local newspapers. Dissemination will be done to the study participants and all stakeholders. Sponsors will get results at the end of the study.

9. Study communication and coordination functions

Conference calls with the study PI will be held on a monthly basis to discuss the progress of the study. This will be done using softphones that uses internet for connectivity. Staff members may access emails offsite using the webmail. The link will be provided to the staff members by data personnel. Communication between clinic and offsite lab will be via email (domain: @phrd.org).

10. Appendix

1.1 Table of content

1.2Abbreviations and Definitions

AE	Adverse Event
ART	Anti-Retroviral Treatment
ARV	Anti-Retroviral Therapy
CD4	Cluster of Differentiation 4
CME	Continuous Medical Education
CTRL	Clinical Trials Research Laboratory
CRF	Case Report Form
DOB	Date of Birth
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B virus
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
PI	Principal Investigator
PTID	Participant ID
RedCap	Research Electronic Data Capture
SDEM	Screening Demographics
SOP	Standard Operating Procedure
VRC	Vaccine Report Card

1.3 Event summaries

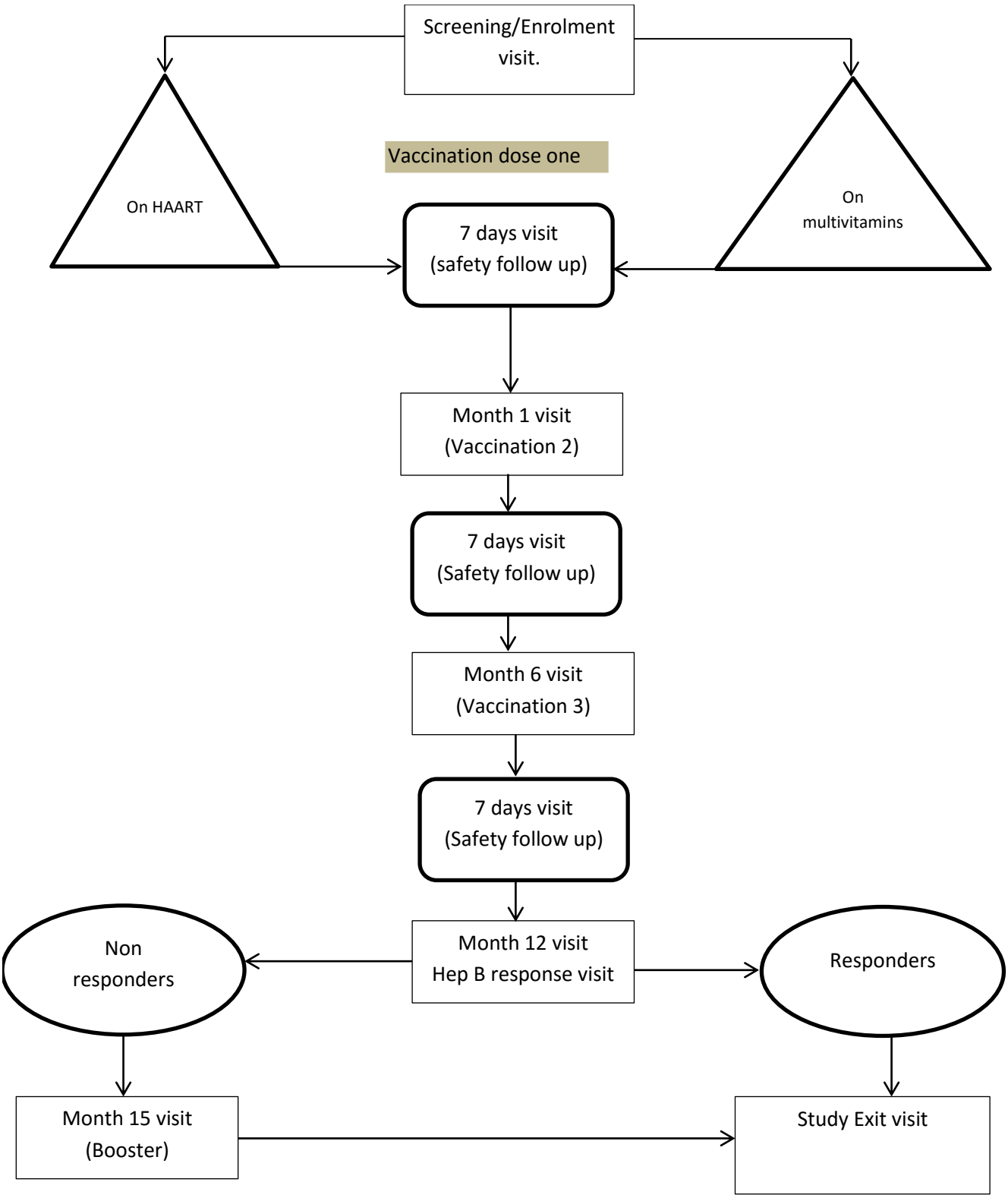
Event	Description	Study document	Staff completing	Update
New patients referred to the site	Registration done at from office	Site register	Receptionist	Link log, local Access database
Screening	Participants assents/parental permission/demographics	Consents	Counselor	Eligibiliy CRF
Screening procedures	Samples are drawn	Lab request forms, results CRF	Clinician	RedCap update
Enrolment	Participants assents/parental permission/locator/CRFs	Enrolment consents/CRFs (MH, ENR, WHO, Vaccination)	Counselors/clinicians	RedCap update, Access database
Safety visit	Retraining and review of AEs	VRC, thermometer, AE, conmed	Clinician	RedCap update
Follow up	Vaccination and sample collection	VRC, vaccination, samples	Clinician	RedCap, local database
Reports generation	Reports are generated indicating study progress	Late for follow up, missed visits, graphs, enrolment numbers	Data manager	RedCap, access database

