FINAL REPORT of the TaMoVac-01 EDCTP Project

Please refer to the section "Guidelines for completing the EDCTP final report form" at the end of this document.

1. Project Profile

This information is used in the Project Profile published on the EDCTP website (http://www.edctp.org/Project_Profiles.245.0.html). Please check the information below and ensure that it is complete and accurate.

Project Coordinator *Please provide a recent photograph for your profile in **Annex H***	Name: Professor Muhammad Bakari
	Email Address: mbakari@muhas.ac.tz; drbakari@yahoo.com
EDCTP grant code	CT.2006.33111.007
Grant title	HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA priming and MVA boosting strategies
Project acronym	TaMoVac-01
Grant start and end date	4 March 2008 – 31 December 2012
Value of EDCTP grant	€ 3,563,533
Total grant budget	€ 6,771,942

1.1 List of collaborators

Please provide details of the work package leaders and other collaborators on the grant, indicating their role in the project (for example, project coordinator, PhD and MSc supervisor, site PI, work package leader, etc). Where collaborators have more than one role, please provide details.

Name	Gender	Institution	Country	Role(s) in consortium
Muhammad Bakari	M	Muhimbili University of Health & Allied Sciences (MUHAS)	Tanzania	Project Coordinator MUHAS site PI for WP 2 PhD Supervisor for Patricia Munseri and Edith Tarimo
Fred Mhalu	M	MUHAS	Tanzania	Collaborator MUHAS site PI for WP 1 PhD Supervisor for Said Aboud & Agricola Joachim
Eligius Lyamuya	M	MUHAS	Tanzania	Co-Project Coordinator PhD Supervisor for Said Aboud
Patricia Munseri	F	MUHAS	Tanzania	PhD student
Agricola Joachim	F	MUHAS	Tanzania	PhD student
Said Aboud	M	MUHAS	Tanzania	PhD student
Eric Sandstrom	M	Karolinska Institute	Sweden	Collaborator PhD Supervisor for Patricia Munseri and Edith Tarimo
Sören Andersson	M	Karolinska Institute	Sweden	Collaborator
Gunnel Biberfeld	F	Karolinska Institute	Sweden	Collaborator PhD Supervisor for Said Aboud & Agricola Joachim
Pontus Blomberg	M	Karolinska Institute	Sweden	Collaborator
Bo Hejdeman	M	Karolinska Institute	Sweden	Collaborator
Charlotta Nilsson	F	Karolinka Institute	Sweden	Collaborator, PhD supervisor for Agricola Joachim
Britta Wahren	F	Karolinska Institutet	Sweden	Collaborator Responsible for development and provision of DNA vaccine

Frances Gotch	F	Imperial College	UK	Collaborator
Nesrina Imami	F	Imperial College	UK	Collaborator
Jonathan Weber	M	Imperial College	UK	Collaborator
Sheena Mc Cormack	F	MRC	UK	Collaborator
Michael Hoelscher	M	Ludwig-Maximilians Universitat Munchen	Germany	Collaborator
Leonard Maboko	M	MMRP	Tanzania	Collaborator
Arne Kroidl	M	MMRP	Germany	Collaborator
Philipp Mann	M	MMRP	Germany	Collaborator
Ilesh Jani	M	Instituto Nacional de Saúde (INS)	Mozambique	Collaborator
Nafissa Osman	F	Instituto Nacional de Saúde (INS)	Mozambique	Collaborator
Paula Vaz	F	Instituto Nacional de Saúde (INS)	Mozambique	Collaborator
Andrew Kitua	M	Special Programme for Research and Training in Tropical Diseases (WHO/TDR)	Switzerland	Collaborator
Sayoki Mfinanga	M	NIMR	Tanzania	Collaborator

1.2 Abstract (max 850 characters)

Give a summary of the project and what it has achieved, including the aims and objectives, the research questions being addressed, the study methods, the results, findings and achievements of the project.

This programme aimed at consolidating and sustaining the capacity building that European partners have invested in HIV vaccine trial preparations in Tanzania, and at the same time to expand a South-South capacity building effort in Mozambique. This has been achieved, and three centres in these countries have been prepared to take part in future phase II/III HIV vaccine studies. The successful completion of a DNA prime modified Vaccinia Ankara (MVA) boost vaccine trial that enrolled 120 participants, and the successful administration of a further adjuvanted protein (rgp 140/GLA) boost, in 40 participants in Dar es Salaam and Mbeya, is testimony to the capacity in Tanzania. In Mozambique, investigators have now completed a DNA prime/MVA boost trial in 24 youths. All three centres are ready to embark on the next multi-centre trial. The results from the main Tanzanian trial (TMV-01) have been presented at the AIDS Vaccine Conference 2012 in Boston, and are being summarised in a series of manuscripts. Evaluation of cellular and humoral responses following the protein boost in Tanzania, and the Mozambique immune responses are ongoing.

1.3 Description of the project

The project description should cover background, objectives, results and outcomes, capacity building and networking (max: 5000 characters).

Background

HIV remains a significant health problem globally, but more so in developing countries. Efforts towards a safe, affordable and efficacious vaccine have seen the development of partnerships between the North and South in the search for such a vaccine.

The problem being addressed

This project addressed the problem of building and sustaining a capacity to conduct HIV vaccine trials in developing countries.

Objectives

The objectives of this work have been to build a sustainable HIV vaccine trial capacity by the specific activities to:

- Optimize HIV vaccine delivery
- Expand capacity to perform future phase IIB and III trials
- Extend the current adult target cohorts to youths
- Develop capacity to investigate preventive HIV vaccines in neonates.

Endpoints

The primary end-point in the vaccine trials was safety and assessment of immunological responses, performed at the trial sites through the interferon (IFN)-gamma enzyme-linked spot assay (Elispot) performed on fresh cells at defined time points.

Secondary endpoints were:

- IFN gamma Elispot on CD4 or CD8 depleted lymphocytes; Interleukin-2 Elispot; lymphoproliferation against inactivated HIV; and intracellular cytokine analysis quantifying IFN-gamma and IL-2.
- Validation of research laboratories for primary and secondary endpoints.
- An increase in the number of staff with GCP or GLP certification, and successful development and approval of HIV-vaccine research protocols
- Development of cohorts of young people and a completed phase I study in that group
- An approved protocol for HIV-vaccination in neonates.

Methodology

The activities undertaken included further immunological and safety evaluation of a DNA prime-MVA boost; an additional rgp/140 boost; a new phase II HIV vaccine trial; enrolment of a youths cohort, and a phase I trial in them; as well as the evaluation of the possibility of conducting HIV vaccine trials among neonates.

Networking

Based on considerable investments by the EU and others, this application strengthened clinical trials and related research and development capacity and contributed to its sustainability. The strong and long term relationships and links between the Swedish and German and the Tanzanian and Mozambique partners guaranteed that capacities and technology transfer were effective. Furthermore, North-North networking and coordination has strengthened between partner institutions and scientists in Tanzania, Mozambique, Sweden, Germany and the UK. Additionally, educational, laboratory and therapeutic collaborations between Sweden and United Kingdom have been strengthened to better serve the needs of developing countries (DCs).

Future perspectives

It is anticipated that the foundations laid by this project will enable Tanzania and Mozambique to eventually participate in Phase IIB and Phase III HIV vaccine clinical trials. The capacity that has been built will also be very useful for studies that will involve interventions related to other poverty-related diseases.

1.4 Relevance to EDCTP's objectives and mission

Public health relevance to developing countries and alignment with the priorities of the EDCTP Joint Programme.

The project has focussed on a promising HIV/AIDS vaccine, the presence of already established cohorts, the presence of basic infrastructure, and the generation and sharing of new knowledge through continued conduct of trials of the most promising concepts of preventive immunizations by European partners in Stockholm and London. This is in full support of the EDCTP statement that 'clinical trials are a critical bottle neck' in the development of an HIV vaccine in Africa and we have accepted that there needs to be a 'focus on phase II trials'.

PROJECT OUTCOMES

2. Summary and results

Please make reference to the original objectives of your proposal and provide a summary of the achievements, results and outcomes from your project

The project objectives were:

1. Extend the findings in the HIVIS studies, i.e. optimize HIV vaccine delivery
2. Expand capacity to perform future phase IIB and III trials
3. Extend the current adult target cohorts to youths
4. Develop capacity to investigate preventive HIV vaccines in neonates

Executive summary of the overall project results

1. HIV vaccine delivery has been further optimized in the WP1 and WP2 of the project. **The HIVIS-03 study (WP1)** has demonstrated that priming with HIV-1 DNA and boosting with HIV-1 MVA was well tolerated. The elicited immunogenicity was very good, and low dose intradermal delivery (i.d.) of DNA was better than high dose DNA given via the intramuscular route (i.m.). The vaccination elicited balanced CD4 versus CD8; and Gag versus Env responses. Responses in the Lymphoproliferative assay (LPA) were broad, cross-reactive and persistent. Additionally, all volunteers were serologically reactive after the 2nd MVA. Neutralizing antibodies were demonstrable in up to 83% of volunteers in PBMC assay, and were ADCC dependent. (**Bakari M**, **et al. Vaccine 2011 29:8417-28**)

   The TaMoVac-01 trial (WP2) has demonstrated that the vaccines were well tolerated. Preliminary analysis shows that there is no difference in giving DNA as Env and Gag plasmids either in separate or combined pools. DNA priming with 2 i.d. injections each containing 300mg (total 600mg) is almost as equivalent to 5 i.d. injections each with 200mg (total 1000mg). Additionally, giving DNA as 0.2 mL i.d. with a Zetajet was well tolerated and feasible.

2. Through conduct of these trials the capacity to perform future phase IIB and III trials has been sustained in Dar es Salaam and Mbeya, but this has now been extended to the Maputo site in Mozambique **(WP-3)**

3. Whereas the cohort that was involved in the HIVIS 03 trial consisted of adults, those involved in the TMV-01 trial included young adults (youths) as well. Significantly, those participating in Mozambique were all youths **(WP-3).**

4. The **WP-4** assessed the acceptability of HIV vaccine research in infants among Mozambican families in Maputo city. Results showed that the majority of the women (89.3%) are willing to allow their babies to be part of an HIV vaccine trial. The main reasons for acceptability are the hope of cure, followed by a reasonable confidence in the health system. However, the overall level of education and knowledge about HIV vaccines is low. More in-depth studies need to be conducted in order to gather more information about the decision-making process regarding health in the families. Education and communication strategies need to be designed to start preparations in order to get the community ready for a potential neonate vaccine trial.

2.1 Were there objectives that were not achieved? Please explain why, making reference to any challenges or setbacks that were experienced during your project. What impact does the non-achievement of objectives have on the project outcomes?

As noted above, to a large extent all the objectives were achieved. Although it was not possible to develop a protocol for neonatal vaccination, we assessed the acceptability of such a potential protocol in an urban African environment. Further studies are needed to better understand the process and effectively prepare the communities for an eventual neonate HIV vaccine trial.

The slow planning and approval process in Mozambique led to a modification of the objectives for the sub-study at CISPOC to be improved to include a novel dosage schedule.

Due to delays in the approval process a no cost extension had to be asked for, which enabled a finalization of all primary objectives.

There were administratively difficult negotiations with collaborators in another EDCTP funded project that were aimed at utilizing the vaccination investment in TaMoVac-01 to have participants receive subsequent boosting with a novel rgp140 and with a novel adjuvant (GLA).

2.2 What are the implications of this work? Please include details of anticipated outputs and outcomes, policy implications and changes in healthcare practice, with timelines.

This work has important implications as summarised below:

- The successful conduct of the project has prepared Tanzania and Mozambique for further HIV Vaccine trials; cohorts have been established, clinical capabilities have been expanded, and laboratories have been strengthened, with validation of endpoint assays.
- New assays have been established to address the opportunities identified in the trials. It is worth noting that all key assays were preformed on site or by local scientists in collaborating laboratories.
- Regulatory capacity has been strengthened as witnessed by the approval process for TaMoVac II. This is particularly true in Mozambique.
- New strategic partner alliances have been forged. The UK HIV Vaccine Consortium has provided the rgp 140 and GLA adjuvant for the amendment of a late protein boost; researchers at WRAIR and Duke University in the USA have generously accepted Tanzanian researchers to be trained and perform advanced antibody analysis.
- Findings from the studies have shown that simplification of intradermal administration is feasible as a first step to a larger trial to study if the vaccine combination is efficacious.
- It has been confirmed that the 2nd MVA boost induces antibodies which are neutralizing with ADCC activity i.e. these antibodies are functional and hence a potentially important characteristic to stop HIV transmission.
- The introduction of a protein boost in a novel adjuvant simulating the successful RV144 pox protein concept used in Thailand has put the trial results in the mainstream of current vaccine concepts.

2.3 What plans are in place to take forward the research findings from this project? Please give details.

Following results of TMV-01, the consortium is engaged in the EDCTP-funded TaMoVac-II trial that will explore the utility of employing electroporation in further optimizing DNA delivery. Additionally, the effect of additional boost with rgp 140/GLA will be further explored. More importantly, the results confirm that the vaccines are ready for a IIB efficacy trial and could form a solid base for further East African collaborative efforts.

2.4 Has this grant enabled you to obtain additional funding and/or led to any complementary/associated projects? If yes, please give details.

Please list the grants, giving the name of the Principal Investigator and Co-applicants; the name of the funding agency, title of project, the total grant amount, role in the project, start and end dates of the grant.

This project has led to a number of associated projects as detailed below:

- The maintenance of the clinical and laboratory capacity has enabled local researchers to address the waning immunogenicity from the prior trial, HIVIS03/TaMoVac-01 (WP1). This was by analysing the immune response 3 years after the last immunization (PI Said Aboud); and through a study aimed at evaluating whether a late 3rd MVA boost could re-establish the immune response (HIVIS 06 project PI Patricia Munseri)
- As mentioned above, the trial has served as a platform for inviting partners to an addendum with rgp140/GLA which has led to a proposal to use rgp140/GLA + MVA in TMVII.
- Investigators at MMRP have initiated a number of immunological sub-studies to address fundamental properties of the vaccines.
- Several socio-demographic studies have addressed the issues of recruitment of volunteers as well as the experiences of study volunteers.
- During the trial, male circumcision has increasingly been discussed as a major issue to address for trial participation. A study was carried out to address this in the Dar es Salaam study population.
- During the study it was found that many volunteers were screened out due to ECG abnormalities. This has become the focus of a sub-study.
- In order to use troponin as an indicator for myocardial disease a sub-study has been carried out to validate that test in an African population. This work may have implications for all safety evaluations of MVA as a vaccine.

2.5 Cofunding changes during the project

*Please indicate whether there were any changes to the cofunding to this project and where applicable include any new cofunding letters in **Annex A**.*

Ludwig-Maximilians Universitat Munchen	In-kind	€ 20,307
Ludwig-Maximilians Universitat Munchen	In-kind	€ 34,729
NACCAP	Cash	€ 200,000
Sida	Cash	€ 193,695
Federal Ministry of Education and Research (BMBF)	Cash	€ 396,222
Imperial College	In-kind	€ 73,950
MRC UK	Cash	€ 95,798
MRC UK	Cash	€ 204,202
BMGF	Cash via EDCTP	€ 1,434,919
Swedish Institute for Infectious Disease Control (SMI)	In-kind	€ 200,000
Walter Reed Army Institute of Research	In-kind	€ 177,927
SIDA	Cash	€ 1,762,804
Embassy of Sweden – Dar es Salaam	Cash	€ 893,376

"[insert text here]"		

Please confirm whether the cofunding amounts listed above are correct or note any changes.

2.6 Changes to management and/or collaboration structure since the last report?

*Please ensure that you have updated the list of collaborators in the basic project information section (section 1.1). For new collaborators, please provide an up-to-date CV in **Annex B**.*

There are no changes to management and/or collaboration structure since the last report.

2.7 Dissemination

Give details of how the activities and results from this grant have been disseminated to the scientific and wider community.

2.7.1 Dissemination to the scientific community

How many accepted (in press or published) peer-reviewed publications (research papers or books) have been produced as a result of this grant?

*Detail each publication in the following order; Author(s); Article Title; Journal Name; Year; Volume; Issue Number; Page Numbers, and confirm that EDCTP funding has been acknowledged in all publications. Please include copies of research papers in **Annex C**.*

1. Muhammad Bakari, Said Aboud, Charlotta Nilsson, Joel Francis, Deus Buma, Candida Moshiro, Eric A. Aris, Eligius F. Lyamuya, Mohamed Janabi, Karina Godoy-Ramirez, Agricola Joachim2, Victoria R. Polonis, Andreas Bråve, Patricia Earl, Merlin Robb, Mary Marovich, Britta Wahren, Kisali Pallangyo, Gunnel Biberfeld, Fred Mhalu, Eric Sandström. Broad and potent immune responses to a low dose intradermal HIV-1 DNA boosted with HIV-1 recombinant MVA among healthy adults in Tanzania. **Vaccine (2011), 29:8417-8428.**

How many additional publications from the ones stated above that you anticipate producing?

- Joachim A, et al. Antibody-mediated inhibition of HIV-1 elicited by HIV-I DNA priming and boosting with heterologous HIV-1 recombinant MVA in healthy Tanzanian adults (HIVIS03 continuation)
- Munseri P, Kroidl A, et al. Priming with a "simplified regimen" of HIV-1 DNA vaccine is as good as a "standard regimen" when boosted with heterologous HIV-1 MVA vaccine (TaMoVac I, comparing 2 vs. 5 HIV-DNA imunizations).
- Podola L, et al. Breadth, phenotype and functionality of Gag-specific T cell responses induced by a heterologous DNA/MVA prime-boost HIV-1 vaccine regimen (TaMoVac I).
- Bauer A., et al. Preferential targeting of conserved Gag regions after vaccination with a heterologous DNA prime Modified Vaccinia Ankara boost HIV vaccine regime (TaMoVac I)
- Viegas E, Tembe N, et al. Phase I/II HIV vaccine trial to assess the safety and immunogenicity of a i.d. DNA prime in combination with an i.m. MVA boost vaccine in 24 healthy volunteers in Mozambique.
- Geldmacher C, Joachim A et al. Safety & Immunogencity following boosting with rgp140/GLA boost; with binding and quantitative rgp140 assays; ELISpot as end-points.
- Nicolao N, Vaz P et al. Feasibility study for HIV vaccination among children in Maputo City, Mozambique.

Please provide details of any other publications resulting from this work

Please confirm that that EDCTP support has been acknowledged on each publication.

"[insert text here]"

Conference and academic workshop presentations

Give details of oral presentations and posters of this work, confirming that EDCTP has been acknowledged.

AIDS Vaccine Conferences

Oct 2009, Paris, France

1. M Bakari, et al. A low dose of multigene, multiclade HIV DNA given intradermally induces strong and broad immune responses after boosting with heterologous HIV MVA. Poster Presentation. EDCTP acknowledged.

2. Said Aboud, et al. HIV-specific T-lymphocyte proliferative responses induced by a multigene multiclade HIV-1DNA/MVA

heterologous vaccine in Tanzanian volunteers. Poster Presentation. EDCTP acknowledged

Oct 2010, Atlanta, USA

1. Said Aboud, et al. Broad and strong immune responses in a trial of a heterologous DNA prime MVA boost HIV vaccine among healthy Tanzanian volunteers (HIVIS03). Poster Presentation. EDCTP acknowledged

2. Edith Tarimo, et al. Experiences of Behavior Change among Volunteers in an HIV Vaccine Trial in Dar es Salaam, Tanzania. EDCTP acknowledged

September 2011, Bangkok, Thailand

1. S Aboud, et al. Persistence of vaccine-induced antibodies following HIV-1 DNA prime MVA boost vaccination among healthy Tanzanian volunteers

2. E Viegas, et al. Incidence of HIV-1 among Youths in Maputo City, Mozambique: a Cohort Study. Poster presentation

3. N Tembe, et al. Reference Values for Clinical Laboratory Parameters among Youths in Maputo City, Mozambique. Poster presentation

September 2012, Boston, USA

1. Joachim A, et al. Antibody-mediated inhibition of HIV-1 elicited by HIV-I DNA priming and boosting with heterologous HIV-1 recombinant MVA in healthy Tanzanian adults Oral Presentation, EDCTP acknowledged.

2. Bakari, M. HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA priming and MVA boosting strategies, TaMoVac-I Project. Oral Satellite Presentation, EDCTP acknowledged.

3. Bauer A, et al. Preferential targeting of conserved Gag regions after vaccination with a heterologous DNA prime Modified Vaccinia Ankara boost HIV vaccine regime. Poster Presentation. EDCTP acknowledged

4. Mann P, et al. High prevalence of ECG variations and abnormalities in young and healthy TaMoVac 01 HIV vaccine trial volunteers from Tanzania. Poster Presentation. EDCTP acknowledged

5. Munseri P, et al. Priming with a “simplified regimen” of HIV-1 DNA vaccine is as good as a “standard regimen” when boosted with heterologous HIV-1 MVA vaccine. Poster Presentation. EDCTP acknowledged

6. Ngatoluwa M, et al. Enrolment and logistical challenges in TaMoVac 01 Phase I/II HIV trial despite the completion of an earlier (HIVIS-03 trial trial) in Dar es Salaam. Poster Presentation. EDCTP acknowledged

7. Podola L, et al. Breadth, phenotype and functionality of Gag-specific T cell responses induced by a heterologous DNA/MVA prime-boost HIV-1 vaccine regimen. Poster Presentation. EDCTP acknowledged

5th EDCTP Forum*, Oct 2009, Arusha, Tanzania:*

1. Chalamilla G, et al. Preparation of Youths Clinic at the Infectious Diseases Centre (IDC) for the recruitment of youths in HIV prevention clinical trials. Oral. EDCTP acknowledged

2. Francis J, et al. Safety profile of a multigene, multiclade HIV-1 DNA plasmid vaccine boosted with HIV-1 MVA among healthy volunteers in Dar es Salaam, Tanzania. Oral presentation. EDCTP acknowledged.

3. Kichenyenge T and Mmbaga S (on behalf of HIVIS03 Volunteers). Experiences of Volunteers participating in a Phase I/II HIV Vaccine Trial (HIVUS 03) in Dar es Salaam, Tanzania. Poster Presentation. EDCTP acknowledged

6th EDCTP Forum*, 2011, Addis Ababa, Ethiopia*

1. Joachim A, et al. HIVIS 03: Antibody-mediated inhibition of HIV-1. Oral presentation. EDCTP acknowledged.

US Military HIV Research Program Science meeting, 2011 Philadelphia, USA

1. Nilsson C, et al. Strong and broad cellular and humoral immune responses to intradermal and intramuscular HIV-1 DNA boosted with heterologous HIV-1 recombinant MVA among healthy adults in Sweden and Tanzania. Oral presentation. EDCTP acknowledged.

INS Research Day

1. Viegas et al. Overview of the HIV incidence and prevalence of other sexually transmitted disease in youths in Maputo, Mozambique.

Oral presentation.

1st National Conference on Public Health in Mozambique

1. Tembe et al. Overview of HIV Vaccine trial in youths using DNA priming and MVA boosting in healthy volunteers in Mozambique. Oral presentation.

XIV National Health Conference in Mozambique

1. Jani et al. Preliminary results of HIV incidence study and prevalence of other sexually transmitted disease in youths in Maputo, Mozambique. Oral presentation.

2.7.2 Public engagement and other communication activities

Give details of presentations to non-academic audiences.
This includes feedback activities to research participants and related communities, meetings with policy makers or health care professionals, media coverage or other related activity.

In Dar es Salaam:
There have been meetings with the Community Advisory Board (CAB); Police & Prisons communities as well as the leadership; and All-Volunteers meetings.

In Mbeya:
Prior to initiation of the trial, a press conference was held. CAB meetings took place regularly (every 3 to 4 months) and CAB members were informed of the progress in these meetings.
In "society sensitization meeting" groups in several areas were informed of HIV Vaccine research in general and the TaMoVac 01 Trial specifically.
In a meeting with all trial participants, the progress of the trial and future improvement possibilities were discussed.

In Maputo:

1. Press conference to launch the TaMoVac 1 trial
2. Interviews to TVs, Radio and Newspapers about the TaMoVac 1 trial
3. Updates on the progress of TaMoVac 1 trial through interviews with media
4. Visit from the Mozambican Parliament to the vaccine trial site in Maputo
5. Article in a Swedish magazine about TaMoVac 1 trial
6. General assembly of the United Nations, photography exhibition, September 2012

Please give details of the outputs or outcomes from these activities.

In Dar es Salaam:
Support from Police and Prisons authority has been enhanced. Feedback from CAB members and Volunteers has helped the retention of volunteers as well as in the recruitment of volunteers for the TaMoVac-II trial.

In Mbeya:. Continuous interactions with the CAB and the communities has strengthened the relationship and trust of the research site and the community. This has helped to tackle any issues that arose fast and also provides the opportunity for improved recruitment of volunteers for further studies.

In Maputo: Better recruitment and retention of volunteers for TaMoVac 1 and increased knowledge of Mozambican society and media about HIV vaccines and HIV vaccine research.

2.7.3 Research resources and intellectual property

Give details of any research resources or intellectual property resulting from this grant.
This includes websites, software or database development, patents, product licenses or other related activity.
The TaMoVac-01 database was developed by Max Kimambo, by then an employee of MMRP. The database's intellectual property has been assigned to the TaMoVac consortium

3. Clinical trials, observational studies and sub-studies

3.1 Clinical Trial or Observational study (including feasibility studies, cohort studies, social science studies). *Please complete or update the information about each clinical trial or sub-study supported by this grant. Please refer to the guidelines section at the end of this report for further details on how to complete this section.*

Study 1	**HIVIS 03 continuation**
Site Principal Investigator(s):	• Fred Mhalu, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (MUHAS)
Clinical Trial/Study Sponsor:	Muhimbili University of Health and Allied Sciences/Swedish Institute for Infectious Disease Control (SMI)
Trial/Study title:	A phase I/II trial to assess the safety and immunogenicity of a plasmid DNA-MVA prime boost HIV-1 vaccine candidate among volunteers in Dar es Salaam, Tanzania
Goal:	Assess the safety and immunogenicity of a plasmid DNA-MVA prime boost HIV-1 vaccine candidate. HIVIS 03 is a follow-up phase I/II HIV vaccine study in Tanzania of HIV plasmid DNA prime MVA boost that was successfully completed in Sweden
Primary Objective(s):	• To determine safety and immunogenicity of HIVIS-DNA priming and MVA boosting candidate vaccine
Secondary Objective(s):	• To build expertise and capability in evaluating HIV-1 vaccine candidates in Dar es Salaam, Tanzania
Study type	Phase I/II Clinical Trial
Study design	Randomised, Double Blind, Placebo Controlled trial
Collaborating site(s):	Swedish Institute for Infectious Disease Control (Sweden)
Study design:	Randomised, controlled, double-blinded phase I/II trial
Number of subjects:	Healthy adults (Police Officers), N= 60
Product(s):	Priming – env (HIV-1 subtype A, B, C), rev (HIV-1 subtype B), gag (HIV-1 subtype A, B) and RTmut (HIV-1, subtype B) Boosting – MVA-CMDR expressing HIV-1 genes – gp160 (subtype E, CM235) and gag and pol (subtype A, CM240)
Manufacturer/ Developer:	Vecura Company at KI in Sweden (DNA); and WRAIR in USA (MVA-CMDR)
Cofunders:	BMGF and Walter Reed Army Institute of Research (WRAIR), BMBF and LMU Munchen (Germany), NACCAP (Netherlands), EU, SIDA and Embassy of Sweden (Sweden), the Regional HIV/AIDS Team for Africa, Embassy of Sweden, Lusaka, jointly funded by Sweden and Norway, MRC UK and Imperial College (UK)
Trial Registration number(s):	• ISRCTN90053831 • ATMR2009040001075080
Sub-studies:	Not applicable
Status:	Completed
Summary of the trial progress made during the course of the entire project, including any setbacks or particular challenges that were faced:	First patient in: Feb 2009 Last patient out: July 2010 42 volunteers out of 60 received the 2nd MVA boost. The vaccine was deemed safe, and a total of 11 SAE unrelated to vaccination have been observed. Study closure visit done June 24 2010. ***Challenges*** 1. Difficult recruitment of female volunteers 2. Public misconceptions, eg volunteers are injected with an HIV virus 3. Staff attrition
Trial completion	**Has the trial been completed? YES** **If YES, please confirm that all trial-related activities have been carried out, giving details and dates as appropriate. See Section 3 Clinical Trial or observational study notes on how to complete this section.** It is confirmed that all trial-related activities have been carried out as detailed above. **If NO, please give details of the activities still to be completed. Provide supporting documentation in *Annex D.***

Study 2	**Phase I/II Tanzania combined project with AfrEVacc (CT.2006.33111.001) (Weber)**
Site Principal Investigator(s):	• Muhammad Bakari, Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, Tanzania • Leonard Maboko, NIMR-Mbeya Medical Research Programme (NIMR-MMRP), Mbeya, Tanzania.
Clinical Trial/Study Sponsor:	Swedish Institute for Communicable Disease Control and MUHAS
Trial/Study title:	A phase I/II trial to assess safety and immunogenicity of i.d. DNA priming, i.m. MVA and i.m. rgp140/GLA-AF boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania
Goal:	Exploration of the optimal delivery method of HIV-1 DNA vaccine
Primary Objective(s):	1. Determine safety of HIVIS-DNA at a dose of 600 µg or 1000 µg delivered ID in combination with MVA-CMDR boost IM 2. Determine immunogenicity of HIVIS-DNA at a dose of 600 µg or 1000 µg delivered ID in combination with MVA-CMDR boost IM.
Secondary Objective(s):	1. Compare immunogenicity of HIVIS-DNA at a dose of 600 µg given as combined plasmid pools or separate plasmid pools ID in combination with MVA-CMDR boost IM 2. Explore the safety and immunogenicity of boosting with two doses of rgp140 in the adjuvant GLA-AF, administered IM 3. To build expertise and capability in evaluating HIV-1 vaccine candidates in Tanzania.
Study type	Phase I/II Clinical trial
Study design	Randomised, controlled, double-blinded phase I/II trial
Collaborating site(s):	National Institute for Medical Research (NIMR), Tanzania; Swedish Institute for Infectious Disease Control (Sweden), WRAIR (USA), University of Munich (Germany), Imperial College (UK)
Study design:	Randomised, controlled, double-blinded phase I/II trial
Number of subjects:	Healthy adults (no less than 30 females), N = 120
Product(s):	Priming Pool 1: env (HIV-1 subtype A, B, C) and rev (HIV-1 subtype B) Pool 2: gag (HIV-1 subtype A, B) and RTmut (HIV-1, subtype B) Boosting: Modified Vaccinia Ankara vaccine (MVA-CMDR) expressing HIV-1 genes – gp150 (subtype E, CM235) and gag and pol (subtype A, CM240) Further boosting (amended protocol): Recombinant C clade trimeric envelope protein (rgp140) derived from the Chinese isolate CN54 mixed with glucopyranosyl lipid A (GLA)
Manufacturer/ Developer:	**DNA**: Vecura (Sweden) **MVA-CMDR**: WRAIR (USA) **CN54gp140**: Polymun Scientific. Address is: Immubiologische Forschung GmbH, Donaustr. 99, 3400 Klosternneuburg, Austria. **GLA-AF**: Infectious Disease Research Institute (IDRI) 1124 Columbia Street, Suite 400, Seattle, Washington 98104, USA. nb: The CN54gp140 & GLA were obtained for the study through Imperial College (London, UK)
Cofunders:	BMGF and WRAIR (USA); BMBF and LMU Munchen (Germany); NACCAP (Netherlands); SIDA and Embassy of Sweden (Sweden); the Regional HIV/AIDS Team for Africa, Embassy of Sweden, Lusaka, jointly funded by Sweden and Norway; MRC UK and Imperial College (UK); AfrEVacc project, Imperial College (UK); Wellcome Trust UK HIV Vaccine Consortium (UK)
Trial Registration number(s):	PACTR2010050002122368
Sub-studies:	Not applicable
Protocol Development **Include the approved, signed protocol or protocol amendment as well as a description of the changes made between protocol or*	Latest version of protocol: Version 4.1, dated **23rd Jan 2012** Actual date of approval: **08th/05/2012** (National Ethics C'tee) Name of independent ethics committee(s) and/or national regulatory authority(ies) that approved the protocol:

*amendment versions as **Annex E**. Also include electronic copies of all ethical or regulatory approvals as **Annex F** if these have not been provided previously,*	1. Tanzania National Ethics Committee at the National Institute for Medical Research (NIMR) 2. MUHAS's Senate Research and Publications Committee (Local IRB) 3. Mbeya Medical Research Committee (Local IRB) Additional comments, amendments (including version of amendment) Latest version (version 4.1) involved collaboration with the AfrEVacc group whereby additional boosting with a protein/adjuvant (rgp140/GLA) was provided to participants who had received DNA prime and MVA boosting.
Monitoring plan **Include an electronic copy of the **external** monitoring reports as **Annex G**.*	***Copy and paste the details below to add additional monitors (if applicable). Indicate whether these are independent external monitors or internal monitors.*** **1. Name and details of External Monitor**: Dr Beryl Wessner WRAIR, USA E-mail: bwessner@hivresearch.org and then, Gail A Smith, a Senior Clinical Research Associate from the: US Military HIV Research Program (MHRP) 6720-A, Rockledge Drive, Suite 400, Bethesda, MD 20817, e-mail: gsmith@hivresearch.org Frequency of monitoring visits? (please provide dates) Dates are as indicated below: • August 2010 • February 2011 • August 2011 • February 2012 • July 2012 • October 2012 • December 2012 **2. Name and details of Internal Clinical Monitor**: Eric Sandstrom Institute of Clinical Research and Education Sodersjukhuset, Karolinska Institutet Sjukhusbacke 10 S 118 83 Stockholm, SWEDEN Phone: +46 8 616 2571 Fax: +46 8 616 2509 E-mail: eric.sandstrom@sodersjukhuset.se Frequency of monitoring visits? (please provide dates) Dates are as indicated below: • October 2010 • February 2011 **3. Name and details of Internal Laboratory Monitor**: Charlotta Nilsson Swedish Institute for Infectious Disease Control (SMI) and Karolinska Institute (KI) Nobelsvag 18 SE 17182 Solna, SWEDEN Phone: +46 8 4572612

E D C T P

	Fax: +46 8 337460 E-mail: charlotta.nilsson@smi.se Frequency of monitoring visits? (please provide dates) Dates are as indicated below: • January 20-21 2009, completion of HIVIS03 part 1, TMV I WP1 was planned to start 2 weeks later • May 14-15, 2009 • September 22-23, 2009 • January 21-22 2010 • August 31-September1, 2010 • January 27-31, 2011 • September 29-31, 2011 • January 26-30, 2012 • September 19-21, 2012 • November 28-29, 2012, completion of TMVI amendment **Indicate the name of the contract research organisation (if applicable)** NOT APPLICABLE
Recruitment/ enrolment	***Copy and paste details below to add additional sites (if applicable)*** **1. Site 1 (MUHAS):** Actual start and end of recruitment (first patient in): 28/**03/2010** to 15/**11/2012** Last update: **27/02/2013** Target number of recruits: **60** Number of volunteers screened: **235** Number of volunteers enrolled: **62** Additional comments (including any SAE, follow-ups, withdrawals, etc.) Of the 62 enrolled volunteers, **58** received the 2nd MVA/placebo vaccination. A further **19** proceeded to receive rgp140/GLA. The vaccines were safe. One Serious Adverse Event, unrelated to vaccination (skull fracture following traumatic assault to the head) has been reported 2. **Site 2 (MMRP)**: Actual start and end of recruitment (first patient in): 07/05/2010 to 01/11/2010 Last update: 21/11/2012 Target number of recruits: **60** Number of volunteers screened: **273** Number of volunteers enrolled: **67** Additional comments (including any SAE, follow-ups, withdrawals, etc.) Of the **67** enrolled volunteers, **58** received the 2nd MVA/placebo vaccination. **21** volunteers proceeded to receive rgp140/GLA. The vaccines were safe. Two Serious Adverse Events, unrelated to vaccination (HIV infections), have been reported.
Summary of the trial progress made during the course of the entire project, including any setbacks or particular challenges that were faced	***Current reporting period*** A total of 509 individuals were screened of whom 129 received the 1st DNA/placebo vaccine in MUHAS and MMRP. 116 received the 2nd MVA placebo, and a further **40** of the above received rgp140/GLA. The vaccines were safe. Preliminary analysis has shown that there is no difference in giving DNA as Env and Gag plasmids either in separate or combined pools. DNA priming with 2 i.d. injections, each containing 300mg (total 600mg) is almost as equivalent to 5 i.d. injections each with 200mg (total 1000mg). Additionally, giving DNA as 0.2 mL i.d. was well tolerated and feasible with a Zetajet. Challenges experienced included: 1. Public misconceptions that we are injecting HIV 2. Inadequate clinical space at MUHAS 3. Limited finances

Trial completion	**Has the trial been completed? NO** **If YES, please confirm that all trial-related activities have been carried out, giving details and dates as appropriate. See Section 3 Clinical Trial or observational study notes on how to complete this section.** "[insert text here]" **If NO, please give details of the activities still to be completed. Provide supporting documentation in *Annex D.*** Follow-up of volunteers has been completed. Data cleaning and analysis is being finalised so as to write the respective manuscripts Additional testing of HIV specific antibody responses induced by the rgp140/GLA boosting vaccinations will be performed.
Study 3	**Phase I Youth Study**
Site Principal Investigator(s):	• Ilesh Vinodrai Jani, Instituto Nacional de Saúde, Maputo, Mozambique • Nafissa Bique Osman, Hospital Central de Maputo, Maputo, Mozambique.
Clinical Trial/Study Sponsor:	Swedish Institute for Communicable Disease Control (SMI)
Goal:	Assess the safety and immunogenicity of a plasmid DNA-MVA prime boost HIV-1 vaccine candidate.
Primary Objective(s):	1. Determine safety of the DNA vaccine at a dose of 600 µg and 1200 µg delivered i.d in combination with MVA-CMDR boost i.m 2. Determine immunogenicity of HIVIS-DNA at a dose of 600 µg and 1200 µg delivered i.d in combination with MVA-CMDR boost i.m.
Secondary Objective(s):	• To build expertise and capability in evaluating HIV-1 vaccine candidates in Mozambique
Study type	Phase I Clinical trial
Study design	A randomized, double blinded, placebo-controlled Phase I HIV vaccine trial among youths
Collaborating site(s):	• Instituto Nacional de Saúde (INS), Maputo, Mozambique • The Swedish Institute for Communicable Disease Control, Stockholm, Sweden • U.S. Military HIV Research Program-Walter Reed Army Institute of Research (MHRP-WRAIR), USA • Imperial College (IC), London, UK
Study design:	A randomized, double blinded, placebo-controlled Phase I HIV vaccine trial among youths
Number of subjects:	A phase I HIV Vaccine Trial performed on 24 consenting youths
Product(s):	Priming Pool 1: env (HIV-1 subtype A, B, C) and rev (HIV-1 subtype B) Pool 2: gag (HIV-1 subtype A, B) and RTmut (HIV-1, subtype B) Boosting: Modified Vaccinia Ankara vaccine (MVA-CMDR) expressing HIV-1 genes – gp150 (subtype E, CM235) and gag and pol (subtype A, CM240)
Manufacturer/ Developer:	DNA: Vecura (Sweden) MVA-CMDR: WRAIR (USA)
Cofunders:	The Regional HIV/AIDS Team for Africa, Lusaka, jointly funded by Sweden and Norway
Trial Registration number(s):	**PACTR2010050002122368**
Protocol Development **Include the approved, signed protocol or protocol amendment as well as a description of the changes made between protocol or amendment versions as **Annex E**. Also include electronic copies of all ethical or regulatory approvals as **Annex F** if these have not been*	Latest version of protocol: 3.0 of 4th May 2011 Actual date of approval: 25/05/2011 Name of independent ethics committee(s) and/or national regulatory authority(ies) that approved the protocol: • National Health Bioethics Committee of Mozambique • Pharmaceutical Department, Ministry of Health of Mozambique Additional comments, amendments (including version of amendment)

provided previously,	
Monitoring plan **Include an electronic copy of the **external** monitoring reports as **Annex G**.*	***Copy and paste the details below to add additional monitors (if applicable). Indicate whether these are independent external monitors or internal monitors.*** 1. **Name and details of Monitor**: Gail A Smith, a Senior Clinical Research Associate from the: US Military HIV Research Program (MHRP) 6720-A, Rockledge Drive, Suite 400, Bethesda, MD 20817, e-mail: gsmith@hivresearch.org Dates are as indicated below: • April 2011 • June 2011 • October 2011 • January 2012 • April 2012 • August 2012 2. **Name and details of Internal Laboratory Monitor**: Charlotta Nilsson Swedish Institute for Infectious Disease Control (SMI) and Karolinska Institute (KI) Nobelsvag 18 SE 17182 Solna, SWEDEN Phone: +46 8 4572612 Fax: +46 8 337460 E-mail: charlotta.nilsson@smi.se Frequency of monitoring visits is as shown below: • June 17-20, 2011 (pre-trial review) • January 18-20, 2012 • May 28-29, 2012 • December 4-7, 2012 • February 13-16, 2013 **Indicate the name of the contract research organisation (if applicable)** NOT APPLICABLE
Recruitment/ enrolment	***Copy and paste details below to add additional sites (if applicable)*** **3. CISPOC Site** Actual start and end of recruitment (first patient in): 14/08/2011 to 22/03/2012 Last update: 20/02/2013 Target number of recruits: **24** Number of volunteers screened:77 Number of volunteers enrolled: **25** Additional comments (including any SAE, follow-ups, withdrawals, etc.) One study withdrawal after 1st vaccination due to impossibility to comply with study visits. One SAE (HIV infection), unrelated to vaccination, has been reported.
Summary of the trial progress made during the course of the entire project, including any setbacks or particular challenges that were faced	***Current reporting period***
Trial completion	**Has the trial been completed? NO** **If YES, please confirm that all trial-related activities have been carried out, giving**

	details and dates as appropriate. See Section 3 Clinical Trial or observational study notes on how to complete this section. "[insert text here]" **If NO, please give details of the activities still to be completed. Provide supporting documentation in *Annex D.*** All vaccinations have been completed. Follow up is expected to be completed by the 2nd week of March 2013 Some immunological assays will continue to be performed throughout the year 2013.
Study 4	**Neonate feasibility study**
Site Principal Investigator(s):	Paula Vaz, Hospital Central de Maputo, Maputo
Clinical Trial/Study Sponsor:	Not applicable
Trial/Study title:	Acceptability study for HIV vaccination among children in Maputo City, Mozambique
Goal:	Assess factors involved in the acceptability of a new-born/infant HIV vaccine trial
Primary Objective(s):	• Evaluate acceptability from mothers and families concerning HIV and vaccines
Secondary objective(s):	n/a
Study type	Observational study
Study design	Cross-sectional study
Collaborating site(s):	Not applicable
Study design:	Mixed qualitative/quantitative
Number of subjects:	150
Product(s):	Not applicable
Manufacturer/ Developer:	Not applicable
Cofunders:	Not applicable
Trial Registration number(s):	Not applicable
Sub-studies:	Not applicable
Status:	Completed
Summary of the trial progress made during the course of the entire project, including any setbacks or particular challenges that were faced	A pilot acceptability study has been undertaken in November 2011 aimed at preparing IEC interventions for an eventual HIV vaccine trial in neonates. The study took place in Maputo Central Hospital (MCH) and Polana Caniço Health Center (PCHC) whereby 36 respondents filled in questionnaires and underwent interviews. These were women and men sitting in waiting rooms at the maternity and pediatric services, as well as husbands and mothers-in-law. After analysis of the data, it has been learnt that husbands and mothers-in-law must be reached by direct invitation to facilitate neonatal vaccination. The conditions have therefore been set to actually implement the study.
Trial completion	**Has the study been completed? YES** **If YES, please confirm that all trial-related activities have been carried out, giving details and dates as appropriate. See Section 3 Clinical Trial or observational study notes on how to complete this section.** "[insert text here]" **If NO, please give details of the activities still to be completed. Provide supporting documentation in *Annex D.*** "[insert text here]"

4. Research staff, training and capacity building

4.1 Please provide the name and details of all staff in receipt of a salary or stipend from this grant (including fellows, students, research assistants, nurses, technicians as appropriate). Please also give details about yourself. (see attached spreadsheet). *Please note: Data nationality and gender is collected in order to help inform EDCTP's monitoring policies. All information collected is confidential and will be reported in aggregate only.*

Please see the attached spreadsheet.

4.2 How has the grant contributed to the professional development of the staff in the aforementioned spreadsheet (including yourself)? Highlight any individuals who have progressed in their careers or been promoted.

This grant has greatly assisted in building scientific and managerial competencies and skills that have contributed to professional development of the staff. This is detailed below:

At MUHAS

1. **Muhammad Bakari** is an Associate Professor of Medicine, and has been promoted from being an Associate Dean, School of Medicine to being the Deputy Vice Chancellor of MUHAS responsible for Planning, Finance and Administration
2. **Eligius Lyamuya** is a Professor of Microbiology and Immunology, and is currently the Deputy Vice Chancellor of MUHAS responsible for Academics, Research and Consultancy
3. **Said Aboud** has been promoted from a Senior Lecturer to an Associate Professor of Microbiology and Immunology at MUHAS, and is currently the Head of Department
4. **Patricia Munseri** continues with Lecturership at the Department of Internal Medicine, MUHAS. Her next promotion to Senior Lecturership will be facilitated by publications from this project
5. **Agricola Joachim** continues with Lecturership at the Department of Microbiology and Immunology, MUHAS. Her next promotion to Senior Lecturership will be facilitated by publications from this project

At MMRP

None

At Maputo

1. **Edna Viegas** is a medical doctor and has been promoted to deputy director of Polana Caniço Reasearch Center (CISPOC) in Maputo, Mozambique.
2. **Bindiya Meggi** is a Pharmacist and has been promoted to quality manager of Polana Caniço Reasearch Center (CISPOC) in Maputo, Mozambique.