Phone contacts	Late for follow up participants	Missed visits, emails to PI	Field coordinator	RedCap, access database, communication log
AE follow up	Participants with AE related to study product needs follow up	AE form, reports to IRBs	Lead physician	RedCap, AE tracking log
Study exit	Participants exited from the study after study completion or withdrawal	Disposition CRF, Referral letter, copy of results	Lead clinician	RedCap, Access database, exit log
Results dissemination	Results shared with study participants and stakeholders after study end	Phone calls, publications, journals, newspapers	Study PI/designee	Results dissemination log

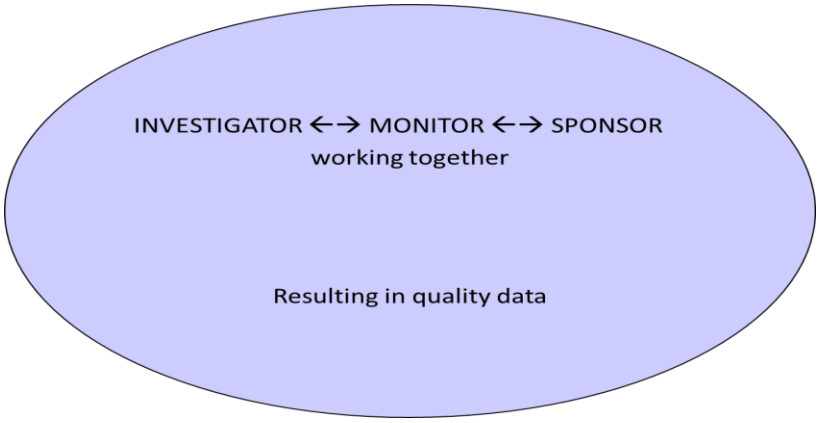
1.4 Table of procedures

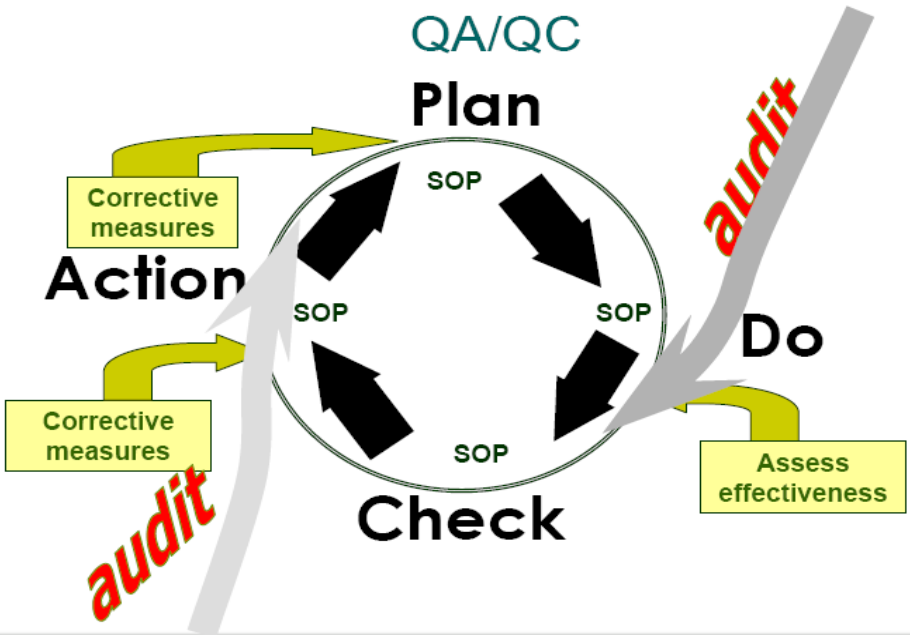
Tests and Procedures	**Screening**	**Enrolment**	**Day 7**	**Month 3**	**Day 7**	**Month 6**	**Day 7**	**Month 12 /Exit**	**Month 15 /Exit**
Informed Consent	X	X							
Inclusion/ Exclusion	X	X							
Medical history	X	X	X	X	X	X	X	X	X
Physical Exam		X						X	
Hep B serology	X							X	
CD4	X					X			
Viral load	X					X			
Hep B vaccine		X		X		X			X*