4.3 Is there anything else you wish to report about your EDCTP grant, e.g. awards, special recognitions, etc.?

There have been no awards or special recognition as such

4.4 Post graduate training

Type of Training	Target number of postgraduate trainees (detailed in the original proposal)
Masters	0
PhD	5
Postdoctoral	0

Please indicate the final list of postgraduate students supported by this grant

Name of trainee and type of training	Nationality	Gender	Institution	Supervisor(s)	Title of proposed study	Start and end date
PhD						
Said Aboud	Tanzania	M	Karolinska Institute	Gunnel Biberfeld and Fred Mhalu	Evaluation of HIV testing strategies and Monitoring of Immune Responses in HIV vaccinated individuals in Tanzania	Dec 2004 – Oct 2011
Edith AM Tarimo	Tanzania	F	Karolinska Institute	Anna Thorson, Aslo Kulane, Thecla Kohi and Eric Sandstom	What motivates participation in HIV vaccine trials: A study among Police Officers in Dar es Salaam, Tanzania	Apr 2007-June 2011
Patricia Munseri	Tanzania	F	Karolinska Institute	Eric Sandstom and Muhammad Bakari	Tuberculosis and HIV infections: Magnitude of HIV in the Police cohort and its suitability for HIV Vaccine trials, Suitability of Rapid tests for Diagnosis of HIV associated TB	May 2007 – May 2013
Agricola Joachim	Tanzania	F	Karolinska Institute	Gunnel Biberfeld, Charlotta Nilsson and Eligius Lyamuya	Studies of immune responses induced by immunization with HIV-1 DNA followed by HIV-1 MVA in healthy individuals in Dar es Salaam, Tanzania	Dec 2011 – late 2015
Nelson Tembe	Mozambique	M	Karolinska Institutet	Charlotta Nilsson Ilesh Jani Soren Andersson	Studies in relation to the establishment of a laboratory framework for the conduct of HIV vaccine trials in Mozambique	May 2013 to February 2016

Final outcome of postgraduate student training

Did you accomplish the targeted recruitment of postgraduate students? If not, briefly summarise why.
YES

Please confirm which MSc or PhD students listed above have successfully received their degrees at the time of submitting this report.

- Edith Tarimo completed her PhD training at the Karolinska Institutet, Stockholm, Sweden in June 2011
- Said Aboud completed his PhD training at the Karolinska Institutet, Stockholm, Sweden in October 2011

Briefly describe the future career plans of the postgraduate students trained on this grant.

- The Postgraduate students trained on this grant at MUHAS are all members of the Academic staff. The scientific training and subsequent publications will be critical for their career development in terms of being better researchers and better teachers. Their promotions to subsequent academic ranks are dependent on publications, some of which will come from work emanating from this grant

- Nelson Tembe will pursue a research career in immunology of HIV and contribute with lectures at the Eduardo Mondlane University, Mozambique.

4.5 Short term training

Please list down the number of people trained at the various collaborating sites

	Type of training							
Collaborating site	**IT, Statistical**	**Clinical research monitors**	**Financial management**	**Project management training**	**Nurses, clinicians, scientists**	**Community representatives**	**Lab personnel**	**Regional GCP courses**
MUHAS	**0**	**0**	**1**	**0**	**19**	**10**	**10**	**45**
MMRP	**1**	**2**	**0**	**0**	**10**	**20**	**5**	**25**
Maputo	**4**	**2**	**0**	**0**	**0**	**20**	**5**	**60**
NIMR	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**

4.6 Have you accomplished all of the short term training goals as set out in the original proposal? If not, why?

In all sites a study specific training was conducted prior to trial initiation for the clinic, laboratory, pharmacy and data management personnel. Additionally, during several exchange visits with the MUHAS team in either Dar es Salaam or Mbeya further training was offered.
A GCP course was conducted in Mbeya through ARMANET prior to the trial and all key staff members have undergone online CITI ethics training. ECG training was performed for clinicians and nurses throughout continuous sessions. Laboratory experience and training of new lab staff members was increased for cellular immunological methods. In collaboration with the AfreVac consortium a new ELISA Protocol for quantification of HIV-Env-specific IgG and IgA antibodies in Plasma was implemented at MMRC.
Throughout the TaMoVac I database development led by Max Kimambo concerning programming and maintenance transfer was provided to the NIMR data management section and handed over for TaMoVac II. Database specific training was performed at MMRP, MUHAS and later on an adapted database to the Maputo team.

4.7 Infrastructure upgrade and capital equipment

4.7.1 Summarise how the infrastructure upgrades and purchasing of capital equipment improved the capacity to conduct future research for each collaborating site (see the guidelines at the end of the report for an explanation of the levels). *We always appreciate before-and-after photos of infrastructure upgrades. Please include them in **Annex H**.*

Collaborating site	How has the capacity improved? Did you reach your targeted level?	Any particular challenges that the site faced during the grant? What else needs to be improved to further the site's capacity?
MUHAS, Clinical	The Clinical Trial Centre at Makuti has been improved. Offices have been renovated, and office furniture has been purchased. Office equipment such as computers, printers and copiers have been bought.	Further improvements are needed to create more space. Preferably a bigger unit has to be built.

MUHAS, Laboratory	The following items have been obtained: • Backup-generator • Centrifuge • Safety cabinets • CO_2 incubator • Liquid nitrogen storage containers • FACSCanto II • Liquid nitrogen plant • Nucleocounter • ELISA reader	
MMRP	There have been structural improvements to the counselling area to provide more privacy and simultaneous counselling of more volunteers. An ECG room was set up and equipped followed by ECG training to clinicians and nurses	
NIMR	The data management office in NIMR has been improved. Office equipment such as laptops, computers and a server have been procured.	Further improvements are needed such as procurement of more computers, office furniture and preferably another server.
Maputo	The CISPOC infrastructure has been improved with renovations, office furniture, air conditioners and security alarm systems. The INS laboratory has also been equipped with air conditioners. The pediatric ward of Maputo Central Hospital, has been equipped with new furniture. New equipments has been purchased for the laboratory: safety hood, CO2 incubator, Centrifuge, waterbath, Cellcounter, Liquid nitrogen storage and freezers/Fridge.	Further improvements are needed to create a better flow of the participants in the clinic, build new clinic rooms, plumbing system needed for clinic rooms and pharmacy, some equipment is needed for the pharmacy.

5. Networking

5.1 Please give details of the collaborations that have developed as a result of this grant.

This grant has brought together institutions from the North and the South. The European institutions are the Karolinska Institutet (KI), the Swedish Institute for Infectious Disease Control (SMI), University of Munich (LMU), and Imperial College London. Even more importantly it has brought together institutions from two developing countries, Tanzania and Mozambique. These are MUHAS, NIMR, and MMRP in Tanzania; along with Maputo Central Hospital and the National Institute of Health in Mozambique.

Additionally the Scientific work has greatly benefitted from the assistance received from the US Military HIV Research Programme (US-MHRP). This has been in terms of provision of MVA vaccine, External Monitoring, as well as advice on critical clinical and immunological issues.

Of particular importance is the collaboration between the TaMoVac and AfrEVac consortia that has enabled additional rgp/GLA boosts to TMV-01 volunteers. Through this collaboration the trial management group (TMG) calls and Steering Committee calls have been better organised and better documented. There has also been significant assistance in data management.

Collaborators meetings have been held every year and these have been important in assessing progress and planning future activities

The TaMoVac website has been developed and is currently being managed by NIMR Tanzania (**http://www.tamovacproject.org**)

5.2 How do you propose to sustain these collaborations and partnerships in the future?

This is an excellent collaboration and has involved significant investment. We strongly propose that this be sustained and be further strengthened through conduct of phase IIB or III trials. We should also explore the possibility of other joint grant applications.

6. Annexes and report checklist

Annex A: Have you included any new cofunding letters (related to question 2.5)?	NO
Annex B: If there are new collaborators in the project (related to questions 1.1 and 2.6), have they provided an updated CV.	NO
Annex C: Have you included copies of any peer-reviewed journal articles? (Please note: it is not necessary to send poster presentations, powerpoint slides, etc.)	YES
Annex D: Is there any supporting documentation with the incompleted trial activities as described in Section 3?	NO
Annex D: Have you included the minutes of management and governance meetings, and documentation referred to in Section 3?	YES
Annex E: Is there an amended version of the protocol included?	NO
Annex F: Ethical and/or regulatory approvals since the last reporting period?	NO
Annex G: External monitoring reports and/or DSMB minutes included?	NO
Annex H: Have you included any photos of your activities (i.e. infrastructure upgrades, project team members, trial-related activities, etc.), see further details in the section “instructions for completing this report”)? **Declaration: I hereby confirm that any photographs submitted to EDCTP can be used for promotional activities. I have also obtained patients’ consent for any photographs involving clinical trial sites.**	YES

Signature and Declaration

I declare the information in this report to be correct and accurate. I have consulted with the collaborators on this project and therefore, I am submitting this report on behalf of the consortium.

Signature ["Project Coordinator"]

Date

Feedback form

As part of its commitment to continuously improve its procedures, EDCTP would appreciate feedback from grant holders. Please provide your comments below. Your response will be kept confidential and not disclosed to others outside of the EDCTP Secretariat.

Final report

Please give your comments on the report template, for example, how easy/difficult it was to complete, whether the guidance notes were informative, time taken to complete the form and whether the guidance was sufficient.

This is a very detailed report. It would be helpful if such a template was given at the start of the project so that as work goes on one fills in the details. Otherwise it is a big challenge to be able to get all the required information after a long lapse of time.

Do you have any comments you would like to make regarding this EDCTP grant, the conduct of this research, or any difficulties you have encountered?

I am very thankful for being given the opportunity to co-ordinate this grant. On behal of my all other collaborators let me express our sincere thanks and gratitude for the support extended to us by EDCTP.

I am also very grateful for the understanding shown by EDCTP in the execution of this grant, in particular the kind acceptance to have no-cost extensions twice, as well as the exceptional approval to have some funds that would have been disbursed to MUHAS at the end of the project be disbursed before the end of the project.

Much as this grant has been very exciting, there were challenges of course. Keeping in tune with the very strict and at times rigid EDCTP rules and regulations has been very draining. This is especially true when one is operating in an environment of sub-optimal financial and administrative support. I suggest that there has to be more flexibility in the regulations so that PI's are given the authority to make pertinent decisions. I believe that the PI of a clinical trial is already haunted by the mammoth task of ensuring that the trial is being conducted to the highest ethical and scientific standards and is ultimately responsible for volunteers safety. It will therefore be very helpful if the administrative aspect was made less demanding.

The second thing is the Clinical Site Infrastructure at MUHAS. This needs further upgrading so that there is enough space and facilities for the conduct of further more sophisticated trials. This would go a long way towards sustaining the excellent human resource that now exists at MUHAS

I will also recommend that EDCTP disburses project funds to institutions in developing countries in full rather than retaining the last 20% until three months after the project ends. Such procedures necessitate borrowing of funds from these institutions, which is not always assured and can lead to unnecessary complications. Linked to this, is the dire need to improve Financial Management expertise for both PI's, Administrators and Project Accountants.

Otherwise this has been a very useful undertaking in fostering scientific collaborations between partners in the North and those of the South, but also among those in the South. We have achieved excellent scientific outputs in our fight against HIV, we have networked, we have built capacity in Tanzania and Mozambique, and to me personally, this has further sharpened my scientific, administrative and managerial skills. THANK YOU VERY MUCH.

E D C T P

5. Networking

5.1 Please give details of the collaborations that have developed as a result of this grant.

This grant has brought together institutions from the North and the South. The European institutions are the Karolinska Institutet (KI), the Swedish Institute for Infectious Disease Control (SMI), University of Munich (LMU), and Imperial College London. Even more importantly it has brought together institutions from two developing countries, Tanzania and Mozambique. These are MUHAS, NIMR, and MMRP in Tanzania; along with Maputo Central Hospital and the National Institute of Health in Mozambique.

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Of particular importance is the collaboration between the TaMoVac and AfrEVac consortia that has enabled additional rgp/GLA boosts to TMV-01 volunteers. Through this collaboration the trial management group (TMG) calls and Steering Committee calls have been better organised and better documented. There has also been significant assistance in data management.

Collaborators meetings have been held every year and these have been important in assessing progress and planning future activities

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5.2 How do you propose to sustain these collaborations and partnerships in the future?

This is an excellent collaboration and has involved significant investment. We strongly propose that this be sustained and be further strengthened through conduct of phase IIB or III trials. We should also explore the possibility of other joint grant applications.

6. Annexes and report checklist

Annex A: Have you included any new cofunding letters (related to question 2.5)?	NO
Annex B: If there are new collaborators in the project (related to questions 1.1 and 2.6), have they provided an updated CV.	NO
Annex C: Have you included copies of any peer-reviewed journal articles? (Please note: it is not necessary to send poster presentations, powerpoint slides, etc.)	YES
Annex D: Is there any supporting documentation with the incompleted trial activities as described in Section 3?	NO
Annex D: Have you included the minutes of management and governance meetings, and documentation referred to in Section 3?	YES
Annex E: Is there an amended version of the protocol included?	NO
Annex F: Ethical and/or regulatory approvals since the last reporting period?	NO
Annex G: External monitoring reports and/or DSMB minutes included?	NO
Annex H: Have you included any photos of your activities (i.e. infrastructure upgrades, project team members, trial-related activities, etc.), see further details in the section "instructions for completing this report")? **Declaration: I hereby confirm that any photographs submitted to EDCTP can be used for promotional activities. I have also obtained patients' consent for any photographs involving clinical trial sites.**	YES

Signature and Declaration

I declare the information in this report to be correct and accurate. I have consulted with the collaborators on this project and therefore, I am submitting this report on behalf of the consortium.

MUHAMMAD BAKARI

Signature ["Project Coordinator"]

28th May 2013

Date

Interim Monitoring Report

Investigative Site Name: **NIMR-Mbeya Medical Research Programme (NIMR-MMRP)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Leonard Maboko**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 2410** **Mbeya, Tanzania**	
Telephone: 255-25-250-6164 Fax: 255-25-250-3134	**Date(s) of Visit: 9-12 Aug 2010**

Investigational Product(s):		**Indication:**		
HIVIS DNA and MVA-CMDR		To assess safety and immunogenicity of HIVIS DNA in combination with MVA-CMDR		
Site staff present (name/role):				
L. Maboko – Principal Investigator (Met in Dar on 13 Aug 2010)	S. Luswema – Data Entry	**RECRUITMENT STATUS** (Cumulative)		
A. Kroidl – Clinical Research Coordinator	L. Khezwan – Data Entry		Last Visit	This Visit As of 9 Aug 2010
B. Kaluwa – Study Doctor	I. Biseko– Data Entry	Total Briefed	N/A	
J. Mwakisioile – Study Clinician	N. Chiwanga – Data Manager	Screened	N/A	181
R. Mashauri– Nurse Counsellor	M. Bwato – Data Enty	Screen Failures	N/A	
T. Muhondwa – Nurse Counsellor	F. Nichombe – Lab Manager	Enrolled	N/A	25
R. Mwilinga – Nurse Counsellor	S. Newagobele – Secretary	Randomized	N/A	25
R. Kunambi – Pharmacist T. Lotto – Back-up Pharmacist	A. Sigauke – Study Secretary	Drop Out or Lost to Follow up	N/A	1
D. Palmba – Community Engagement Officer	E. Sanga – Community Outreach	Withdrawn by investigator	N/A	0
Sponsor/Monitor personnel present (name/role): Bèryl Wessner, PharmD/External Monitor Gail Smith, CCRA/External Monitor		Active:	N/A	24
Others present: N/A		Completed:	N/A	None
Prepared by: Christine Ingram, Gail Smith, Béryl Wessner		Signature(s):		Date prepared: 1 September 2010

Interim Monitoring Report

Investigative Site Name: **NIMR-Mbeya Medical Research Programme (NIMR-MMRP)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Leonard Maboko**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 2410** **Mbeya, Tanzania**	
Telephone: 255-25-250-6164 Fax: 255-25-250-3134	**Date(s) of Visit: 9-12 Aug 2010**

	YES	NO	NA	Comments
CONTINUING SITE ASSESMENT AND ACTIONS/CHANGES SINCE PREVIOUS VISIT				
1. Have study goals and timelines been reviewed with the staff?	X			
2. Has the Principal Investigator maintained adequate study staff personnel in order to conduct the clinical study?	X			
3. Have all outstanding action items noted in previous visit been completed by the Investigator?			X	
4. Have all outstanding action items noted in previous visit been completed by the CRA?			X	
5. Have staff or facilities changed or are changes anticipated? *(If yes, update documents and arrange appropriate action)*	X			Dr. Yesaya Mwasubila is no longer working on the study, and Dr. Bahati Kaluwa has joined the team.
6. Are facilities still adequate?	X			
7. Have all communications been documented and retained appropriately?	X			
RECRUITMENT STATUS/PROTOCOL ADHERENCE				
8. Are there issues related to the recruitment status?		X		
9. Were all subjects enrolled since last visit eligible for this trial?	X			

	YES	NO	NA	Comments
10. Is the enrollment to date sufficient to meet target enrollment goals?	X			
11. Were there protocol compliance issues/protocol violations detected?		X		A memo to the IRB dated 10 March 2010 mentions revisions to the ICF but no acknowledgement letter was received just the stamped revised ICF.
12. Are informed consent forms properly executed and available for each subject?	X			Verified for vaccinated subjects: 2003, 2004, 2016, 2020, 2027, 2032, 2040, 2043, 2044, 2066, 2078
CRF REVIEW/SOURCE DATA VERIFICATION				
13. Are CRF's being completed promptly, signed appropriately, and kept in double locked, limited access storage areas?	X			Some CRFs list different dates: 2 Jan. 2010, 1 Apr. 2010, 1 June 2010, 18 Sept. 2008, March 2010. CRFs are kept in sturdy, lockable cabinets in a limited access lockable room.
14. Are the entries in the CRF legible, complete and accurate?	X			The checkboxes confirming data entry were completed. It is documented in the checklist that a copy of the consent form was offered to the subjects. CRF 2-III V1.2 dated 01 April 2010 at MMRP does not match V1.1 dated 30 Nov. 2009 at MUHAS. Several boxes were not checked, and overwriting on source documents and CRFs was present.
15. Were all required source documents available, accurate, complete and current?	X			The checklists at V1 say that the ECG was not performed but the checklist at V2 does not say that the ECG was performed. Site was asked to document in the source if the time of assessment in Diary Card is in "Swahili" time (-6 hour difference from what is captured on CRF). Clinical Chemistry reports listed incorrect date of birth for several subjects.
16. Were CRF's reviewed and source data verification performed during the visit?	X			

	YES	NO	NA	Comments
17. Do the source documents provide evidence of the investigator's involvement in the study?	X			
18. Overall, is there consistency between CRFs and the source documents?	X			Some values from lab reports were rounded up or down due to lack of decimal points on the CRF. This should be documented in the MOP (SOP).
19. Have CRF's been corrected appropriately?	X			Some corrections were not initialed and dated along with some overwriting as previously noted.
20. Have CRF's been retrieved?			X	Data entry is performed at the site.
21. Have all data clarifications and queries been resolved?			X	
22. Have Deviations and violations been documented appropriately?			X	
23. Have deviations and violations been reported to the appropriate ethical and/or regulatory authorities, and documentation maintained in the site regulatory binder.			X	
ADVERSE EVENTS				
24. Have SAEs occurred since last visit? *(List in comment section)*		X		
25. If yes, have reporting procedures been followed?			X	
26. Have all previous SAE follow-ups been performed and information obtained?			X	

	YES	NO	NA	Comments
27. Has new relevant information for previously reported SAEs been detected and communicated appropriately?			X	
INVESTIGATOR'S/REGULATORY FILE				
28. Has the Investigator's File been reviewed? If yes comment on any deficiencies.	X			See comments on regulatory file at the end of report.
29. Has the monitoring log been signed and dated?	X			
30. Is IRB approval up-to-date? Exp. Date	X			MMREC approval expires 7 March 2011 NIMR approval expires 30 Dec 2010.
31. Is there adequate documentation of IRB notification regarding any of the following: SAEs, amendments to protocol, informed consent or Investigator's Brochure, or changes in study personnel or facilities?	X			Memo to local IRB dated 10 March 2010 documents minor changes to protocol and associated documents including Informed Consent, Assessment of Understanding, Diary Card, Briefing Slides.
32. Is the current approved version of the protocol/protocol amendment present?	X			The current protocol version 2.0 dated Sept. 2009 was present; however, pages 43, 44, 71, 73, 109, and 120 still have V1 dated May 27th 2009.
33. Is there evidence that all amendments to the protocol are being implemented?	X			Above 10 March 2010 memo is implemented.
34. Is the current version of the Investigator's Brochure present?	X			Current HIVIS-DNA IB is present. New MVA IB dated 10 June 2010 was given to site.

	YES	NO	NA	Comments
35. Are the reference ranges and certification for applicable laboratories current?	X			CAP Certificate and current reference ranges were not in the regulatory binder. Site was instructed to add to regulatory binder. Ranges for some labs were on individual lab reports.
INVESTIGATIONAL PRODUCT (IP)				
36. Have storage area/conditions been inspected/reviewed?	X			
37. Do IP supplies reconcile with records?	X			All vials were accounted for.
38. Have randomization envelopes or blinded labels been opened, or are they missing?		X		
39. Are supplies adequate and expiration dates acceptable for continuation of the study?	X			
40. Has the designated IP been prepared for return or destruction?			X	
41. Are the temperatures recorded in the temperature chart within the specified ranges?	X			The use of a Min/Max thermometer was recommended for the -20°C freezer.
42. Have the equipment maintenance logs been completed and maintained appropriately?			X	
43. Has the pharmacy binder been completed and maintained appropriately?	X			

Interim Monitoring Report

Investigative Site Name: **NIMR-Mbeya Medical Research Programme (NIMR-MMRP)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Leonard Maboko**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 2410** **Mbeya, Tanzania**	
Telephone: 255-25-250-6164 Fax: 255-25-250-3134	**Date(s) of Visit: 9-12 Aug 2010**

	YES	NO	NA	Comments
LABORATORY AND BIOLOGICAL SAMPLES				
44. Are the inventory and shipment records for samples current?			X	
45. Have procedures for labeling and shipment of samples been reviewed/discussed?			X	
46. Have laboratory collection and processing documents been completed and maintained appropriately?		X		An inconsistency was found on the Lab Requisition and BMSF was noted: some checkboxes were not marked but tests were run, so the specimens must have been collected. Found that Time Collected of specimen not completed in one instance and overwriting found, particularly of date.
47. Have storage area/conditions for the samples been inspected/reviewed?		X		
48. Have the laboratory equipment logs been completed and maintained appropriately?			X	Not reviewed
ACTIONS PRIOR TO THE NEXT MONITORING VISIT				
49. Actions for the Investigator?	X			Sign the two additional pages of Delegation of Responsibilities. Request a copy of the signed signature pages of Version 2.0 of the protocol from Dr. Bakari.
50. Actions for the CRA?		X		
51. Actions for study coordinator?	X			Add relevant documents to regulatory binder such as Lab certificate and reference ranges. Add stop date of Dr. Yesaya Mwasubila's involvement with TaMoVac.
52. Actions for sponsor?	X			Ship DNA and MVA (will come to Mbeya via Dar)
53. Actions for IRB?		X		
54. Are study supplies (other than IP) adequate? (If no, specify)	X			

Interim Monitoring Report

Investigative Site Name: **NIMR-Mbeya Medical Research Programme (NIMR-MMRP)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Leonard Maboko**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 2410** **Mbeya, Tanzania**	
Telephone: 255-25-250-6164 Fax: 255-25-250-3134	**Date(s) of Visit: 9-12 Aug 2010**

OTHER STUDY SPECIFIC ISSUES/REQUIREMENTS (list and comment below. List can be extended if required)

Procedural Issues

1. There was no written key for the TOU at MMRP. The key was given at a training at MMRP and differs from the key used at MUHAS (Q 13 and 15). As question 13 is about information not given in the briefing nor the ICF, it should be removed at both sites and the English version of question 15 should be corrected. The IRB must be informed. Subsequent information from the TaMoVac teleconference is that one question was removed and the other was clarified on the English version as the Swahili version was correct.
2. For the preparation of DNA the use of a 1mL syringe instead of the 3mL could be helpful, especially for Group 3 where 0.4mL will need to be delivered in 0.1mL aliquots.
3. Vaccine Request form CRF 10-II and Vaccination Randomization form CRF 8-II should be kept with all other CRFs.
5. CRF 10-I the vaccination reaction form should not be filled out before the injection. We found that this was done as a pre-vaccination documentation. This can be confusing.
6. There is a need for more communication and visits between the MUHAS and MMRP sites.
7. It was recommended that the next version of the DCFs/CRFs should be all one version and one date to alleviate confusion and use of incorrect versions.
8. The current approved ICF is v2.1 dated 9 March 2010, which was stamped by the IRB on 11 May 2010; however, the site uses a copy without the IRB stamp.