1.5 Study Design



1.6 QA/QC processes





1.7 Sample CRFs

ELIGIBILITY DETERMINATION FORM

SCREENING ID ☐☐—☐☐☐☐ **PTID:** ☐☐—☐☐☐—☐ **Visit Date: _____**
dd mm yy

1.	Did the participant provide independent, written, informed assent for enrollment into the study? ☐ Yes ☐ No 2a. When was the informed assent for enrollment marked or signed? ☐☐ ☐☐ ☐☐ (*dd mm yy*)
2.	Did the parent/guardian provide independent, written, informed consent for enrollment into the study? ☐ Yes ☐ No 3a. When was the informed consent for enrollment marked or signed? ☐☐ ☐☐ ☐☐ (*dd mm yy*)
	INCLUSION CRITERIA *Items 3-4 must be **YES** for the participant to be eligible*
3.	Is the participant HIV infected? ☐ Yes ☐ No
4.	Is the participant 12-16 years old? ☐ Yes ☐ No
	EXCLUSION CRITERIA *Items 5-14 must be **NO** for the participant to be eligible*
5.	Is the participant severely ill (karnofsky score < 70)? ☐ Yes ☐ No
6.	Does the participant have diagnosis of malignancy? ☐ Yes ☐ No
7.	Does the participant have an ongoing febrile illness (temperature ≥ 37.8^{o}c) ? ☐ Yes ☐ No
8.	Is the participant on active treatment for an opportunistic infection? ☐ Yes ☐ No
9.	Has the participant received systemic corticosteroids within one year prior to enrollment? ☐ Yes ☐ No
10.	If female, is participant pregnant as determined by a positive urine $^{\beta}$HCG test? ☐ Yes ☐ No ☐ N/A
11.	Is the participant currently enrolled in another clinical study of an investigational agent or agents? ☐ Yes ☐ No
12.	Does the participant have known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections? ☐ Yes ☐ No
13.	Does the participant plan to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits would need to be scheduled? ☐ Yes ☐ No
14.	Other Specify_____ ☐ Yes ☐ No
15.	Based on the above, is the participant eligible? ☐ Yes ☐ No

Version 1.0 08-03-16 **English** **Completed by: _____**

LOCATOR INFORMATION **Date _____ (dd/mm/yyyy)**

SUBJECT INFORMATION:

Full Name:	
Address1:	
Address2:	
Primary Telephone Number:	
Alternative Telephone Number:	
Email Address:	
Place of Birth	

CONTACT INFORMATION FOR PARENT/GUARDIAN:

Full Name:	
Relationship to Subject	
Address1:	
Address2:	
Primary Telephone Number:	
Alternative Telephone Number:	
Email Address:	

Describe how to get to participants/guardian house in writing and/or drawing a map

……

……

……

……

……

……

Does the subject and his/her parent/guardian intend to remain at this address throughout the duration of the clinical trial?

☐ Yes ☐ No

If no, will the subject still be able to return to the clinic for all required visits? ☐ Yes ☐ No

Version 1.0, 08-03-16 **Completed by: _____** (initials/date

SCREENING DEMOGRAPHICS (SDEM)

SCREENING ID: ☐☐-☐☐☐☐ **PTID:** ☐☐-☐☐☐-☐ **Visit Date:** _____
dd mm yy

☐ Not Administered

1	Date of Birth: ☐☐ dd ☐☐ mm ☐☐ yy or Age: ☐☐ years
2	Sex: ☐ female ☐ male
3	How many years of school has the participant completed? (Do not count repeat levels) ☐☐ years
4	4a. Is the participant enrolled in an HIV care program? ☐ Yes ☐ No → Go to item 5 4b. Where is the participant enrolled? _____ 4c. When did the participant enroll in the HIV care program? ☐☐ *mm* ☐☐ *yy*
5	Is the participant on cotrimoxazole/dapsone for prophylaxis? ☐ Yes ☐ No
6	Is the participant on multivitamins? ☐ Yes ☐ No
7	7a. Is the participant on HAART? ☐ Yes ☐ No → End of Form 7b. When did the participant initiate HAART? ☐☐ *mm* ☐☐ *yy* 7c. List the ARVs being taken _____