Regulatory File/SOP Issues

1. MMRP needs a copy of the signed signature pages of Version 2.0 of the protocol.
2. The laboratory section of the Regulatory Binder was missing. This section should include certificates, reference ranges, etc.
3. The pharmacy plan (v1.0 dated 23 Nov. 2009) was not signed.
4. Data Management Plan and SOPs have version and date but were not signed or dated by data manager/author.
5. Data Logs have versions but no dates
6. CVs are in a central CV file. The pharmacist's CV needed to be updated and was done prior to the end of our visit.
7. Some recruitment materials have incorrect age of eligibility.

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 4-6 Aug 2010**

Investigational Product(s):		**Indication:**		
HIVIS DNA and MVA-CMDR		To assess safety and immunogenicity of HIVIS DNA in combination with MVA-CMDR		
Site staff present (name/role):				
M. Bakari – Principal Investigator	D. Buma – Study Pharmacist	**RECRUITMENT STATUS** (Cumulative)		
P. Munseri – Study Coordinator	M. Ngatoluwa – Principal Study Nurse		Last Visit	This Visit As of 4 Aug 2010
T. Masawa – Study Nurse	M. Janabi – Clinical Investigator	Total Briefed	N/A	
D. Neema – Study Nurse	G. Kiwelu – Data Manager	Screened	N/A	85
S. Chum – Deputy Study Coordinator		Screen Failures	N/A	
Sponsor/Monitor personnel present (name/role):		Enrolled	N/A	16
Bèryl Wessner, PharmD/External Monitor		Randomized	N/A	16
Gail Smith, CCRA/External Monitor		Drop Out or Lost to Follow up	N/A	0
Others present: N/A		Withdrawn by investigator	N/A	
		Active:	N/A	16
		Completed:	N/A	None
Prepared by: Christine Ingram, Gail Smith, Béryl Wessner		Signature(s):		Date prepared: 1 September 2010

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 4-6 Aug 2010**

Please specify any "No" answers in Comments field.

	YES	NO	NA	Comments
CONTINUING SITE ASSESMENT AND ACTIONS/CHANGES SINCE PREVIOUS VISIT				
1. Have study goals and timelines been reviewed with the staff?	X			
2. Has the Principal Investigator maintained adequate study staff personnel in order to conduct the clinical study?	X			
3. Have all outstanding action items noted in previous visit been completed by the Investigator?			X	
4. Have all outstanding action items noted in previous visit been completed by the CRA?			X	
5. Have staff or facilities changed or are changes anticipated? *(If yes, update documents and arrange appropriate action)*			X	
6. Are facilities still adequate?	X			
7. Have all communications been documented and retained appropriately?		X		All relevant correspondence (memos, email, letters) between site and sponsor or monitors needs to be kept in the regulatory binder and available for review.
RECRUITMENT STATUS/PROTOCOL ADHERENCE				
8. Are there issues related to the recruitment status?		X		
9. Were all subjects enrolled	X			

	YES	NO	NA	Comments
since last visit eligible for this trial?				
10. Is the enrollment to date sufficient to meet target enrollment goals?	X			The site planned for an enrollment period of 1 year.
11. Were there protocol compliance issues/protocol violations detected?	X			The current approved ICF is V2.0 dated Sept. 2009. A memo to the IRB dated 10 March 2010 mentions the ICF & TOU revisions; however, no acknowledgement was received and not expected per PI. The more recent ICF is being used at the site, but does not list a version # nor date. Risk assessments, and diaries being used are V1.0 dated 18 Sept. 2008 instead of the approved V2.0 dated Sept. 2009. V1.0 (18 Sep 2008) was used for Subj. 3044 at Visit 1, which is a deviation from the one created per the 10 March 2010 memo to the IRB.
12. Are informed consent forms properly executed and available for each subject?	X			Verified for vaccinated subjects: 3003, 3032, 3036, 3041, 3043, 3044, 3048, 3053, 3055, 3057, 3062, 3063, 3069, 3070, 3071, 3082
CRF REVIEW/SOURCE DATA VERIFICATION				
13. Are CRF's being completed promptly, signed appropriately, and kept in double locked, limited access storage areas?	X			Some CRFs list different dates: 5 Jan. 2010, 14 Nov. 2009, 17 Sept. 2009, 25 Sept. 2009, 18 Sept 2008. CRFs are kept in lockable metal cabinets in a lockable room. A number of Eligibility Forms not countersigned by Dr. Bakari after completion and signature of Dr. Munseri.
14. Are the entries in the CRF legible, complete and accurate?	X			The checkboxes confirming data entry were rarely completed. As agreed in Feb. 2010, the assignment number should be removed from source documents and CRFs. It must not be replaced by the serial number from the Randomization list.

	YES	NO	NA	Comments
15. Were all required source documents available, accurate, complete and current?	X			
16. Were CRF's reviewed and source data verification performed during the visit?	X			Subjects reviewed 100%: 3044 (V1-V5), 3048 (V1-V6), 3053 (V1-V5) Exclusion Question 10 of the Inclusion/Exclusion was not answered for any of the subjects. It is not exclusionary but it must be answered.
17. Do the source documents provide evidence of the investigator's involvement in the study?	X			
18. Overall, is there consistency between CRFs and the source documents?	X			
19. Have CRF's been corrected appropriately?	X			Some corrections were made prior to our departure, but the remainder were left pending.
20. Have CRF's been retrieved?			X	Data entry is performed at the site.
21. Have all data clarifications and queries been resolved?			X	
22. Have Deviations and violations been documented appropriately?	X			There are deviations sent by Patricia July 3 & 15 for glucose not collected, PE not done, urine not collected, unsigned IC before TOU, underage signed IC but not enrolled.
23. Have deviations and violations been reported to the appropriate ethical and/or regulatory authorities, and documentation maintained in the site regulatory binder.		X		Deviation for subject 3044 needs to be submitted for use of incorrect Assessment of Understanding (TOU) at Visit 1 (Version 1.0, 18 Sept. 2008 used). Previous protocol deviations sent by Dr. Munseri should also be submitted per IRB requirements. They were documented as not needing IRB submission. All can be submitted with the progress report.

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 4-6 Aug 2010**

	YES	NO	NA	Comments
ADVERSE EVENTS				
24. Have SAEs occurred since last visit? *(List in comment section)*			X	
25. If yes, have reporting procedures been followed?			X	
26. Have all previous SAE follow-ups been performed and information obtained?			X	
27. Has new relevant information for previously reported SAEs been detected and communicated appropriately?			X	
INVESTIGATOR'S/REGULATORY FILE				
28. Has the Investigator's File been reviewed? If yes comment on any deficiencies.	X			See comments on regulatory file at the end of report.
29. Has the monitoring log been signed and dated?	X			
30. Is IRB approval up-to-date? Exp. Date	X			MUHAS IRB ethical clearance expires 29 Oct 2010; NIMR approval expires 30 Dec 2010.
31. Is there adequate documentation of IRB notification regarding any of the following: SAEs, amendments to protocol, informed consent or Investigator's Brochure, or changes in study personnel or facilities?	X			Memo to IRBs dated 10 March 2010 documents minor changes to protocol and associated documents including Informed Consent, Assessment of Understanding, Diary Card.

	YES	NO	NA	Comments
32. Is the current approved version of the protocol/protocol amendment present?	X			The current protocol version 2.0 dated Sept. 2009 was present; however, pages 42, 43, 70, 72, 109, and 120 still have V1 dated May 27th 2009.
33. Is there evidence that all amendments to the protocol are being implemented?	X			Above 10 March 2010 memo is implemented.
34. Is the current version of the Investigator's Brochure present?	X			Current HIVIS-DNA IB is present. New MVA IB dated 10 June 2010 was added.
35. Are the reference ranges and certification for applicable laboratories current?	X			Current reference ranges were not found in the regulatory binder but in the SOP binder. Site was instructed to add to regulatory binder. Ranges for some labs were on individual lab reports. Site also noted that lab does have certifications. Will also be added to regulatory binder.
INVESTIGATIONAL PRODUCT (IP)				
36. Have storage area/conditions been inspected/reviewed?	X			
37. Do IP supplies reconcile with records?	X			All vials were accounted for.
38. Have randomization envelopes or blinded labels been opened, or are they missing?		X		
39. Are supplies adequate and expiration dates acceptable for continuation of the study?	X			DNA vials expire March 2013. Saline expires 2012.
40. Has the designated IP been prepared for return or destruction?			X	

	YES	NO	NA	Comments
41. Are the temperatures recorded in the temperature chart within the specified ranges?	X			There is a chart where temperature is manually recorded twice a day from an electronic temperature recorder; the use of a Min/Max thermometer would be better. If difficult to obtain in Tanzania, we could provide one for the -20°C freezer.
42. Have the equipment maintenance logs been completed and maintained appropriately?			X	
43. Has the pharmacy binder been completed and maintained appropriately?	X			There are no records of shipment in the binder. Preparation for subject 3062 was not recorded in the Vaccine Preparation Form. The pharmacist of record was reminded that the preparation must be recorded immediately. If prepared by the back-up pharmacist, the pharmacist of record must supervise.
LABORATORY AND BIOLOGICAL SAMPLES				
44. Are the inventory and shipment records for samples current?			X	Not reviewed
45. Have procedures for labeling and shipment of samples been reviewed/discussed?			X	Not discussed
46. Have laboratory collection and processing documents been completed and maintained appropriately?			X	Not reviewed
47. Have storage area/conditions for the samples been inspected/reviewed?			X	Not reviewed

	YES	NO	NA	Comments
48. Have the laboratory equipment logs been completed and maintained appropriately?			X	Not reviewed
ACTIONS PRIOR TO THE NEXT MONITORING VISIT				
49. Actions for the Investigator?	X			Sign Eligibility Forms not previously signed with current date at time of signing.
50. Actions for the CRA?	X			Send site template of Roles and Responsibilities Log.
51. Actions for study coordinator?	X			To maintain and add needed documents to the regulatory binder with assistance of PI.
52. Actions for sponsor?	X			Ship DNA and MVA vaccines
53. Actions for IRB?		X		
54. Are study supplies (other than IP) adequate? (If no, specify)	X			

OTHER STUDY SPECIFIC ISSUES/REQUIREMENTS (list and comment below. List can be extended if required)

Procedural Issues

1. It was confirmed by the team that a copy of the consent form was offered to the subjects. A check box mentioning that a copy of the consent form was given to the subjects should be added to the checklist.
2. Although a systematic comparison to the database was not conducted, the following were noted:
Subject 3044 vaccination occurred 30 June, not 16 June
Subject 3041 vaccination occurred 16 June, not 30 June.
The dates were verified against the pharmacy records and the Visit/contact CRF2-II.

Regulatory File/SOP Issues

1. TOU answer key was added to the Regulatory file.
2. Eleven individual SOPs detailing different procedures were present. The SOPs were missing signatures, headers and footers, and individual pagination (pages were continuous from SOP to SOP).
3. The roles and responsibilities logs in the Regulatory binder were missing some signatures and/or dates.
4. Revised ICF and TOU and other updated documents need to be added to the Regulatory binder.

	YES	NO	NA	Comments
5. Laboratory reference ranges (found in SOP binder) need to be added to the Regulatory binder. 6. Laboratory certificates/proficiency panels need to be added to the Regulatory binder. 7. Correspondence were not included with the regulatory binder while reviewing, but the binder was presented at our debrief by Dr. Bakari. Site needs to understand that correspondence (letters, memo, emails) with the sponsor, monitors, manufacturers and MMRP site are part of the regulatory files. Internal correspondence, however, does not need to be included. *After monitoring the MMRP site, it was found that the version of some CRFs at MUHAS and the key to the TOU were different.*				

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 31 Jan-3 Feb 2011**

Investigational Product(s):		**Indication:**		
HIVIS DNA and MVA-CMDR		To assess safety and immunogenicity of HIVIS DNA in combination with MVA-CMDR		
Site staff present (name/role):				
M. Bakari – Principal Investigator	D. Buma – Study Pharmacist	**RECRUITMENT STATUS** (Cumulative)		
P. Munseri – Study Coordinator	M. Ngatoluwa – Principal Study Nurse		Last Visit	This Visit As of 3 Feb 2011
T. Masawa – Study Nurse	M. Janabi – Clinical Investigator	Total Briefed	N/A	327
D. Neema – Study Nurse	G. Kiwelu – Data Manager	Screened	85	229
S. Chum – Deputy Study Coordinator	A. Swarlehe – Study Nurse L Kabadi - Back-up pharmacist	Screen Failures	N/A	
Sponsor/Monitor personnel present (name/role):		Enrolled	16	53
Bèryl Wessner, PharmD/External Monitor		Randomized	16	53
Gail Smith, CCRA/External Monitor		Drop Out or Lost to Follow up	0	2
Others present: N/A		Withdrawn by investigator	N/A	
		Active:	16	51
		Completed:	none	None
Prepared by: Béryl Wessner, Christine Ingram, Gail Smith,		Signature(s):		Date prepared: 1 March 2011

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 31 Jan-3 Feb 2011**

Please specify any "No" answers in Comments field.

	YES	NO	NA	Comments
CONTINUING SITE ASSESMENT AND ACTIONS/CHANGES SINCE PREVIOUS VISIT				
1. Have study goals and timelines been reviewed with the staff?	X			
2. Has the Principal Investigator maintained adequate study staff personnel in order to conduct the clinical study?	X			
3. Have all outstanding action items noted in previous visit been completed by the Investigator?	X			
4. Have all outstanding action items noted in previous visit been completed by the CRA?	X			
5. Have staff or facilities changed or are changes anticipated? *(If yes, update documents and arrange appropriate action)*		X		
6. Are facilities still adequate?	X			
7. Have all communications been documented and retained appropriately?	X			
RECRUITMENT STATUS/PROTOCOL ADHERENCE				
8. Are there issues related to the recruitment status?	X			**Issues/challenges for enrollment** ECG-Last week on 8 subjects 5 had abnormal

	YES	NO	NA	Comments
				ECG. Creates a lot of anxiety for the subjects. Influence of the family
9. Were all subjects enrolled since last visit eligible for this trial?	X			
10. Is the enrollment to date sufficient to meet target enrollment goals?	X			
11. Were there protocol compliance issues/protocol violations detected?	X			Version 2 dated Sep 09 Amendment 3.0, 19 Aug 10 approved by TFDA 16 Dec 10 Some discrepancies discovered by Patricia. Lab flowchart for Visit 11, 12, 13, 14 is correct for blood volumes. Text in protocol is incorrect. A letter of clarification will be submitted for the CF (amount of blood collected) and the protocol. How will the subject be informed of the increase of blood taken if not thru an amended CF? Will all the subjects be affected by this increase? From p122 to p147 the header has v3.0, 13 Aug 2010.
12. Are informed consent forms properly executed and available for each subject?		X		No Missing CFs, all 53 were signed before or at the time of V1. v. 2.0 dated Sep 2009 used from 29 March to 4

	YES	NO	NA	Comments
				Aug 2010 but the version and date do not appear on the form v. 2.1 dated 10 Mar 2010 used from 16 Aug to 23 Sept 2010 v. 2.2 dated 18 Oct 2010 used from 19 Oct until 4 Jan 2011 v. 3.0 dated 19 Aug 2010 used from 10 Jan 11 **For some subjects in the youth group there is a type of "assent/informational" form signed by parent and subject. This form was not submitted to the IRB. (3183, 3159, 3154)** **3161, 3159, 3146, 3109, 3083, 3071 the name is printed but there is no signature of either the subject or the consenter. (only 3109, 3159, 3161, remain to be signed now)** 3083, 3201 missing pg 1 of CF. They were added. A check box mentioning that a copy of the consent form was offered to the subject was added in the checklist. At Eric's request all CFs were removed from the subject binders to 2 separate binders. The reason was for confidentiality but still the full name of the subject appears on some checklists in the subject chart. It is now replaced by the

	YES	NO	NA	Comments
				subject's initials.
CRF REVIEW/SOURCE DATA VERIFICATION				
13. Are CRF's being completed promptly, signed appropriately, and kept in double locked, limited access storage areas?	X			Backload seems resolved Many different version and dates are in use. CRF 2-III has two V 1.2, one dated 01 April 2010 and another dated 16 Aug 2010. They were also used interchangeably even after the 16 Aug version was used.
14. Are the entries in the CRF legible, complete and accurate?	X			
15. Were all required source documents available, accurate, complete and current?	X			
16. Were CRF's reviewed and source data verification performed during the visit?	X			3091 Visits 1-10 3041 Visits 1-12 Visits 1-3 3209 3201 3205 Incl/excl criteria Answer Q10 3202
17. Do the source documents provide evidence of the investigator's involvement in the study?	X			

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 31 Jan-3 Feb 2011**

	YES	NO	NA	Comments
18. Overall, is there consistency between CRFs and the source documents?	X			
19. Have CRF's been corrected appropriately?	X			Some corrections were made prior to our departure, but the remainder were left pending.
20. Have CRF's been retrieved?			X	Data entry is performed at the site.
21. Have all data clarifications and queries been resolved?			X	
22. Have Deviations and violations been documented appropriately?	X			Some due to wrong calculations from the database
23. Have deviations and violations been reported to the appropriate ethical and/or regulatory authorities, and documentation maintained in the site regulatory binder.		X		Parental/subject "assent/informational" form not submitted to IRB
ADVERSE EVENTS				
24. Have SAEs occurred since last visit? *(List in comment section)*	X			1 not related assault (3117)
25. If yes, have reporting procedures been followed?	X			Submitted to MUHAS IRB. Will verify if forwarded to NIMR and TFDA.
26. Have all previous SAE follow-ups been performed and information obtained?			X	
27. Has new relevant information for previously reported SAEs been detected and communicated appropriately?			X	

Interim Monitoring Report

Investigative Site Name: **Muhimbili University of Health and Allied Sciences (MUHAS)**	**Protocol Number: TaMoVac I**
Principal Investigator: **Muhammad Bakari (MD, MMed, PhD)**	**Protocol Title:** ***A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.***
Address: **P.O. Box 65001** **Dar Es Salaam** **Tanzania**	
Telephone: +255 754 387328	**Date(s) of Visit: 31 Jan-3 Feb 2011**

	YES	NO	NA	Comments
INVESTIGATOR'S/REGULATORY FILE				
28. Has the Investigator's File been reviewed? If yes comment on any deficiencies.	X			See comments on regulatory file at the end of report.
29. Has the monitoring log been signed and dated?	X			
30. Is IRB approval up-to-date? Exp. Date	X			MUHAS IRB approval of Version 3.0 dated 18th November 2010; NIMR approval of Version 3.0 dated 25th November 2010.
31. Is there adequate documentation of IRB notification regarding any of the following: SAEs, amendments to protocol, informed consent or Investigator's Brochure, or changes in study personnel or facilities?	X			Need to verify submission of SAE for 3107.

	YES	NO	NA	Comments
32. Is the current approved version of the protocol/protocol amendment present?	X			Version 2 dated Sep 09 Amendment 3.0, 19 Aug 10 approved by TFDA 16 Dec 10 Some discrepancies discovered by Patricia. Lab flowchart for Visit 11, 12, 13, 14 is correct for blood volumes. Text in protocol is incorrect. A letter of clarification will be submitted for the CF (amount of blood collected) and the protocol. How will the subject be informed of the increase of blood taken if not thru an amended CF? Will all the subjects be affected by this increase? From p122 to p147 the header has v3.0, 13 Aug 2010.
33. Is there evidence that all amendments to the protocol are being implemented?	X			
34. Is the current version of the Investigator's Brochure present?	X			MVA IB dated 29 May 10 was added MVA IB dated 10 June 2010 was added New MVA IB #5 dated 21 Oct 2010 to be added. Only Buma had received it.
35. Are the reference ranges and certification for applicable laboratories current?	X			Reference ranges nor certification were not found in the regulatory binder. Will request site to add.
INVESTIGATIONAL PRODUCT (IP)				

	YES	NO	NA	Comments
36. Have storage area/conditions been inspected/reviewed?	X			
37. Do IP supplies reconcile with records?	X			Buma is in the process of reconciling what was received, what was used and what is remaining. He will send us his numbers ASAP. Issues due to the back and forth shipments between MUHAS and MMRP. Also, the the vials in quarantine from MMRP were not counted due to the feezer drawer being blocked by the ice.
38. Have randomization envelopes or blinded labels been opened, or are they missing?		X		Randomization list reviewed
39. Are supplies adequate and expiration dates acceptable for continuation of the study?	X			DNA vials expire March 2013. Saline expires 2012.
40. Has the designated IP been prepared for return or destruction?			X	
41. Are the temperatures recorded in the temperature chart within the specified ranges?	X			Min/Max thermometers were provided for the -20°C freezers.
42. Have the equipment maintenance logs been completed and maintained appropriately?			X	Not checked this time

	YES	NO	NA	Comments
43. Has the pharmacy binder been completed and maintained appropriately?	X			
LABORATORY AND BIOLOGICAL SAMPLES				
44. Are the inventory and shipment records for samples current?			X	Not reviewed
45. Have procedures for labeling and shipment of samples been reviewed/discussed?			X	Not discussed
46. Have laboratory collection and processing documents been completed and maintained appropriately?			X	Not reviewed
47. Have storage area/conditions for the samples been inspected/reviewed?			X	Not reviewed
48. Have the laboratory equipment logs been completed and maintained appropriately?			X	Not reviewed
ACTIONS PRIOR TO THE NEXT MONITORING VISIT				
49. Actions for the Investigator?	X			**Submit to the IRB the "assent/informational" form signed by parent and subject.**
50. Actions for the CRA?	X			Follow-up with missing documents in regulatory file and pharmacy issues.
51. Actions for study coordinator?	X			Roles and Responsibilities Log still missing some signatures

	YES	NO	NA	Comments
52. Actions for sponsor?	X			
53. Actions for IRB?		X		
54. Are study supplies (other than IP) adequate? (If no, specify)	X			

OTHER STUDY SPECIFIC ISSUES/REQUIREMENTS (list and comment below. List can be extended if required)

Procedural Issues

For some subjects in the youth group there is a type of "assent/informational" form signed by parent and subject. This form was not submitted to the IRB. (3183, 3159, 3154)

3161, 3159, 3146, 3109, 3083, 3071 the name is printed but there is no signature of either the subject or the consenter. (only 3109, 3159, 3161, remain to be signed now)

Regulatory File/SOP Issues

Brief review of files for new documents-no major findings
Roles and Responsibilities Log still missing some signatures

Database

Patricia said that NIMR download data on a flash drive on a regular basis
Max said NIMR has access to the server.

Webdata still has a wrong date of vaccination (already signaled in Aug 2010):
3044 vacc1 was 30/June not 16/June as in database. Enrollment 18 June
3041 vacc1 was 16/June not 30/June as in database. Enrollment 1 July
Patricia checked that the Clinic db has been corrected.
Max's explanation is that the correction was possibly only done at MUHAS in the last couple of weeks when the server was down.

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

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TaMoVac I:

A Phase I/II trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.

Responses to External Laboratory Monitor Report

Study site: Department of Microbiology and Immunology,
Muhimbili University of Health and Allied Sciences,
United Nations road, Upanga, P.O.Box 65001,
Dar Es Salaam, Tanzania

Date of Monitoring: January 27-31, 2011

The specific findings and responses (bolded) are as follows:

II. Equipment

Freezers- Temperature reading logs were verified. Readings were taken twice daily on charts that included tolerance limits and corrective actions taken in response to out-of–range values. For the period September, 2010 to January, 2011 the two freezers in the ICS room (Euron serial numbers 017206711000679 and 3368000112X094) did not have thermometers and reading were not taken.

Corrective actions were taken, thermometers were put to the freezer number 017206711000679 and 3368000112X094 and temperature readings have now been recorded twice daily on charts.

For two months the thermometer for refrigerator Euron 017206711000679 in the ICS room was note to be out of order and no readings were taken.

Corrective action was taken, thermometer was replaced and temperature readings have now been recorded twice daily on charts.

Liquid nitrogen storage of cryopreserved cells- Log sheets for the two cryocontainers having temperature indicators were verified. At no time had the temperature been above -185°C. A third cryocontainer (F) with temperature indicator was taken into use on December 14, 2010. Log sheet for LN_2 refilling was verified for all cryocontainers A-D, F. Cryo-container E had not been put to use.

Cryo-container E has been reserved to serve as a back-up for now should the other two cryocontainers develop any technical problem.

Centrifuges- Calibration and preventive maintenance log sheets were verified for the two centrifuges in cell room 1 and 2 as well as for the centrifuge in the ICS room. However, the two centrifuges in cell room 1 and 2 had not had their annual service. The last service was

done 8/12/2009. The centrifuge in the ICS room had been serviced on January 11, 2011 by a technician from SLS Swiss Lab Sytems GmbH.

Corrective actions have been taken, the centrifuges in cell room 1 and 2 have been serviced now and technical reports have been kept in the file

Biosafety cabinets- Daily maintenance records were verified. The annual preventive maintenance and check by SLS Swiss Lab Systems GmbH had been performed on January 11, 2011 on four of the bio safety cabinets. However, neither the safety cabinet in the serology room and nor the safety cabinet in the flow cytometer room had been serviced since 8/12/2009.

During preventive maintenance service, the safety cabinets in the serology and in the flow cytometer rooms were found to be defective and required replacement of filters. New filters have been ordered and shipped. These will be fixed in the two safety hood cabinets once they have cleared customs and have been delivered to the laboratory.

CO_2- incubators- Preventive maintenance records were verified for the two CO_2-incubators in cell room 1 and 2 as well as the two CO2-incubators in the ICS room. The one CO_2-incubators in the ICS room and one CO_2-incubator in the cell lab had been switched off because of shortage of CO_2.

CO_2 has been procured and the two incubators in the ICS and in the cell lab rooms have been switched on now.

Pipettors- Certificates of calibration for the pipettors were verified. Next calibration is due in May, 2011.

All pipettors which are due for calibration have been identified. Preparations for recalibrations have started.

CTL ELISpot reader- Annual preventive maintenance of the instrument had been performed on June 28, 2010 by technical staff from CTL, Germany.

CTL engineer from Germany has been informed about the visit for the preventive maintenance service in June 2011. Preparations for the annual service including booking for return air ticket, hotel accommodation and payment for labour charge have started.

III. Testing facilities operation

Over all, revisions had been made and operator sign-offs were verified. One SOP (IFN-γ ELISPOT) needs additional revision.

Corrective actions have been taken, IFN-γ ELISPOT SOP has been revised to include new peptides and dilution schemes that are currently in use.

IV. Physical facilities

Cellular immunology lab 1 was clean and tidy. With two new safety cabinets in place, this room has the capacity to house four operators sharing two biosafety cabinets. Furthermore, it is equipped with a CO_2-incubator, a Hettich centrifuge, a cell counter (NucleoCounter), a water bath, a refrigerator/freezer unit. It is equipped with an AC unit. However, the AC unit was defective and had been so for some time. Immediate repair of the AC unit is needed.

Corrective actions were taken immediately by engaging another vendor to come and to do the repair after the previous repairs done by the primary vendor to be unsuccessful. The AC was fixed immediately and the room temperature has been within the acceptable limit.

Cellular immunology lab 2 was clean but unorganised and would according to GCLP standards not be considered fit for purpose. Since it is meant to be a cellular immunology laboratory it is equipped with a safety cabinet, a CO_2-incubator, a Hettich centrifuge, a refrigerator/freezer unit, a-86°C freezer and a beta-counter. It is also equipped with two AC units. However, currently it housed five cryo-containers and LN_2 refill containers. Thus, it had the appearance of a cryo storage facility rather than a cellular immunology laboratory.

Corrective actions were taken, the cryostorage containers and LN_2 refill containers have been shifted to virology preparation room to decongest the cellular immunology lab 2 room

Furthermore, both AC units were out of order. Immediate repair of these AC units are needed.

Corrective actions were taken immediately by engaging another vendor to come and to do the repair after the previous repairs done by the primary vendor to be unsuccessful. The two AC units were fixed immediately and the room temperature has been within the acceptable limit.

The ICS laboratories were clean and looked partly tidy. The ICS labs are equipped with two biosafety cabinets, two CO_2-incubators, a centrifuge and two new fridge/freezer units which were being used for ICS work. Furthermore, an ELISPOT reader (CTL), T-cell proliferation plate harvester and a biochemistry analyzer were also present. A functioning AC unit is present. Electrical cables were running across the floor in the inner lab and would potentially be a safety hazard. Rewiring is needed.

Corrective actions were taken, rewiring has been done and electrical cables have now been kept in the trunks running across the walls to prevent any safety hazard.

The flow-cytometry room was clean and tidy. It is equipped with a FACSCalibur, a FACSCanto II, a Coulter AcT5 diff analyser and a safety cabinet. It is equiped with an AC unit. However, the AC unit was defective. Immediate repair of the AC unit is needed.

Corrective actions were taken immediately by engaging another vendor to come and to do the repair after the previous repairs done by the primary vendor to be unsuccessful. The two AC units were fixed immediately and the room temperature has been within the acceptable limit.

The biosafety cabinet had not received annual preventive maintenance and check up.

During preventive maintenance service, the safety cabinet in the flow cytometry room was found to be defective and required replacement of filters. New filters have been ordered and shipped. These will be fixed in the safety hood cabinet once they have cleared customs and have been delivered to the laboratory.

The serology room was not clean and did not look tidy. It is equipped with a biosafety cabinet, laboratory benches housing three ELISA washers, an ELISA reader, a FACSCount and an incubator. Furthermore, it houses two –30°C freezers, one –70°C freezer and two refrigerator/freezer units. It is equipped with an AC unit. However, the AC unit was out of order and the door and a window to the corridor was left open. Windows are now left closed. The biosafety cabinet had not received annual preventive maintenance and check up.

The serology room will be decongested by shifting the two freezers to relieve more space after finding a suitable location to keep these two freezers. Corrective actions were taken immediately by engaging another vendor to come and to do the repair after the previous repairs done by the primary vendor to be unsuccessful. The AC unit was fixed immediately and the room temperature has been within the acceptable limit. During preventive maintenance service, the safety cabinet in the serology room was found to be defective and required replacement of filters. New filters have been ordered and shipped. These will be fixed in the safety hood cabinet once they have cleared customs and have been delivered to the laboratory.

VI: Procedures specific for the TaMoVac I phase I/II clinical trial

Sample processing

PBMC purifications had been performed according to HIVIS SOP and good cell yields were generally recorded. However, on a few occasions (see Appendix for details) the yield was low and on one occasion the cell yield was exceptionally low ($22x10^6$).

Corrective actions have been taken to address the problem noted and to prevent low yield of cells.

Documentation

- Daily sampling file records were generally well kept. However, on two occasions documents could not be verified. Furthermore, for one volunteer sample collected at visit 3 (3128, 05/01/2011) and two volunteer samples collected at visit 9 (3044, 06/10/10 and 3070, 27/10/2010) the cell count was incorrect. Thus, these samples will have invalid ELISpot, TLP and ICS results at the respective visit time point. See Appendix for details.
- All ELISPOT worksheets were verified. The details of missing documentation are found in the Appendix.
- HIV antibody testing worksheets were verified. Details of missing documentation are found in the Appendix.

Responses to individual issues raised have been inserted in the appendix below

IFN-γ ELISPOT assay

Thirty-one ELISpot tests had been performed. Documentation of all tests had been excellent. As noted previously, three volunteers have invalid tests at visit 3 or 9 due to an incorrect cell count. See above and Appendix.

An investigation revealed that wrong dilution factor of 1:1 was used during cell counting for volunteers' number 3044v9 and 3128V3. Corrective actions have been taken to ensure the correct dilution factor used is 1:2. The sample from volunteer number 3070v9 was tested using a dilution of 1:2 which was correct and the ELISpot result was considered valid. Corrective actions have been taken to ensure a correct dilution for PHA in RPMI is 1:2 instead of 1:3. The lab will engage in discussion to decide if repeat ELISpot testing can be performed using cryopreserved cells for 3 invalid results.

T-cell proliferation assay

Thirty-six TLPs had been performed, all according to SOP. Documentation of the tests had been excellent. Note that due to an incorrect cell count three volunteers have invalid tests at visit 3 or 9. For several of the TLP runs it was noted that an expired RPMI batch had been used. See above and Appendix.

Corrective actions have been taken to ensure expired RPMI is not used for testing in the future TLP runs

^{3}H-thymidine dilutions had been correct for most plates. However, it was noted that often the volumes of ^{3}H thymidine dilution used had exceeded the amounts needed. Thus, the lab had run out of stock in the middle of December, 2010. The dilution scheme used needs to be updated so that the correct amount of ^{3}H thymidine is prepared. Harvesting of the LPA plates had recently started and only 9 plates had been harvested.

Corrective actions have been taken; dilution scheme has been revised to show the correct amount of ^{3}H thymidine during preparation

4- colour ICS testing

A total of eighteen ICS tests had been performed. Documentation of all tests had been excellent. Note that due to an incorrect cell count one volunteer has an invalid test at visit 3. See above and Appendix.

Corrective actions have been taken to ensure correct cell count is used to prevent future invalid test

During October 2010 ten volunteer samples collected at visit 9 were set up in 4-c ICS although at this time point ICS should not have been performed. This was noted by Karina Godoy at Smi, Sweden and visit 9-testing was stopped.

Old version of the TaMoVac I lab flow chart was in use and this was a source of confusion. Corrective actions have been taken by retraining of all lab and clinic personnel on amended TaMoVac I protocol (Version 3.0 of 19th August 2010) on 12th February 2011 including thorough discussion of the lab flow chart. Furthermore, copies of old version of lab flow chart have been removed and new copies of updated version of lab flow chart have been distributed to various sections in the laboratory including flow cytometry.

Serology

HIV antibody testing had been performed. Testing was done using, Dade Behring Enzygnost anti-HIV-1/2 Plus ELISA and Abbott Murex antigen antibody ELISA and Inno-Lia HIVI/II Score. Documentation was verified for most tests. See Appendix for details.

Please find responses in the appendix below

SUMMARY AND RECOMMENDATIONS

A filing cabinet is needed to secure essential documents for the TaMoVac I trial. Furthermore, a general review of laboratory security is recommended. Currently all documents are kept in rooms with open access to others, which is a violation against GCLP practices.

A filing cabinet has been requested and once delivered to the laboratory, it will be dedicated for TaMoVac I trial documents and secured with locks. Only authorized personnel will be given access to the documents

There is a shortage of space for storage of samples at -86°C in the freezer allocated for TaMoVac samples due to the storage of samples not related to the project. This is a violation of GCLP and these samples should be removed as soon as possible to enable good organization of trial related samples.

Corrective actions have been taken; samples not related to the project have been removed. Requisition for a new -86°C freezer has been made to relieve the acute shortage of freezer space. The space to locate the freezer is still expected after reorganization of the virology preparation room.

Tanzania Oxygen Company had stopped delivery of liquid nitrogen for two weeks and liquid nitrogen was being provided by MMRP in Mbeya. A plan to secure liquid nitrogen at MUHAS should be considered. In view of the above, it is essential that the team recognises that the laboratory facilities, human resources and procurement operations need strengthening, especially considering the planned TaMoVac II clinical trial that is scheduled to start later this year.

Funds (85,476 Euros) have been allocated in the EDCTP 2011/2012 no-cost extension budget and some (10774 Euros) will be used from Sida Lusaka to purchase a liquid nitrogen plant with production capacity of 60 litres/day at a cost of 96,250 Euros from Stirling cryogenics of Holland.

Appendix I. Monitor report January 27-31, 2011.

DETAILS OF FINDINGS

Daily sampling files

Date	Volunteer	Time point	Comments
20/10/2010	3003	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point **Old version of lab flow chart was used and has been removed; retraining of amended TaMoVac I protocol has been done and copies of updated version of lab flow chart has been distributed in all sections including ICS**
20/10/2010	3032	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point **Same as in row 1 above**
16/09/2010	3036	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point **Same as in row 1 above**
22/09/2010	3041	Visit 11	Serology performed. Not indicated on the daily sampling form. **Corrective action has been taken by documenting in the daily sampling form**
22/09/2010	3043	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above** Serology performed. Not indicated on the daily sampling form. **Corrective action has been taken by documenting in the daily sampling form**
06/10/10	3044	Visit 9	Cell count incorrect. Yield given as 56 x 10^6 but should be 112 x 10^6. ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
29/09/2010	3048	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
06/10/2010	3052	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
06/12/2010	3053	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
06/12/2010	3055	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above** CRF 3.7 and 3.8 not completed by operator. Signature, data and time of receipt is missing. **Corrective actions have been taken by the operator (SCM) to sign, date and document time of receipt**
20/10/2010	3062	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
16/9/2010?	3063	Visit 7	Incorrect date on daily sampling form. **Corrective action has been taken to document correct date (30/09/10) on daily sampling form**

03/09/2010	3070	Visit 6	Incorrect date of sample collection given on" Cell separation and cryopreservation" worksheet. **Corrective action has been taken to document correct date of sample collection**
27/10/2010	3070	Visit 9	Cell count incorrect. Yield given as 74 x 10^6 but should be 147 x 10^6. ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
?	3071	Visit 7	Documents are not available. **Volunteer did not come at visit 7 as scheduled**
17/11/2010	3071	Visit 9	ICS performed although it is not indicated in the daily sampling file or in the flow chart for this time point. **Same as in row 1 above**
27/10/2010	3082	Visit 8	Samples for visit 8 (time of third HIV-DNA vaccination) arrived on two days, 13/10/2010 and 27/10/2010. Which is the correct date? **Correction has been done; 13/10/2010 was for V7j and 27/10/2010 was for V8.**
1/09/2010	3086	Visit 3	Cell count print out Is not available. **Retrieved and filed**
	3091	Visit 4	Documents are not available**.** **Volunteer did not attend the visit as scheduled.**
25/11/2010	3091	Visit 8	Sampling form is not available. **Retrieved and filed**
1/09/2010	3092	Visit 3	Cell count print out Is not available. **Retrieved and filed**
25/11/2010	3092	Visit 8	Sampling form is not available. **Retrieved and filed**
15/09/2010	3097	Visit 3	CD4/CD8 testing was not performed. Report is given. **Operator urged to follow SOP**
27/10/2010	3097	Visit 6	Low cell yield (49 x 10^6) **Corrective actions have been taken to prevent the future occurrence**
22/12/2010	3097	Visit 9	Low cell yield (55 x 10^6) **Corrective actions have been taken to prevent the future occurrence**
15/09/2010	3098	Visit 3	CD4/CD8 testing was not performed. Report is given. **Operator urged to follow SOP**
01/10/2010	3098	Visit 4	Incorrect date given on the sampling form. **Correct date has been documented on the sampling form**
01/09/2010	3099	Visit2	Cell count print out does not give yield and viability. **Retrieved and filed**
15/09/2010	3099	Visit 3	CD4/CD8 testing was not performed. Report is given. **Operator urged to follow SOP**
10/11/10	3109	Visit 6	The number of vials frozen are given as 14>02. **Correction has been done; accurate number of cells were 10 vials**
14/09/2010	3117	Visit 3	Low cell yield (53x10^6) **Corrective actions have been taken to prevent the future occurrence**
29/09/2010	3117	Visit 3	Low cell yield (53x10^6) **Corrective actions have been taken to prevent the future occurrence**

17/11/2010	3117	Visit 6	Low cell yield ($50x10^6$) **Corrective actions have been taken to prevent the future occurrence**
19/01/2011	3117	Visit 9	Low cell yield ($52x10^6$) **Corrective actions have been taken to prevent the future occurrence**
02/11/2010	3146	Visit 2	Low cell yield ($22x10^6$) **Corrective actions have been taken to prevent the future occurrence**
05/01/2011	3128	Visit 3	The cell count is incorrect. **Correct multiplication factor was 3 instead 6**
01/12/2010	3173	Visit 3	The cell count for PBMCs prepared from the EDTA sample is incorrect. **The correct cell count is 6.59×10^5, it has been corrected on the sampling form**
2/12/2010	3169	Visit 3	The cell count for PBMCs prepared from the EDTA sample is incorrect. **The correct cell count is 2.57×10^5, it has been corrected on the sampling form**

ELISpot work sheets

ELISpot number	Volunteer #	Date	Comment
ELI2010-20	3044v9	06/10/2010	Incorrect cell count. Thus, the assay is invalid for this sample. **Incorrect cell count due to wrong dilution factor. Corrective action has been taken to prevent future occurrence**
ELI2010-23	3070v9	27/10/2010	Incorrect cell count. Thus, the assay is invalid for this sample. **Corrective action has been taken to prevent future occurrence**
ELI2010-33	3078v9, 3086v9, 3088v9	9/12/2010	Noted that dilution of PHA was done 1:3 in R **Corrective action has been taken to ensure accurate dilution of 1:2 is used**
ELI2010-34	3091v9, 3092v9	9/12/2010	Noted that dilution of PHA was done 1:3 in R **Corrective action has been taken to ensure accurate dilution of 1:2 is used**
ELI2010-39	3128v3	05/01/11	Incorrect cell count. Thus, the assay is invalid for this sample. **Correct multiplication factor was 3 instead 6**

TLP work sheets

TLP number	Volunteer	Date	Comment
TLP-13	3097v3, 3098v3, 3099v3	15/09/2010	The wrong dilution of 3H-thymidine was used on the Day 2 plate. **Corrective actions have been taken; dilution scheme has been revised to show the correct amount of ^{3}H thymidine during preparation**
TLP-21	3044v9	06/10/2010	The cell count is incorrect and the result for this sample is therefore invalid. **Operator urged to follow SOP**
TLP-25/26	3069v9, 3070v9, 3130v3	27/10/2010	The wrong dilution of 3H-thymidine was used on the Day 2 plate. 3070v9 has an incorrect cell count and the result for this sample is therefore invalid. **Corrective actions have been taken; dilution scheme has been**

			revised to show the correct amount of ^{3}H thymidine during preparation
TLP-33	3173v3	01/12/2010	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-34	3155v3, 3166v3, 3169v3		The wrong dilution of ^{3}H-thymidine was used on the Day 2 plate. RPMI expired 11/10. **Corrective actions have been taken; dilution scheme has been revised to show the correct amount of ^{3}H thymidine during preparation. Operator urged to check expiry dates of each batch of RPMI before use**
TLP-35	3158v3	08/12/2010	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-36/37/38	3078v9, 3086v9, 3088v9, 3091v9, 3092v9	09/12/2010	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-39	3159v3	16/12/2010	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-40/41	3097v9, 3098v9, 3099v9	22/12/2010	^{3}H-thymidine was not added due to lack of reagent. **Preventive actions have been taken to prevent future stock-out of reagents**
TLP-42	3183v3, 3185v3	30/12/2010	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-43	3128v3	05/01/2011	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-44	3076v9	10/01/11	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-45	3109v9, 3111v9	11/01/11	RPMI expired 11/10. **Operator urged to check expiry dates of each batch of RPMI before use**
TLP-46/47	3204v3, 3160v3, 3117v9, 3122v9	19/01/2011	RPMI expired 11/10**.** **Operator urged to check expiry dates of each batch of RPMI before use**

Serology protocols/work sheets for murex HIVab/ag combination assay and enzygnost HIV integral ii

date	ELISA number	Comments
24/09/2010	unknown	run # missing as note by the microbiologist **Corrective actions have been to prevent occurrence**
03/09/2010- 05/11/2010	murex #20-30 enzygnost #20-30	cut off calculations are not shown on the worksheet **Corrective actions have been taken to calculate and document cut off values on the worksheet**
26/11/2010	murex #32	cut off calculations are not shown on the worksheet **Corrective actions have been taken to calculate and document cut off values on the worksheet**
21/01/2011	enzygnost #39	not available.

		Retrieved and filed
	murex #23, 24, 38 enzygnost #23, 24, 38	Worksheets were not available. **Worksheets # 23 & 24 were accidentally omitted; corrections will be made to renumber the worksheets.** **Worksheet # 38 was retrieved and filed**

Prepared by: Emanuel Salala, Laboratory Manager Date: 18/04/11

Dr Agricola Joachim Date: 18/04/11

PhD trainee

Reviewed by: Dr. Said Aboud Date: 18/04/11

Deputy Lab Coordinator

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Responses to the Laboratory Monitor Report for TaMoVac I, October 2010

Missing SOPs:

1. Cell harvesting of proliferation plates.

   SOP for cell harvesting of proliferation plates could be retrieved, printed and kept in the master file and working bench binders

2. Equipment and room temperature charts.

   SOP for equipment and room temperature charts could be retrieved, printed and kept in the master file and working bench binders

3. FACSCalibur immunophenotyping.

   SOP for equipment and room temperature charts could be retrieved, printed and kept in the master file and working bench binders

4. Behring Enzygnost Anti-HIV-1/2 ELISA.

   SOP for Behring Enzygnost Anti-HIV-1/2 ELISA has been retired, the assay is no longer used; new assay called Siemens Enzygnost Integral ELISA is now used

In general, revisions had been made and operator sign-offs were verified. However, occasionally SOPs had been introduced yet very few operators had signed off, i.e. indicated that they had read them.

Operators were urged to read, understand and sign SOPs before starting to perform assay.

Documentation

Daily sampling file records were verified. However, due to missing data (NucleoCounter printouts and cell calculations relevant to ELISpot, LPA and ICS testing) the records were poorly kept. Please see Appendix for details.

Corrective actions have been taken; missing NucleoCounter printouts and calculations relevant to ELISpot, LPA and ICS testing were located and kept in the appropriate files.

All ELISPOT worksheets were verified. Throughout, the use of CEF2008 was indicated but it was recognised that the "old" CEF indicated in the dilution scheme had been used in some of the assays. Modifications to the worksheets are needed to clarify which the two peptide pools were used.

Corrective actions have been taken; modifications to the worksheets have been done to clarify the two peptide pools used

IFN-γ ELISPOT assay

Eleven ELISPOT tests had been performed. As noted previously, four of the test runs had failed QA/QC due to negative/too high CEF results for the in-house control. Corrective actions had been taken and these were thoroughly documented. Documentation of all tests had been good. However, throughout the use of CEF 2008 was indicated in the worksheets yet the dilution scheme used indicated use of the "old" CEF peptide pool.