Version 1.0 08-03-16 **English** **Completed by:** _____ (initials/date)

VACCINATION RECORD ☐ **Administered**

SCREENING ID: ☐☐-☐☐☐☐ **PTID:** ☐☐-☐☐☐-☐ **Visit Date:** _____
dd mm yy

	Date of vaccination: ☐☐ ☐☐ ☐☐ *dd mm yy*
	Time of vaccination: ☐☐.☐☐ **(24 hour clock)**
	Lot number of vial : _____ **Expiry Date** _____ dd mm yy
	Site of injection: ☐ Left arm ☐ Right arm ☐ Left thigh ☐ Right thigh
	Vaccination Administred by: _____
	Observation time start: ☐☐.☐☐ **(24 hour clock)**
	Observation time stop: ☐☐.☐☐ **(24 hour clock)**
	Observation done by: _____
	Were any adverse events noted during the observation period? ☐ Yes ☐ No → End of form
	List noted adverse events: *(update these in the AE logs)* _____ _____

Version 1.0 08-03-16 **English** **Completed by:** _____(initials/date)

FIRST YEAR BUDGET

The study will enroll up to 200 HIV infected preadolescents (100 boys and 100 girls)

Detailed budget for the IHHV study; protocol No. 10452		**FROM: 01 APR 2016**		**THROUGH: 31 MAR 2016**		
INVESTIGATOR PERSONNEL COST						
Name	**Role on Project**	**% effort**	**Institutional base salary**	**Salary requested**	**Fringe Benefits**	**Total**
Data Manager	Data management	80	12000	10200	2400	12600
Biostatistician	Data analysis	30	12000	10800	2400	13200
Data officer	QA/QC	100	6000	5400	2400	7800
Physician	Vaccination	40	18000	18000	2400	20400
			SUB TOTAL (USD)	**44400**	**9600**	**54000**
EQUIPMENT COSTS						
HP desktop x2						1700
HP laptop						1000
Sharp a318 printer						4000
Internet router						500
					SUB TOTAL (USD)	**6350**
SUPPLIES COSTS						
Binders						800
Spring files						300
90 gsm paper						100
Toner cartridge						540
Sticky notes						20
					SUB TOTAL (USD)	**1760**
PATIENT EXPENSES						
Patient reimbursement						**100,000**
TRAVEL						**3000**
OTHER EXPENSES						
Staff medical cover						3000
Training						700
Staff team building						700
Equipment service contract						600
Internet fee						5400
CD burner						30
					SUB TOTAL (USD)	**10430**
					TOTAL BUDGET COST FOR FIRST YEAR (USD)	**177240**

Budget Justification

Personnel costs:

A data manager, biostatistician, data officer and a physician will be recruited before study activation. Each staff member will sign a 1 year renewable contract, and wages will be paid at the end of every month.

The **data manager** will be responsible for RedCap project creation and management. He/She will work full time and will get a yearly salary of USD 10200 with a house allowance of USD1300 and a transport allowance of USD1100.

The study **biostatistician** will be very instrumental to the study during the study design and final analysis. He/She will come to the research site on an interim basis to review the study progress with the PI. The total salary will be USD13200 which will include house and transport allowance.

The study **data officer** will be expected to work on a full time basis. He/She will be expected to print out CRFs, assemble binders, file loose paper, and enter data into RedCap. He/She will be entitled a house and transport allowance, and the total salary will be USD 7800 per year.

A **study physician** will be responsible for vaccination and review of Adverse Events. He/She will also be the lead clinician. The physician will be available on phone for 24 hours. The yearly package will be 20400 inclusive of transport and house allowance.

Equipment costs:

Two computers will be necessary for RedCap data entry and local database updates. The two computers will be located in data office and will be installed with genuine softwares. A laptop computer will be used for onsite trainings. The overall cost including preinstalled softwares for the two computers is USD.

Each participant will have a **binder** for filing of case report forms and chartnotes. The total cost of 200 binders is estimated to be USD 800. This is a one off expense.

Participants that contain names will be filed separately from those with PTIDs to assure confidentiality. **Spring files** will be used to file this documents. The cost of 200 spring files is USD 300. CRFs will be printed on paper. Consents will also need to be printed. This will require a printer with the capability of scanning and photocopying. The combined cost of printer

and printing papers will be USD 4100. The printer will also require a toner cartridge and a service contract.

Patients will be **reimbursed** each visit they visit the clinic. This will USD 10 which will include transport and a token for time spent at the clinic. A participant will be expected to visit the clinic for at least 5 times within the first year of follow.

Staff members will also be provided with a **medical cover** for them and three members of their family. One **team building** event per year will also be planned with the aim of improving staff cohesiveness. Regular trainings will also be planned to improve the skills of the workers.