Corrective actions have been taken; modifications to the worksheets have been done to clarify the two peptide pools used

Serology

HIV antibody testing had been performed. Testing was done using; Dade Behring Enzygnost anti-HIV-1/2 Plus ELISA, Vironostika HIV-Uni-form II Plus O, Abbott Murex antigen antibody ELISA and Inno-Lia HIVI/II Score. Documentation related to these tests was verified. In five tests the cut-off indicated was incorrect. See appendix for details.

Corrective actions have been taken, the cut-off of the five tests was rectified, however, the change in cut-off did not change the HIV results reported earlier. In addition cut-off value is inserted now in every ELISA working template.

SUMMARY AND RECOMMENDATIONS

All tests are being performed according to SOPs and laboratory personnel are continuously working towards Good Clinical Laboratory Practice. The documentation relevant to the ELISPOT, TLP and ICS assays was in part excellent. None the less, it should be noted that an overall assessment of the quality of the work could not be made due to the lack of information in the daily sampling files on cell counting (NucleoCounter printouts) and calculations for the three assays mentioned above.

Corrective actions have been taken; missing NucleoCounter printouts and calculations relevant to ELISpot, LPA and ICS testing were located and kept in the appropriate files.

The documentation on serological testing was excellent. Alarmingly, an incorrect cut-off was noted for 5 ELISA test runs. For patient safety, revision of the ELISA worksheets must be made. The cut-off calculation formula must be given on each ELISA worksheet and the clinical microbiologist reviewing the tests must double check calculations. A retrospective check of all assays performed so far is also needed.

Corrective actions have been taken, the cut-off of the five tests was rectified, however, the change in cut-off did not change the HIV results reported earlier. In addition, retrospective check of all assays was performed; ELISA worksheet has been revised to include the cut-off calculations.

All defective equipment must be either repaired or replaced. One of the centrifuges was broken and no action has been taken since June. A shortage of CO_2 was noted and only one incubator was presently being used. For the ELISpot and the LPA tests, incubation in a CO_2-incubator is needed for 20h and 6 days, respectively. Thus, it is imperative that at least one additional CO_2 incubator is on all the time as a back-up. Measures should be taken to secure CO_2 access.

Corrective actions have been taken to repair the broken centrifuge machine. Additional incubator has been already been installed by the engineer and it is operational now to serve as a back-up.

A filing cabinet is needed to secure essential documents for the TaMoVac I trial. Furthermore, a general review of laboratory security is recommended. Currently all documents are kept in rooms with open access to others, which is a violation against GCLP practices.

Procurement of a new file cabinet has been initiated and the procurement process is ongoing.

In light of the planned TaMoVac II clinical trial that is scheduled to commence next year, it is important that the team recognises that the laboratory facilities, human resources and procurement operations will continue to need strengthening.

The team will continue to work to strengthen the laboratory facilities, human resources and procurement operations in preparations for the TaMoVac II clinical trial.

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Responses to issues raised by the Internal Monitoring of

TaMoVac I, performed at MUHAS, on Oct 8-11, 2010 by Eric Sandström

Scope

- Confirm eligibility
- Review reactogenicity and AEs
- General overview of conduct

All files were reviewed up to todays date. Files outside the scope have been inspected, but not systematically scrutinized for entry mistakes or omissions.

Eligibility

All had signed *informed consent*.

Assessment of understanding forms used in 3 versions as noted by external monitor.

Action: Changes have to be documented in Regulatory binder

Response

Three versions of the Test of Understanding tool have been used. These were version 1.0 dated 18th September 2008; version 2.1 dated 9th March 2010 and version 2.2 dated 17th August 2010. A memo to the regulatory binder dated 21st of December 2010 indicating the reasons for change to the various versions has been written.

Eligibility not always signed by PI/deputy or countersigned. It has on occasion been signed even with incomplete records such as incomplete inclusion/exclusion criteria, ECG forms, HIV serostatus. However in no case did source documents indicate profound protocol violation. See special discussion of form 5-II Inclusion Exclusion criteria.

Action: PI/designee to sign Eligibillity form only after checking that all preconditions are met.

Response

This has been rectified, and the PI or designee signs eligibility after careful review of documents

In one instance were *Randomization forms* not found.

Action: Find and insert.

Response

PI has been informed of this, and the randomization form for volunteer number 3083 that was missing was actually inappropriately filled in the source documents. This has now been rectified; the form has been appropriately inserted into visit 3 CRF section

Reactogenicity and AEs

Since there has been recorded more reactogenicity at the MUHAS site special attention was paid to that, CRF 10-I.

Reactogenicity

The form as were generally well filled in.

They are not consistently filed under the visit they refer to, especially visit 8 was most often filed under visit 9.

They seem to have been directly transcribed from the diary card. A systematic comparison between Diary cards and 10-I has not been performed at this review. The dates on the forms suggest that they may be filled in after the actual visit without the presence of the volunteer. They thus seem to reflect a participant report rather than a clinical report.

Some grade 3 events have been recorded. These events coincide with a recorder with less experience. They have not caused special visits to the clinic for verification, as per protocol, and they have been signed off by recorder and person checking the forms without comments.

Some grade 3 events have been changed to grade 2. Source documents have not been checked if this is further documented there at this review.

There is a special problem that CRF 2-III seems to have been filled in for each day of the diary and that this has caused inconsistencies in where the visit took place.

Action:

1. Better organize 10-I forms, including use of 2-III and agreement of place of assessment

2. Grade 2 or 3 grades should be check with volunteer for accuracy. As a minimum those entered as grade 3 should retrospectively be checked with volunteers and changed/commented on in CRFs (and if appropriate in source documents).

3. Report any grade 3 events to PI

4. Checking person go through form

5. Update counseling on behavior with perceived grade 2 or 3 events

6. Place Diary charts in correct places

Response

1. *Form 10-I has not been placed in the CRF sections for each volunteer's folders with respect to visits 3,5 and 8 and instead the form was erroneously filled in for visit 4, 6 and 9. This was so because the diary card is assessed during these visits. All staff who transcribe the diary cards have been informed that henceforth all vaccine reaction forms should be appropriately filled in during the vaccination visits.*
2. *The grade 2 and 3 events were re-evaluated and there have been changes for these events that have been reflected in the vaccine reaction forms and in the source documents of the respective volunteers who have been called in and reassessed for the reactions.*
3. *No grade 3 events were so far noted.*
4. *Emphasis has been placed to have staff members who do the checking go through all the forms*
5. *Members of staff were reminded to inform the volunteer and remind themselves if any grade 3 events were noted that these were reportable and the volunteer had to be called in to the clinic for further evaluations.*
6. *Diary cards have now been placed in the source documents in the vaccination visits*

Adverse events

Adverse event forms are not at the end of the file and continuously filled in. They are rather scattered in the file and this has caused some duplicates to be entered and it is hard to get an overview.

The same is true for CRF 4-I *Concommitant mediciation* with even more confusion.

It would also be useful to have *Protocol violations* filed at the end for easy overview. They were however not targeted for this review.

Expedited Adverse Events, EAE, seems to have been misunderstood both by recorder and checking personnel. This should be reviewed and changed in the database. Of note is that the registration of EAE has not caused an appropriate action. Expedited Adverse Event reporting has to be reviewed.

Action:

1. Review all EAEs, correct and comment on in source documents. It is nt enough just to change the forms considering the consequences of an EAE.

2. Introduce stricter signing procedures for AE

2. Educate personnel regarding EAE and SAE grading and reporting.

Response

1. *All the documented EAEs that were reported by the deputy clinical coordinator were not actual EAEs but rather a misunderstanding of the form. The reported EAEs have now been changed to read that there were not EAEs and a memo to file has been included describing the incident.*
2. *All clinical staff have been retrained on the 28th of October 2010 on how to grade AEs and what EAEs and SAEs mean and how they should be reported and the relationship of the adverse event with the vaccination. A memo to the regulatory file has been included regarding this training.*

General overview

Order

Most files are in good order, but there is often a lack of consistency in the order of forms under a specific visit as suggested by the checklist. Checklists, white, are rarely signed. Checklist visit 3 gives CRF8-II referred to as 'Clincal copy' instead of 'Vaccine Randomization'.

There are no blank CRFs in the proper order for coming visits, which could contribute to the misarrangements. Due to this extra visits x.k for instance are randomly inserted in the given visit and hard to indentify.

Action:

1. Adhere to checklist organization

2. Have forms ready in anticipation of visits

Response

1. *Study staff had an opportunity to travel to Mbeya on the 16-18/08/2010 to share experiences and exchange ideas with the MMRP colleagues. One of the lessons brought back to our site is the use of an extensive checklist that is color coded and this has been adopted at our site.*
2. *Forms are now being prepared prior to the volunteer's visit to the site.*

Data management

There does not seem to be a system were unentered forms can be indentified. There are scattered doubly or singly unentered forms throughout the files. This should be reviewed and a method deviced. There should in principle never be an unentered form before the last visit being entered as a minimum.

Action:

1. Go through backlog of unentered forms.

2. Device system so that unentered forms can be easily identified

Response

1. *While responding to the monitor's comments all the data that was not entered is now been entered. However of note is the constant fluctuation of power and internet access such that there are times when the data entry is not real time resulting into backlog.*
2. *The devised system for easily identifying un-entered data is in place whereby a a log book containing the respective volunteers ID number, visit number and specfic CRFs that require data entry for a specific visit have to be signed out by the receptionist, 1st and 2nd data clerks and the data manager only when the data has been entered.*

Confidentiality

Source documents are in the same binder as CRFs. This means that the name on the *Informed Consent i*s linked to all other documentation.

New checklists – colored – have been introduced that often contain the name of the participant. They are stored with the CRFs. Some of these checklists ie visit 3 contain clinical information that better belong with source documents. There is great risk for involuntary exposure of the participants with the present system. A note was made during a meeting that in study matters names have started to be used rather than study ID.

Some incomplete source files were found in another office outside a locked cabinet.

Action:

1. Separate personal identifiers from CRFs

2. Store al study files in locker

Response

1. *All consent forms are now kept in a special file for all volunteers who have been enrolled into the study.*
2. *The volunteers initials instead of the name is now included in the colored checklist.*
3. *All volunteer-related documents including folders and informed consent forms are stored in a locker.*

Comment on specific CRFs

A summary action form in front of the source document, like From 11 in HIVIS 03, would facilitate to keep track of action clinical points. Ie 3069 with progressing anemia, etc.

Action: Contemplate introduction of such a form

Response

An Important event tracking form (Form 6) version 1 of 23 September 2010 had been designed for the purpose of following up the various events.

Diary cards No instance of other than version 2.0 was found as indicated by the external reviewer. Some cards were mistakenly stored with the CRFs.

CRF 2-III Visit contact form is overused and the information of type of visit often misunderstood, especially in conjunction with CRF 10-I.

Action: Review use of 2-III

Response

It would be best if form 2-III is no longer used as this is more of additional paper work, however it would be best if the usefulness of this form be discussed in a larger forum with both the Mbeya and Dar site clinical teams. We plan to do this during the Feb 2011 all collaborators meeting in Bagamoyo.

CRF 5-II Inclusion/Exclusion criteria lacks a smiley for exclusion item 10 (previous vaccines..). This has resulted in very few notifications of this item. Some very bad copies have been accepted, where Inclusion item 5 and 6 are invisible. Sometimes a smiley has been introduced covering both, but with the text blocked out. There are a few instances where items have not been filled in. However this has been accepted by the persons signing the eligibility forms. The form seems to initially have been filled in at visit 3 and sometime later this seems to have shifted to visit 1. They are inconsistently stored in visit 2 or 3 without relation to when it was filled in.

Action:

1. Create and use immaculate copy

2. Store at correct place. Could be visit 3 as long as it is consistent.

3. Fill in at a consistent visit

4. The final version has to be reviewed at lest when eligibility is signed

Response

1. *A copy that is clear has now been printed and is in use soon after the monitoring visit. However the volunteers who were enrolled prior to the monitoring visit maintain the same "bad copy forms"*
2. *The form is stored in visit 3 slot, however there were a few instances when the Senior study staff had to travel to Atlanta and therefore this form was filled in prior to visit 3 resulting in the form to be filed in visit 2.*
3. *The other CRF 5-II have been filled in visit 3 were they belong*
4. *Senior study Physicians have been reminded to always review the final version of CRF 5-II when signing eligibility*

CRF 4-I Concomitant medication seems to be placed where it was first filled in. This has caused a number of forms to be filled in for some volunteers. Not always paginated. Should be at the end of the file under a special insert.

Action:

1. Store at end.

2. Continous sequence of numbered medications on consequtive numbered forms

3. Continued mediciations constantly reviewed for discontinuation.

Response

1. *All concomitant medication forms are now being placed at the end of the volunteers folders*
2. *The concomitant medication forms have now been sequentially numbered and all redundant forms have been cancelled.*
3. *The events tracking form has now been designed that is placed in the first page of the volunteers' folder. It alerts on what events need to be tracked and includes the start and stop date of the event.*

CRF 6-I Adverse events seems to be placed where first filled in. Several scattered forms were found for some. AEs are not countersigned by senior physician, which has allowed misunderstanding of EAEs to continue. It is advised, for a period, that even of grade 1 are signed by senior physician to avoid this, since some of these 'EAEs' were grade 1. Abnormal lab values found registered as AEs. Should be at the end of the file under a special insert.

Action:

1. Store at end.

2. Continous sequence of numbered AEs on consequtive numbered forms

3. Continued AEs constantly reviewed for resolution.

4. Review of severity before signing of.

5. Review of current grade 3 and EAE

6. Agreement if abnormal lab values should be registered as AEs

Response

1. *The AE forms are now being stored at the end of the volunteers' folders*
2. *The AE forms are sequentially numbered and the AEs have also been sequentially numbered*
3. *The events tracking form has now been designed that is placed in the first page of the volunteers' folder. It alerts on what events need to be tracked and includes the start and stop date of the event.*
4. *The study staff are informed that they should discuss AEs with senior staff so as to be certain of the grade of the event*
5. *Grade 3 and EAEs have been reviewed and it was noted that there weren't any EAEs or grade 3 events.*
6. *This was a question raised in one of the conference calls and it was agreed that abnormal values that fulfill the DAIDS criteria should be registered as AEs*

CRF 7-I Termination Form. Better at end of file. Are now difficult to locate.

Action: Locate at end (at least a copy)

Response

CRF 7-1 is now being placed at the end of the volunteers' binder and a copy in the respective visit slot.

Protocol violations were encountered scattered in the files. Since these were not individually documented in this review their location cannot be given. Would be easier to find if collected at end.

Action: Locate at end (at least a copy)

Response

The protocol deviations/violations are now made in 2 copies; one copy is kept in the respective visit where the deviation occured, and the other copy is kept at the end of the volunteers' binder.

*CRF 9-IV and V. T*he absence of reference values on the form facilitates that out of range values are not noticed. This review did not focus on the quality of data transfer from source data to CRFs and their interpretation.

Action: Consider inclusion of local reference values on form and consistent comments on out of range values

Response

This would be the best practice as was observed in the HIVIS 03 trial, however for the current trial the CRFs were designed without the reference ranges. All study doctors who transcribe the laboratory CRFs or who countercheck the laboratory CRFs have a laminated sheet that is comprised of the normal reference ranges to refer to for the study. However it would be helpful to the clinician to have the reference range on the CRF. This could also be discussed with Mbeya group probably at Bagamoyo

CRF 10-I Vaccine/reaction form should be uniformly stored with the corresponding visit. Every entry does not have to be preceeded by 2-III. It is also suggested that page 2 only has to be filled in for the whole review of the diary card. All grade 2 and 3 events should be confirmed in dialogue with the participant and if changes are made these should be detailed on page 2. There seem to be inconsistencies in how relationship to vaccine is filled in, ie 3, 4 or 5.

Action:

1. Store in consistent place.

2. Review use of 2-III - and page 2.

3. Agree on 'clinic'and 'home' assesment

3. Review in the presence of volunteer

4. Record any changes from diary

5. Agree on evaluation on relatedness

6. Instruct counselors to instruct volunteers to the nature of grade 2 and 3 events and what they should do

7. Review actions caused by confirmed grade 3 events in the clinic

8. Review procedures for checking form

Response

1. *The CRF 10-I is now placed in the CRF section of the corresponding vaccination visit, ie visits 3, 5 and 8.*
2. *We are in agreement that CRF 2-III requires to be reviewed. This will be discussed further by the clinical teams from Mbeya and Dar in the presence of the PI.*
3. *We are in agreement that all the diary information that is transcribed should be regarded as "home" rather than "clinic" assessment*
4. *The diary card is now reviewed in the presence of the volunteer, and this has been emphasized to the study staff*
5. *Changes that different from what is recorded in the diary card are noted in the comments section of the vaccine reaction form on page 2*
6. *Study staff members have been urged to consult when in doubt regarding the relationship of the reactions to the study agent.*
7. *All counselors have been educated on the importance of informing the volunteer that all grade 2 and 3 need attention and that the volunteer should call in if they have a grade 2 or 3 event and this is to be communicated to the study doctor and or senior study physicians*
8. *All grade 3 events were re-reviewed by the study coordinator after re-interviewing the volunteer and none of the recorded grade 3 events were of grade 3 severity, rather they were of grade 1 severity. The changes made are reflected in the CRFs and have also been communicated to the data entrants.*
9. *The procedure for reviewing the forms has now been changed such that at the end of each day study staff review all volunteers' folders that have been seen for the day.*

NARRATIVES for complicated histories would be of great value. Filed at end and updated as necessary. For example 3069, 3083.

Action:

Recommended to create for all cases with complications or being discussed in TMG calls as soon as possible after the events. Can be amended with time.

Response

Narratives for 3069 and 3083 have been prepared and have been filed at the end of the respective volunteer's folders.

Specific actions

Study #	Visit	Date	Forms	Comments	Action Taken
3003	2	23.6.10	5-II	Item I3 and E10 not ticked	Item 3 has now been ticked on 7.1.11. The smiley face has been hand drawn on 19/10/10
3003	3	15.7.10	5-IV	filled in reasons (- item 4 and 12 not ticked)	The reasons should not be filled in as they are not applicable, however items 3 and 4 that had not been filled in have now been filled and dated 19/10/10 and the reasons have been deleted. Therefore item 12 does not need to be filled in.
3003	3	15.7.10	10-I	mix of reactogenicity data from home and clinic visits filled in at a later date?	The assessment has been changed from clinic to home on the 19/10/10. The date is ok which was the day the information from the diary was recorded in the clinic.
3003	5	12.10.10	10-I	unentered forms	The forms had been entered in the database, date of entry was on the 18/10/10. However data entry was done erroneously into the database before the forms had been counterchecked by a second person. The date of entry into the database was not documented into the forms. This was done at a later date and the date entered was wrong.The date of actual entry is now changed in the study and now reads 18/10/10. This is not procedural and the concerned staff were warned of their actions.
3003	7	9.9.10	4-I; 6-I	Concom. med and AE froms	The respective Concomitant medication form has been moved to the end of the volunteer's folder, however this volunteer does not have any AE.
3032	3	14.7.10	5-II	item 10 missing	The item is not ticked, however N/A which signifies not applicable is recorded. Indeed this is so for all male volunteers. Item 10 has now been ticked however the smiley face has been missing in all forms. The smiley face has been hand drawn on 19/10/10
3032	3	14.7.10	3-II 3 vs 3.A	duplicate forms one seems after vaccination, both entered	This is per standard operating procedures. The form may be useful after vaccination.
3032	3	14.7.10	10-I	filled in 29.7.10, mix clinic an home	The assessment has been changed from clinic to home on

					the 19/10/10.
3032	7	9.9.10	4-I	Concom. med and AE froms	The respective Concomitant medication form has been moved to the end of the volunteers folder, however this volunteer does not have any AE.
3036	3	10.7.10	5-II	item 10 missing tick	Item 10 has now been ticked however the smiley face has been missing in all forms. The smiley face has been hand drawn on 19/10/10
3036	3	10.7.10	10-I	Clinic - homevisit ?	The assessment has been changed from clinic to home on the 19/10/10. This has been corrected for all the other visits
3036	5	13.7.10	10-I	multipe modifications of grading by munseri	The volunteer happened to have moderate to severe reactions post first vaccination that necessitated the Clinical Coordinator (Munseri) to reevaluate her during the next visit that was visit 6. The explanation of the changes have been reflected in the source document for 22nd July 2010
3036	6	28.7.10	4-I, 6-I	Concom med och AE forms found here.Not at end	All forms have been moved to the end of the volunteers folder
3036	8	1.9.10	7-I	Better placed at end	This has been placed at the end of the volunteers folder
3041	3	16.6.10	5-II	item 10 missing filled in in v3	The CRF is filled in as NA, meaning not applicable as this is a male volunteer. Item 10 for the exclusion section has also been filled in on the 7.1.11.This specific CRF is to be filled in visit 3
3041	5	15.7.10	4-II	Previous con comit med form found here in two copies with different content both labelled page 1	The CRFs have been moved to the end of the file
3041	5	15.7.10	4-I	concom med found here. 2 different copies on labelled page 1	The concomitant medication form has been moved to the end of the volunteer's folder. The two copies of concomitant medication and previous condition forms have been condensed to 1 form on the 15.11.10 and the other form has been cancelled.
3041	5	15.7.10	6-I	AE form found here	The AE form has been moved to the back of the volunteers folder

3041	8	8.9.10	3-II	not entered	Data entry has now been done on the 21.10.10
3041	9	11.9.10	10-I	visit 8 forms found here	CRFs 10-I for visit 8 have now been moved from visit 9 to visit 8
3043	3	16.6.10	5-II	item 10 missing filled in in v3	Item 10 is now entered on the 7.01.11 and is filled appropriately in visit 3 as it is one of the documents required prior to enrollment in visit 3
3043	3	16.6.10	4-I	con com med found here	The concomitant medication form has been moved to the back of the volunteer's folder.
3043	9	22.9.10	10-I	visit 8 forms found here	CRFs 10-I for visit 8 have now been moved from visit 9 to visit 8
3044	3	30.6.10	5-II	item 10 missing	The CRF is filled in as NA, meaning not applicable as this is a male volunteer. Item 10 in the exclusion criteria was filled in on the 15.11.10
3044	4	28.7.10	4-I, 6-I	Concom med och AE forms found here. Not at end	The concomitant medication form and AE has been moved to the back of the volunteer's folder.
3044	9	6.10.10	10-I	Visit 8 10-I (23.9.10) forms filed here. Not entered	CRF 10-I for visit 8 has been appropriately filled in visit 8 after moving them from visit 9. Data entry was performed on 19.10.10 and 20.10.10 for first and second data entry respectively.
3048	3	23.6.10	5-II	item 10 missing	Item 10 was filled as NA which is not applicable on the 23.06.10. Item 10 on the exclusion criteria has been filled in on the 18.11.10
3048	3	23.6.10	10-I	3 forms not all entered	The vaccine reaction form CRF 10-I has been entered on the 26.10.10. The forms had been entered in the database, date of entry was on the 18/10/10. However data entry was done erroneously into the database before the forms had been counterchecked by a second person. The date of entry into the database was not documented into the forms. This was done at a later date and the date entered was wrong.The date of actual entry is now changed in the study and now reads 26/10/10.This is not procedural and the concerned staff were warned of their actions.

3048	5	31.7.10	6-I	AE from found here; Hypoglycemia no outcome or resolution date	The date of outcome that the hypoglyceamia is entered as resolved on 19.08.10
3048	5	31.7.10	10-I	mix home and clinic assess	All forms have been changed from “clinic” to “home” on the 7.1.11
3048	9	29.9.10	10-I	Visit 8 10-I forms filed here. Not entered	The vaccine reaction forms for visit 8 were appropriately filled in during visit 8. These forms have been moved from visit 9 to visit 8
3052	3	30.6.10	5-II	item 10 missing	The item is not ticked however N/A, which signifies not applicable and this is so for all male volunteers. Item 10 in the exclusion criteria has now been filled in on the 7.1.11
3052	3	30.6.10	4-I	comcom. Med form found here	The respective Concomitant medication form has been moved to the end of the volunteer’s folder.
3052	3	30.6.10	10-I	3E headache 1 - no relationship filled in	The relationship has been filled in and dated to reflect that this has been entered on the 15.11.2010. However this has been filled in as 4 after extrapolating from visit 3 D that was filled in as a 4.
3052	6	12.8.10	4-I	New concomm med from	One form has been used so as to maintain continutity. The additional form has been cancelled but is maintained in the volunteers folder.
3052	9	28.9.10	10-I	Visit 8 10-I forms filed here not entered	These have now been entered on the 21.10.10
3053	3	20.6.10	5-II	incl item 12 - normal ECG not ticked. Ecxlusion item 10 missing	CRF 5-II item 12 has been ticked and dated 15.11.10. Item 10 is filled in as NA not applicable for male volunteers. Item 10 in the exclusion has been filled in on the 7.1.11
3053	3	20.6.10	10-I	correction 3C skin redeness unclear to what;3H arthralgia, itching, 3I malaise -relationship?	For skin redness visit 3C this has been cancelled on the 9.08.10 after interviewing the volunteer and finding out that there was no skin redness. Both the arthralgia and itching, as well as malaise were considered definitely related to the vaccine and have been filled in as 5 on the 15.11.10
3053	5	29.7.0	CFR 4-I	comcom. Med form found here	The respective Concomitant medication form has been moved to the end of the volunteers folder
3053	5	29.7.0	CRF 6-I	AE from found here	The respective AE form has been moved to the back of the volunteers folder as suggested.

3053	9	23.9.10		Visit 8 10-I forms filed here .Forms singel entry	The CRF 10-I has been moved from visit 9 to visit 8. Second data entry was done on 12.10.10
3055	3	30.6.10	5-II	item 10 missing	This has been filled in and dated 7.1.11
3055	5	29.7.10	CFR 4-I	comcom. Med form found here	The form has now been moved to the end of the volunteers folder
3055	5	29.7.10	CRF 6-I	AE from found here	The form has now been moved to the end of the volunteers folder
3055	5	29.7.10	10-I	10-I '5. ' should be '5.A'; Blue marker on CRF for easier detection	The letter A signifying that the visit was 30 minutes after vaccination has been added and dated 15.11.10
3055	7	26.8.10	CFR 4-I	comcom. Med form found here	The form has now been moved to the end of the volunteers folder
3055	8	27.9.10	CRF 6-I	AE from found here OBS Rhinitis reg. As EAE/tm	The form has now been moved to the end of the volunteers folder. The EAE has also been changed in the form and in the database. Explanation of this has been made and included in the volunteers folder and regulatory binder.
3055	8	27.9.10	9-IV , 9-V	Not checked and signed	The forms have been counterchecked and signed on the 19.10.10 and 21.1010 respectively
3055	9	27.9.10		diary card for third immunization filed here	The diary card has now been moved to visit 8.
3055	9	6.10.10	2-III; 10-I	Visit 8 10-I forms filed here .Forms singel entry. Visit 8.D 'home visit' - not confirmed in source data.	The vaccine reaction forms for visit 8 has now been moved to visit 8. For visit 8 D this has been changed from home to clinic visit as all diary cards are transcribed at the clinic.
3062	3	14.7.10	5-II	item 10 missing	This item was filled in as NA meaning not applicable as this is a male volunteer and therefore the question was irrelevant. Item 10 for the exclusion criteria has been filled in and dated 7.1.11
3062	3	14.7.10	CFR 4-I	comcom. Med form found here	The concomitant medication forms has been moved to the end of the volunteers folder.
3062	3	14.7.10	9-V	Comment 'grade 1 AE ..' does not specify what test	This has been added that the grade 1 AE is for elevated glucose that has been added on the 15.11.10
3062	7	9.9.10	CRF 6-I	AE from found here OBS Rhinorrhea no resolution date	The resolution has now been filled in the date of resolution was on the 12.09.10

3063	3	4.8.10	5-II	item 10 missing filled in in v3	Item 10 was filled and filling is appropriately in visit 3
3063	6	16.9.10	10-I	There are forms for this visit that should not be there, labeled visit 6. Not filled in and not entered but signed. Visit 5 forms found here	The forms have now been moved from visit 6 to visit 5. The forms labeled visit 6 have now been changed to visit 5 however the dating of the forms seem to be back dated and dated 24.09.10. Dr Chum and both data entrants have been warned and this has been included in the memo to file. All visit 5 forms have been transferred from visit 6 to visit 5
3069	2	6.7.10		Forms not entered	Data entrants have entered the data and this has been documented on the 15.11.10
3069	3	21.7.10	5-II	item 10 missing	Item has been filled in on the 15.11.10
3069	5	18.8.10	9-IV	Low Hb, progessing according to note. Nothing in Source doc. No reminder of action. Tired, headache taking paracetamol	The falling HB was discovered on 31.08.10. The volunteer was then called in for an unscheduled visit on the 3 of September 2010 and was investigated and followed up. Appropriate documentation was done in the source document. The stop dates for tired, headache and tiredness were 21.08.10. While paracetamol stop date is documented to be 19.08.10
3069	5	18.8.10	CFR 4-I	comcom. Med form found here	Concomitant medication form has been moved to the end of the volunteers folder
3069	6	7.9.10	3-III	Epigastric tenderness. Bleeding gastric ulcer?	Source documentation for the visit 06-K on the 7.09.10 and there is documentation that there is no melaena
3069	6	7.9.10	6-I	AE for found here, Anemia and gastitis noted. A new 6-I form also here with 3rd event: URTI. Page not labeled 2 nor empty spaces on page 1 crossed over.	The AE forms have been moved to the end of the volunteer's folder. The AEs have all been collated in one form and the redundant forms have been cancelled on the 15.11.10
3069	6	7.9.10	CFR 4-I	New comcom. Med form found here wrongly labelled page 1	Concomitant medication forms is filed at the end of the volunteer's folder and all condensed in one form all other forms cancelled on the 21.10 10 and maintained in volunteer's folder.
3069	7	15.9.10	CFR 4-I	Third comcom. Med form found here wrongly labelled page 1	Concomitant medication forms filed at the end of the volunteer's folder and all condensed in one form all other forms cancelled on the 21.10 10 and maintained in

					volunteer's folder.
3069	7	15.9.10	3-III	Referred for heamatol review	The report from the hematologist dated 17.09.10 has been included in visit 6
3070	1	21.6.10	5-II	item 10 missing	Item 10 has now been filled in on the 15.11.10
3070	3	28.7.10	5-III	Form not counter checked	Counter-checking has been done on the 15.11.10
3070	4	5.8.10	6-I	AE from found here	The AE has been moved to the end
3070	5	18.8.10	2-III	5--I noted as home visit which is not supported by source data	The documentation for home visit has been cancelled on the 15.11.10
3070	7	15.9.10	3-II ; 6-I	AE forms found here. Tonsilitis noted as EAE. Not resolved	The AE forms have been moved to the end of the volunteer's folder and the EAE has been changed from "YES" to "NO" on the 13.10.10. The date of resolution for the tonsillitis has been entered to be the 18.09.10
3076	3	29.9.10	5-II	Bad print	After the monitoring visit CRF 5-II has been amemended and item 5,6,7 and 8 have now been rectified on the CRF
3076	3.I?	6.10.10	3-II	Joint pain, malaise - no AE 6-I	The joint pain was considered as a vaccine reaction and not an adverse event. There was no joint pain noted on visit 3-I and the stop date for the symptoms were on the 9.10.10. This has been entered in the vaccine reaction form on the 15.11.10
3076	3.I?	6.10.10	4-I	concom. Med found here	The form for concomittant medications has been moved to the end of the volunteer's folder
3078	2	18.8.10	9-III	forms not entered or checked	The forms have been counter-checked on the 18.10.10 and have been entered in the database on the 25.10.10
3078	3	19.9.10	5-II	Dated and done v2 but filed here	CRF 5-II is usually filed in visit 3 and filling of this form was from visit 2 but completed in visit 3
3078	4	16.9.10	10-I	Visit 3 forms filed under visit 4.	All the vaccine reaction forms CRF 10-I have now been transferred from visit 4 to visit 3 where they belong.
3078	5	29.9.10	CFR 4-I	comcom. Med form found here	The concomitant medication form has been moved to the end of the volunteer's folder.
3078	5	29.9.10	6-I	AE from found here. General body malaise grade	The AE form has been moved to the end of the volunteers

				1, noted as EAE, note checked by physician . Not entered	folder and the EAE has been changed from “YES” to “NO” on the 29.10.10, a memo to file has also been included
3082	3	4.8.10	5-II	item 10 missing	Item 10 has been filled in and dated 16.11.10
3082	3	4.8.10	6-I	AE form found here; lab abnormality; Both version 1.1 and 1.2 filled in ie duplicate; Both entered in database	The AEs has been condensed to one form and the data entrant has been informed.
3082	5	1.9.10	5-II	No 5-II	CRF 5-II is filed in visit 3 dated 4.08.10
3082	6	16.9.10	5-II	5C 'x' instead of numbers all 5-II forms here instead of visit 5; Diary card filed here	CRF 10-I for visit 5C the cross marks have now been changed to 0 and dated 16.11.10. The diary card and all the vaccine reaction forms have been filed in visit 5 CRF and source documents respectively
3082	7	30.9.10	4-I &6-I	AE motor accident. Con com med forms here.	Both the AE and concomitant medication forms have been filed at the back of the volunteer’s folder.
3083	3	18.8.10	!	No randomization form or vaccine requisition form	The randomization and vaccine requisition forms were inappropriately filed in visit 3 source documents. These forms have now been appropriately filed in the visit 3 CFR section.
3083	3	18.8.10	4-I	concom med found here	The concomittant medication form has been shifted to the end of the volunteer’s folder
3083	3	18.8.10	5-II	item 10 missing	Item 10 has now been included and dated 15.11.10
3083	4	2.9.10	10-I	Reactogenicity visit 3 found here	All CRF10-I have now been appropriately transferred from visit 4 to visit 3.
3083	6	30.9.10	10-I	Vist 5 B-G reactogenicty forms here	All CRFs 10-I visit 5B-G have been transferred from visit 6 and filed in visit 5
3083	5JK		3-II	facial palsy, final D/ sinusitis. New 2-III forms out of order under vist.No reason given for the unscheduled visits.	The CRFs have been arranged in proper order. The reasons for the unscheduled visits are documented in the source documents and are also included in CRF 2-III and dated 15.11.10
3086	3	1.9.10	5-II	Documented at visit 1, filed here. Tick for item 9 inclusion (contraception and item 9&10 exclusion missing.	CRF 5-II is initially filled in from visit 1 however the final filling may happen at visit 1,2 or 3 depending on whether the volunteer will be enrolled or not since this volunteer was enrolled the CRF was appropriately filed in visit 3. The

					tick marks for item 9 and for exclusion item 9 and 10 have now been completed and dated 16.11.10
3086	4	17.9.10	4-I	concom med found here	The CRF 4-I for concomittant medication has been moved to the back of the volunteer's folder.
3086	4	17.9.10	6-I	AE form found here; lab abnormality; malaria; reg as EAE/sc	The AE form has been transferred from visit 4 to the end of the volunteer's folder. The Malaria event that was erroneously documented as an EAE has been changed (it was not an EAE) on the 29.10.10
3088	3	1.9.10	5-II	item 10 missing	Item 10 of the exclusion criteria has been filled in and dated 16.11.10
3088	4	16.9.10	6-I	AE form filed here, swollen left foot grade 1 after truama, Reg as EAE/sc	The AE form has been moved to the back of the volunteer's folder and the EAE has now been changed to "NO" on the 4.11.10 and a memo to file is also included
3088	4	16.9.10	10-I	Vist 3 reactogenicity filed here	All CRF 10-I for visit 3 have been transferred from visit 4 to visit 3.
3088	5	29.9.10	6-I	New AE ancle oedema, no sequenteial numer no number on page. Reg as EAE/sc	The AE of ankle oedema that was documented in a new AE form has been combined in the initial AE form and is regarded as the second AE for the volunteer. The EAE has been changed that it was not an EAE on the 29.10.10 and a memo to file is also included
3091	3	1.9.10	5-II	Item 3 (ELISA) Inclusion missing; HIV neg	Item 3 has now been filled in and dated 16.11.10
3091	4	29.9.10	10-I	Reactogenicity 5B-I visit 3 filed here	The vaccine reaction form 5B-I have been transferred from visit 4 and filed in visit 5
3091	4	29.9.10		Diary card filed here	The diary card has been transferred from visit 4 to visit 3
3092	3	9.9.10	5-II	item 10 missing	Item 10 has been filled in and dated 16.11.10
3092	3	9.9.10	3-II	Reactogenicity 3B-I missing. Dieary in source doc	The vaccine reaction forms 3B-3I might have been missing because they were inappropriately filed. Not they are filled in visit 3. The diary card was placed in the source documents for visit 2 and is now placed in the source documents for visit 3
3097	2	31.8.10	5-II	Item 3 (ELISA) Inclusion item 10 exclusion missing. Filed under visit 2. HIV neg.	Item 3 has now been filled in and dated 16.11.10. Item 10 on the exclusion criteria has now been filled in and dated

					16.11.10. The form has now been transferred from visit 2 and filed in visit 3
3097	3	15.9.10	10-I	Visit 3 reactogenicity filed here. 3Cand D recorded as 'home visit' No indication of that i source doc.3B,g-I as 'clinic visit'	The visit contact form for visit 3C and 3D are documented as home as the volunteer fills in the diary card at home. But the diary card was reviewed at the clinic in the presence of the volunteer.
3097	3	15.9.10	4-I	concom med found here	The concomittant medication forms has now been moved to the back of the volunteer's folder
3097	3	15.9.10	6-I	AE form filed here,headache abdominal fullness, grade 1, Recorded as EAE/sc	The AE form has now been transferred to the back of the volunteer's folder and the EAE has been changed from YES to NO dated 3.11.10 a memo to file has also been included
3098	1	16.8.10	5-I	Single entered	The data has been double entered on the 16.11.10
3098	2	31.8.10	5-II	item 10 exclusion missing. Filed under visit 2.	CRF 5-II has been filed in visit 3 and item 10 has been circled.
3098	4	1.10.10	10-I	Reactogenicity vistt 3 found here	The vaccine reaction forms have been moved from visit 4 and are now placed in visit 3
3098	4	1.10.10	4-I	concom med found here	The concomittant medication forms has been placed at the end of the volunteer's folder.
3098	4	1.10.10	6-I	AE found here. Headache grade I EAE/sc	The AE form has now been placed at the end of the volunteer's folder and the EAE is now changed from "YES" to "NO" a memo to file has also been included.
3099	2	1.9.10	5-II	item 10 exclusion missing. Filed under visit 2.	Item 10 has now been filled in. CRF 5-II that was filed in visit 2 has now been transferred and filed in visit 3
3099	4	1.10.10	10-I	Reactogenicity vistt 3 found here	The vaccine reaction forms that were initially filed in visit 4 are now filed in visit 3
3099	4	1.10.10	4-I	concom med found here	The concomittant medication form has now been filed at the end of the volunteer's folder
3099	4	1.10.10	6-I	AE found here. Heartburn grade I EAE/sc	The AE form has now been moved to the back of the volunteer's folder and the EAE has now been changed from YES to NO on the 29.10.10 a memo to file has also been concluded.
3109	2	9.9.10	5-II	Bad copy. Item 5&6 missing inclusion and item 10	After the monitoring visit CRF 5-II has been amemended

				exclusion. Not signed or counter signed. Rg visit 1 found here	and item 5,6,7 and 8 have now been rectified on the CRF. The form is now contersigned and date 21.10.10.
3109	2	9.9.10	9-III	ECG. Not filled in. ECG tracings found in source, but no interpretation.	The ECG was filled in on the 22.09.10. The ECG tracings are kept in the source documents of visit 2 and the interpretation from Dr. Chaitman dated 9.9.10 is also in the source documents for visit 2 while the interpretation of the ECG CRF 9-III is in visit 2 CRF and was filled in on the 22.09.10 and counterchecked on the
3111	2	15.9.10	5-II	Bad copy, filed here	After the monitoring visit CRF 5-II has been amemended and item 5,6,7 and 8 have now been rectified on the CRF
3111	3	29.9.10	5-IV	form answered in spite of 3 and 4 'yes' and item 4 indicated 'yes' to not healthy. Not supported by source documents	The form that was filled in for reasons have all been cancelled on the 25.10.10. For item 4 the answer is yes that the subject is healthy based on the medical history and physical exam.
3117	1	31.8.10	Inf cons	Study number overwritten	The overwriting of the study number was done by the volunteer however this has been crossed off on the 15.11.2010 and written clearly.
3117	2	23.9.10	5-II	Bad copy, item 5, 6 inclusion and item 10 missing exclsion, filed here	This has been noted and soon after the monitoring visit CRF 5-II has been corrected for all the new volunteers but not for this particular volunteer. Item 10 is now filled in and the form is filled in visit 2 since the forms were filled in visit 2 and not 3 as is usually the case the senior physicians had to travel and therefore volunteers were seen before they travelled
3117	2	23.9.10	5-III	done at this visit instead of visit 3	The senior Physicians who fills in CRF 5-III and assess the volunteers eligibility were to travel to Atlanta for the HIV vaccine conference and therefore it was discussed and authorized by the study PI that they be evaluated before visit 3 that would have coincided with the Atlanta trip.
3122	3	6.10.10	5-II	Bad copy item 5 or 6 inclusion missing	This has been noted and soon after the monitoring visit CRF 5-II has been corrected for all the new volunteers but not for this particular volunteer.
3122	3	6.10.10	5-II and 5-III	forms not countersigned	The forms have been countersigned however of note is

					back dating on countersigning the respective forms. Dr Chum who was reposible for back dating has been warned and instructed to fill in the actual dates of countersigning and not to back date any study documents.

Correct EAE now in database

				Comments
3055	MUHAS	2	VIRAL RHINITIS	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3070	MUHAS	3	TONSILITIS	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3078	MUHAS	1	GENERAL BODY MALAISE	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3082	MUHAS	2	WOUND ON RIGHT LEG	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.

3083	MUHAS	1	URTI/UPPER RESPIRATORY TRACT INFECTION	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3083	MUHAS	2	MALARIA	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3086	MUHAS	1	JOINT PAIN AND ABDOMINAL FEVER	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3088	MUHAS	1	SWOLLEN LEFT 3RD TOE AFTER TRAUMA	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3098	MUHAS	1	HEADACHE	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.
3099	MUHAS	1	HEARTBURN	This has been corrected and it no longer appears as an EAE. A memo to file has also been included that decribes that the EAEs

reported were not EAEs but was a misunderstanding of Dr Chum who misunderstood and AE for an EAE.

Report Prepared by:

……

Patricia Munseri

Clinical Co-ordinator

Date: ……

Counterchecked by:

……..

Muhammad Bakari

Principal Investigator

Date:……..

Responses to issues raised by the Internal Monitoring of

TaMoVac I, performed at MUHAS, on Feb 7-15, 2011 by Eric Sandström

Monitoring TaMoVac I 2011-02-11

Eric Sandström

Given the concomitant monotoring by WRAIR immediately prior to this visit and the monthly MRC sponsored TMG reviews, this review focuses on the quality of the online reports that serve as a basis for the daily follow-up of events in the trial.

The visit was restricted to the Makuti site at MNH Febr 7-15, 2011.

Action points in bold italics; A-Q. Volunteer numbers marked for action in YELLOW

Database

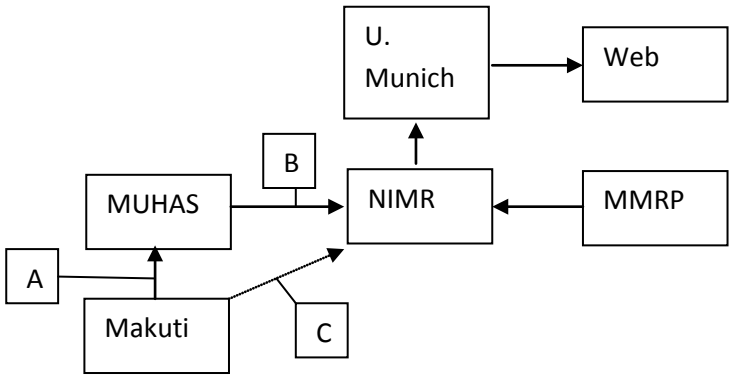
The Web based database (Munich) has not been updated since mid December 2010 for MUHAS based on latest entries in several reports and minutes from weekly meetings. MMRP not reviewed.

Breakdown in internet connection between local server at Makuti and (NIMR? Munich?) seems to have occurred several times. Data has been continued to be entered at Makuti in the local server and manually transferred to the NIMR server, no MUHAS data have been transferred to Munich. A new server has been established at MUHAS with data entered via intranet from Makuti since 2011-2-9.

Multiple power failures during the visit. The Makuti generator did not work, ie the local network and site computers did not work. This often coincided with loss of access to the internet via MUHAS and via Zantel.

A. Enable Makuti generator to function

Informed that the current structure of the database is as below. However there is not a complete consensus that this is the case.



A. Current connection via Intranet from client at Makuti (no data stored) to MUHAS server which has uninterrupted solar power supply. Data entry works when there is power at Makuti, regardsless of internet access.

B. Transfer of data from MUHAS and NIMR via internet provider (different from NIMR – Munich). B. ***B. Establish back-up at MUHAS for data entered at Makuti***

C. Prior link via Makuti and NIMR subject internet access and power failures.

According to this scheme the main data base is kept at NIMR with a mirror at U. Munich. However this is in contrast with the statement that difficulties with synchronization are due to internet failures at MUHAS, since the database is claimed to have been updated 'manually' (C, dotted line) from Makuti during the period of difficulties since Dec 2010. No internet failure between NIMR and U. Munich has been reported.

Is MUHAS server now backed up? There does not seem to be a copy of the study database at Makuti anymore.

C. A clear SOP for internet questions at Makuti need to be established:

- Makuti contacts one defined person/deputy at NIMR in case of connection/database problems. Tel…….
- NIMR contacts Msangi/deputy at MUHAS or Max/deputy in Munich for further resolution if needed.

The goal should be that the master database and the mirror in Munich should be updated to within a week of data acquisition.

General problems with the database/reports

Downloading excel sheets from the **Web** based report yields two formats for Dates. One is a date ex. 01-jan-10, the other unspecified ex. 01 Jan 2010. The latter can not be used in computations in Excel. Unclear if this is an entry error or if some other transformation takes place. Occurrences are random and refer to both sites. Downloads from NIMR does not suffer this problems.

AEs 2011-02-11 based on web report (for reference only, see Appendix E)

Latest updated mid Dec 2010.

AEs 2011-02-13 based on NIMR report, MUHAS only

Latest reported date 22-Jan-2011

Not a problem with date formats in this file.

Use of event number not informative. ***D. Include visit number in report.***

Ok will include it in our report

3076.3 No data on relationship or previous condition, Since it is urticartia it is important.

Corrected on 21sth February 2011, Now Relationship reads –"Not relatated" (1) and previous condition as "No" (N)

'StudyID.Event' format below

3183.2 AE description '111' resolved after crosschecking with CRFs

Corrected on 21st February 2011. Apparently it was entered by mistake by the first entrant and could not be picked by the 2nd entrant as a result of internet problems leading to syntax for AEs in the database being unable to compare and harmonise the entries

The probleam has already been reported to the IT people for resolution

3083.1 Start date 31-jan-2011 – this is remarkable since it is the corrected date in the Makuti data base!*(see below)

Corrected on 21st February 2011. Apparently it was entered by mistake by the first entrant and could not be picked by the 2nd entrant as a result of internet problems leading to syntax for AEs in the database being unable to compare and harmonise the entries. But now the database reads 31/08/2010 as in the CRF.

3130.1 AE grade '0'

Corrected on 21st February 2011. Apparently no value was indicated in the CRF and consequently the database generated a '0' as a default value for missing data. The value has now been filled in the CRFs and updated in Database and now it reads '1'

3078.2 AE outcome '0' but with resolution date

Corrected on 21st February 2011. Apparently no value was indicated in the CRF and consequently the database generated a '0' as a default value for missing data. The value has now been filled in the CRFs and updated in Database and now it reads '1'

3117.5 AE outcome '1' without resolution date

Corrected on 21st February 2011, as it was not indicated in the CRF during the time of data entry. This has now been filled in the CRF and updated in the database. It reads '02/12/2010'

3048.2, 3117.1 AE outcome '3' without resolution date

Since '3' indicates 'ongoing' the date for resolution is not expected.

3173.2, 3173.3, 3183.2 without investigatrors signature

Corrected 23rd/02/2011, at the time of data entry the signature was not indicated on CRFs. The Data clerk did rise a querry. This is now resolved

3183.2, 3052.1 recorded date missing

Corrected on 14th March 2011

3117.2 SAE – check reporting

Corredted on 10th March 2011, by that time the outcome was entered as '3' but now is '2'

E. Review all marked in YELLOWabove

Numer of events per volunteer

Number of events	Frequency	Percent	Valid Percent	Cumulative Percent
1	39	41,1	41,1	41,1
2	25	26,3	26,3	67,4
3	16	16,8	16,8	84,2
4	8	8,4	8,4	92,6
5	4	4,2	4,2	96,8
6	2	2,1	2,1	98,9
7	1	1,1	1,1	100,0
Total	95	100,0	100,0	

39 reported at least one event.

The most affected; Number of events.

	1	2	3	4	5	6	7	TOTAL
3069	1	1	1	1	0	0	0	4
3076	1	1	1	1	0	0	0	4
3078	1	1	1	1	0	0	0	4
3086	1	1	1	1	0	0	0	4
3036	1	1	1	1	1	0	0	5
3082	1	1	1	1	1	0	0	5
3117	1	1	1	1	1	1	0	6
3083	1	1	1	1	1	1	1	7

All these are ok when entries were compared between the database and CRFs except for ID 3036 where the events number 6 and 7 need to be deleted.

Case Summaries of those with 4 or more events

subject_id	AE_description	AE_ grade	AE_ relate_ agent	AE_ effect	event_id
3036	AMODIAQUINE SIDE EFFECTS JOINT PAIN AND MALAISE	1	3	1	1
3036	ACUTE ENTERITIS SECONDARY TO ?FISH POISONING	2	3	1	2
3036	ITCHY STRIAE	2	1	1	3
3036	SCARS AND EXCORIATION AT VACCINATION SITES SECONDARY TO PERSISTANT ITCH/SCRATCH	2	3	4	4
3036	MISSED ONE MENSTRUAL CYCLE	1	3	1	5
3069	ANAEMIA? CAUSE	1	3	1	1
3069	UPPER RESPIRATORY TRACT INFECTION (URTI)	1	1	1	2
3069	DYSPEPTIC SYMPTOMS	1	2	1	3
3069	HEADACHE	1	3	1	4
3076	LEFT ARMPIT ABSCESS	1	1	1	1
3076	PRURITUS	1	2	1	2
3076	URTICARIA	1	.???	1	3
3076	FEVER	2	1	1	4
3078	GENERAL BODY MALAISE	1	1	1	1
3078	SOFT TISSUE INJURY	1	1	1	2
3078	HIGH CREATININE LEVEL	1	2	1	3
3078	INJURED LEFT FORE FINGER	1	1	1	4
3082	ELEVATED ALT	1	3	1	1
3082	WOUND ON RIGHT LEG	2	1	1	2
3082	BACKACHE	1	1	1	3
3082	ECZEMA	1	2	1	4
3082	ELEVATED GLUCOSE LEVEL	1	1	1	5
3083	URTI/UPPER RESPIRATORY TRACT INFECTION	2	3	1	1
3083	MALARIA	2	3	1	2
3083	FACIAL PALSY	1	3	1	3
3083	SINUSITIS	1	3	1	4
3083	LOW NEUTROPHILES	2	3	1	5
3083	MONOCYTES BELOW NORMAL RANGE	1	2	1	6
3083	EUSINOPHILS BELOW NORMAL RANGE	1	5	1	7
3086	MALARIA	1	1	1	1
3086	ELEVATED ALT	1	2	1	2
3086	ELEVATED GLUCOSE	2	2	1	3
3086	ELEVATED ALT	1	2	1	4
3117	ENTERITIS	1	3	1	1
3117	CUT WOUND ON THE FORE HEAD	3	1	3	2
3117	LOW TOTAL WHITE CELL COUNT	1	1	1	3

3117	LOW RANDOM BLOOD GLUCOSE		2	1	1	4
3117	NEUTROPENIA		2	1	1	5
3117	LOW WHILE CELL COUNT (LEUKOPENIA)		2	2	1	6
39		39	39	38	39	39

These are correct when a comparison was made between the CRFs and the database except for Number 3076 with ??? URTICARIA. The AE_relate_agent is now corrected to read '1'

Also FACIAL PALSY was discussed and the clinic canceled due the fact that it was ultimately regarded as a complication of sinusitisand was agreed upon at a TMG call

F. Review all marked in YELLOW above

AE_grade * AE_relate_agent Crosstabulation

Count

		AE_relate_agent				
		1	2	3	5	Total
AE_grade	0	0	1	0	0	1
	1	45	15	12	1	73
	2	10	2	6	0	18
	3	2	0	0	0	2
Total		57	18	18	1	94

These have now been reviewed and they are the same in the databaseas in the CRFs

A previously noted high frequency of grade 2 events is no longer noted at MUHAS

Severe grade

event_id	subject_id	AE_description	AE_grade	AE_relate_agent	Duration
2	3043	TUBALIGATION	3	1	6,00
2	3117	CUT WOUND ON THE FORE HEAD	3	1	.
2	2		2	2	1

Reviews and reads the same as in database and on CRFs

Moderate grade

event_id	subject_id	AE_description	AE_grade	AE_relate_agent	Duration
3	3036	ITCHY STRIAE	2	1	15,00

1	3044	BODY ITCH SECONDARY TO INSECTS CATAPILLAR	2	1	1,00
1	3071	TONSIL ITIS	2	1	6,00
2	3055	VIRAL RHINITIS	2	1	3,00
2	3082	WOUND ON RIGHT LEG	2	1	10,00
2	3122	ELEVATED GLUCOSE LEVEL	2	1	15,00
4	3076	FEVER	2	1	1,00
1	3109	ELEVATED SERUM GLUCOSE	2	1	.
4	3117	LOW RANDOM BLOOD GLUCOSE	2	1	.
5	3117	NEUTROPENIA	2	1	.
3	3086	ELEVATED GLUCOSE	2	2	28,00
6	3117	LOW WHILE CELL COUNT (LEUKOPENIA)	2	2	.
2	3036	ACUTE ENTERITIS SECONDARY TO ?FISH POISONING	2	3	1,00
4	3036	SCARS AND EXCORIATION AT VACCINATION SITES SECONDARY TO PERSISTANT ITCH/SCRATCH	2	3	17,00
2	3083	MALARIA	2	3	3,00
1	3083	URTI/UPPER RESPIRATORY TRACT INFECTION	2	3	224,00*
2	3153	MONORRHAGIA	2	3	.
5	3083	LOW NEUTROPHILES	2	3	.
18	18	18	18	18	12

Reviews and reads the same as in database and on CRFs

Possible or > relationship

event_id	subject_id	AE_description	AE_grade	AE_relate_agent	Duration
1	3036	AMODIAQUINE SIDE EFFECTS JOINT PAIN AND MALAISE	1	3	5,00
2	3036	ACUTE ENTERITIS SECONDARY TO ?FISH POISONING	2	3	1,00
5	3036	MISSED ONE MENSTRUAL CYCLE	1	3	36,00
4	3036	SCARS AND EXCORIATION AT VACCINATION SITES SECONDARY TO PERSISTANT ITCH/SCRATCH	2	3	17,00
1	3070	URINE DIPSTICK +	1	3	20,00
1	3082	ELEVATED ALT	1	3	13,00
2	3083	MALARIA	2	3	3,00
1	3083	URTI/UPPER RESPIRATORY TRACT INFECTION	2	3	224,00*31/08-12.09
1	3098	HEADACHE	1	3	5,00

3	3083	FACIAL PALSY	1	3	10,00
4	3083	SINUSITIS	1	3	10,00
1	3117	ENTERITIS	1	3	2,00
4	3069	HEADACHE	1	3	,00
2	3044	LOW PLATELETS	1	3	15,00
1	3069	ANAEMIA? CAUSE	1	3	83,00
2	3153	MONORRHAGIA	2	3	.
5	3083	LOW NEUTROPHILES	2	3	.
1	3097	HEADACHE	1	3	32,00
7	3083	EUSINOPHILS BELOW NORMAL RANGE	1	5	.
19	19	19	19	19	16

These have been reviewed. The entries in the database are same as in the CRFs for all except for the duration of 224 of ID 3083which was wrongly entered, instead of being enterd as 31/08/2010 it was entered as 31/Jan/2010. This is now is corrected.

G. Review Yellow above , It is not evident that there is a relationship, please review.

Duration all

H. Check dates 3044.3 , 3088.2, 3122.3 negative durations. Wrong start or end date.

3044.3 The date for resolution was wrongly entered. It is now corrected and reads 24th/Jan/2011
3088.2 The date for resolution was missing but is now corrected and reads 10th/11/2010
3122.3 This was wrongly entered but is now corrected, it reads 05th/01/2011

AEs noted as not resolved

	subject_id	AE_description	AE_start_date	AE_grade	AE_relate_agent	AE_effect
1	3003	ELEVATED CREATININE	03-nov-2010	1	2	1
2	3063	UPPER RESPIRATORY INFECTION	07-nov-2010	1	2	1
3	3091	HYPERGLYCEMIA	25-nov-2010	1	1	1
4	3109	ELEVATED SERUM GLUCOSE	28-dec-2010	2	1	1
5	3148	BURNING SENSATION ON THE RIGHT LEG AND FOOT	02-dec-2010	1	1	1
6	3154	HYPOCHROMIA	22-dec-2010	1	1	1
7	3155	LOWER ABDOMINAL PAIN	10-jan-2011	1	1	1
8	3169	PLATELETS ABOVE THE NORMAL RANGE	16-dec-2010	1	1	1
9	3173	IRON DEFICIENCY ANAEMIA	01-dec-2010	1	1	1
10	3183	BORDERLINE HEMOGLOBIN LEVEL	13-jan-2011	1	1	1

11	3185	MYALGIA	11-jan-2011	1	1	1
12	3048	COUGH	15-jan-2011	1	1	1
13	3062	LOW GLUCOSE	04-nov-2010	1	1	1
14	3117	CUT WOUND ON THE FORE HEAD	22-okt-2010	3	1	3
15	3130	BODY MALAISE	19-jan-2011	1	1	1
16	3148	ELEVATED ALT	05-jan-2011	1	1	1
17	3153	MONORRHAGIA	06-jan-2011	2	3	1
18	3173	ARHTALGIA	31-dec-2010	1	1	1
19	3183	111	11-jan-2011	1	1	1
20	3185	ARTHALGIA	11-jan-2011	1	1	1
21	3043	ABDOMINAL PAIN FOLLOW BILATERAL TUBALIGATION	12-jan-2011	1	1	1
22	3071	ELEVATED SERUM CREATININE	01-dec-2010	1	2	1
23	3078	HIGH CREATININE LEVEL	25-nov-2010	1	2	1
24	3097	UPPER RESPIRATORY TRACK INFECTION	11-nov-2010	1	1	1
25	3173	HEADACHE	31-dec-2010	1	1	1
26	3082	ECZEMA	12-nov-2010	1	2	1
27	3086	ELEVATED ALT	09-dec-2010	1	2	1
28	3117	LOW RANDOM BLOOD GLUCOSE	03-nov-2010	2	1	1
29	3082	ELEVATED GLUCOSE LEVEL	10-nov-2010	1	1	1
30	3083	LOW NEUTROPHILES	30-sep-2010	2	3	1
31	3083	MONOCYTES BELOW NORMAL RANGE	25-nov-2010	1	2	1
32	3083	EUSINOPHILS BELOW NORMAL RANGE	25-nov-2010	1	5	1
33	3153	MICROCYTOSIS	06-jan-2011	1	1	1
34	3158	MICROCYTIC HYPOCHROMIC ANEMIA	08-dec-2010	1	1	1
35	3117	NEUTROPENIA	17-nov-2010	2	1	1
36	3117	LOW WHILE CELL COUNT (LEUKOPENIA)	18-nov-2010	2	2	1
37	3076	URTICARIA	08-dec-2010	1	.	1
Total N	37	37	37	37	36	37

3003 The elevated Creatinine is now cancelled since this is not an AE according to lab values for MUHAS site. It has already been deleted in the database

3063,Upper Respiratory Infection 07/Nov/2010, was reviewed. It reads the same in CRF and database

3091, Hyperglycemia,25-Nov-2010, was reviewed. It reads the same in CRF and database

I. Review those marked in YELLOW above for possible enddates

Duration of AE by relation

Duration

AE_relate_agent	Median	N	Range
1	6,0000	32	140,00
2	10,0000	10	25,00
3	11,5000	16	224,00*
Total	8,0000	58	317,00

* Due to one wrong date. See above

This has now been corrected in the database

Effect on vaccination

event_id	subject_id	AE_description	AE_grade	AE_relate_agent	Duration	AE_Effect
2	3117	CUT WOUND ON THE FORE HEAD	3	1	.	3
2	3055	VIRAL RHINITIS	2	1	3,00	3
1	3071	TONSIL ITIS	2	1	6,00	3
4	3036	SCARS AND EXCORIATION AT VACCINATION SITES SECONDARY TO PERSISTANT ITCH/SCRATCH	2	3	17,00	4
4	4	4	4	4	3	4

.

These have been reviewed, and they read the same in both the database and CRFs

Vaccinated 2011-02-11. Data from **MUHAS** server

Three labeled with Visit number + .'J' in addition to only visit number. Those with only visit numbers are double entries without vaccination. 3055 v8; 3071 v5; 3117 v5;

3055 v8; 3071 v5; 3117 v5-*This was iscussed in a weekly meeting held on 11th March 2011. Apparently this was due to a tick in the yes box on the CRFs while the visit was not a vaccination visit. It was hence agreed that if a volunteer was not vaccinated on the visit then the question for 'Was the visit a vaccination visit will be ticked as "NO"*

J. Correct so that there is only one entry per vaccinated-

This is not corrected yet but has been reported to the IT for corrections

Total of 54 vaccinated; 3036 (AE) and 3142 (own wish) withdrawn; 45 twice, 31 trice and 5 four times.

3036-*Yes withdrawn due to multiple AEs,*
3142 *Yes withdrawn for his own wish*

Interval Vac1 and_2

Days		Frequency	Percent	Valid Percent	Cumulative Percent
	27	6	11,1	13,3	13,3
	28	28	51,9	62,2	75,6
	29	8	14,8	17,8	93,3
	30	1	1,9	2,2	95,6
3071	35	1	1,9	2,2	97,8
3117	36	1	1,9	2,2	100,0
	Total	45	83,3	100,0	
Missing	System	9	16,7		
Total		54	100,0		

3071 *it is true that interval betwwen vacc1(28th/Jul/2010) and Vacc 2 (02/sep/2010) was 36 and not 35 (possibly 3071 interchanged with 3117) days. This was apparent after reviewing CRFs and database*

3117 *it is true that interval betwwen vacc1(29th/09/2010) and Vacc 2(02/11/201) was 35 and not 36 (possibly IDs were interchanged) days. This was apparent after reviewing CRFs and database*

Interval Vac2 and 3

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	55	4	7,4	12,9	12,9
	56	13	24,1	41,9	54,8
	57	8	14,8	25,8	80,6
	60	1	1,9	3,2	83,9
	61	1	1,9	3,2	87,1
	62	2	3,7	6,5	93,5
	63	2	3,7	6,5	100,0
	Total	31	57,4	100,0	
Missing	System	23	42,6		
Total		54	100,0		

Interval Vac3 and 4

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	126	3	5,6	60,0	60,0
	127	2	3,7	40,0	100,0
	Total	5	9,3	100,0	
Missing	System	49	90,7		
Total		54	100,0		

Missing CRFs

subject_id	visit_id	crf_name
3003	V3	CRF 10-1 Vaccine Reaction Form
3003	V4	CRF 10-1 Vaccine Reaction Form
3003	V5	CRF 10-1 Vaccine Reaction Form
3003	V6	CRF 10-1 Vaccine Reaction Form
3003	V8	CRF 10-1 Vaccine Reaction Form
3003	V9	CRF 10-1 Vaccine Reaction Form
3032	V3	CRF 10-1 Vaccine Reaction Form
3032	V4	CRF 10-1 Vaccine Reaction Form
3032	V6	CRF 10-1 Vaccine Reaction Form
3032	V8	CRF 10-1 Vaccine Reaction Form
3032	V9	CRF 10-1 Vaccine Reaction Form
3036	V3	CRF 10-1 Vaccine Reaction Form
3036	V4	CRF 10-1 Vaccine Reaction Form
3036	V5	CRF 10-1 Vaccine Reaction Form
3036	V6	CRF 10-1 Vaccine Reaction Form
3036	V8	CRF 10-1 Vaccine Reaction Form
3036	V9	CRF 10-1 Vaccine Reaction Form
3041	V3	CRF 10-1 Vaccine Reaction Form
3041	V4	CRF 10-1 Vaccine Reaction Form
3041	V5	CRF 10-1 Vaccine Reaction Form
3041	V6	CRF 10-1 Vaccine Reaction Form
3041	V8	CRF 10-1 Vaccine Reaction Form
3041	V9	CRF 10-1 Vaccine Reaction Form
3043	V3	CRF 10-1 Vaccine Reaction Form
3043	V4	CRF 10-1 Vaccine Reaction Form
3043	V5	CRF 10-1 Vaccine Reaction Form
3043	V6	CRF 10-1 Vaccine Reaction Form
3043	V8	CRF 10-1 Vaccine Reaction Form
3043	V9	CRF 10-1 Vaccine Reaction Form
3044	V3	CRF 10-1 Vaccine Reaction Form
3044	V4	CRF 10-1 Vaccine Reaction Form
3044	V5	CRF 10-1 Vaccine Reaction Form
3044	V6	CRF 10-1 Vaccine Reaction Form
3044	V8	CRF 10-1 Vaccine Reaction Form
3044	V9	CRF 10-1 Vaccine Reaction Form
3048	V3	CRF 10-1 Vaccine Reaction Form
3048	V4	CRF 10-1 Vaccine Reaction Form
3048	V5	CRF 10-1 Vaccine Reaction Form
3048	V6	CRF 10-1 Vaccine Reaction Form
3048	V8	CRF 10-1 Vaccine Reaction Form
3048	V9	CRF 10-1 Vaccine Reaction Form
3049	V1	CRF 9-VII Urinalysis Form
3052	V3	CRF 10-1 Vaccine Reaction Form
3052	V4	CRF 10-1 Vaccine Reaction Form
3052	V5	CRF 10-1 Vaccine Reaction Form
3052	V6	CRF 10-1 Vaccine Reaction Form
3052	V8	CRF 10-1 Vaccine Reaction Form

3052	V9	CRF 10-1 Vaccine Reaction Form
3053	V3	CRF 10-1 Vaccine Reaction Form
3053	V4	CRF 10-1 Vaccine Reaction Form
3053	V5	CRF 10-1 Vaccine Reaction Form
3053	V6	CRF 10-1 Vaccine Reaction Form
3053	V8	CRF 10-1 Vaccine Reaction Form
3053	V9	CRF 10-1 Vaccine Reaction Form
3055	V4	CRF 10-1 Vaccine Reaction Form
3055	V5	CRF 10-1 Vaccine Reaction Form
3055	V6	CRF 10-1 Vaccine Reaction Form
3055	V8	CRF 9-I HIV Status Form
3055	V8	CRF 9-II Pregnancy Result Form
3055	V8	CRF 9 - IV Haematology Form
3055	V8	CRF 9 - V Chemistry Form
3055	V8	CRF 9-VII Urinalysis Form
3055	V8	CRF 10-1 Vaccine Reaction Form
3055	V9	CRF 10-1 Vaccine Reaction Form
3060	V1	CRF 9-II Pregnancy Result Form
3062	V3	CRF 10-1 Vaccine Reaction Form
3062	V4	CRF 10-1 Vaccine Reaction Form
3062	V5	CRF 10-1 Vaccine Reaction Form
3062	V6	CRF 10-1 Vaccine Reaction Form
3062	V8	CRF 10-1 Vaccine Reaction Form
3062	V9	CRF 10-1 Vaccine Reaction Form
3063	V3	CRF 10-1 Vaccine Reaction Form
3063	V4	CRF 10-1 Vaccine Reaction Form
3063	V5	CRF 10-1 Vaccine Reaction Form
3063	V6	CRF 10-1 Vaccine Reaction Form
3063	V8	CRF 10-1 Vaccine Reaction Form
3063	V9	CRF 10-1 Vaccine Reaction Form
3069	V4	CRF 10-1 Vaccine Reaction Form
3069	V5	CRF 10-1 Vaccine Reaction Form
3069	V6	CRF 10-1 Vaccine Reaction Form
3069	V8	CRF 10-1 Vaccine Reaction Form
3069	V9	CRF 10-1 Vaccine Reaction Form
3070	V4	CRF 10-1 Vaccine Reaction Form
3070	V5	CRF 10-1 Vaccine Reaction Form
3070	V6	CRF 10-1 Vaccine Reaction Form
3070	V9	CRF 10-1 Vaccine Reaction Form
3071	V3	CRF 10-1 Vaccine Reaction Form
3071	V4	CRF 10-1 Vaccine Reaction Form
3071	V5	CRF 9-I HIV Status Form
3071	V5	CRF 9-II Pregnancy Result Form
3071	V5	CRF 9 - IV Haematology Form
3071	V5	CRF 9 - V Chemistry Form
3071	V5	CRF 9-VII Urinalysis Form
3071	V5	CRF 10-1 Vaccine Reaction Form
3071	V6	CRF 2-III Visit Contact Form
3071	V6	CRF 3-II Physical Exam Form
3071	V6	CRF 9 - IV Haematology Form
3071	V6	CRF 9 - V Chemistry Form

3071	V6	CRF 10-1 Vaccine Reaction Form
3071	V8	CRF 10-1 Vaccine Reaction Form
3071	V9	CRF 10-1 Vaccine Reaction Form
3076	V3	CRF 5-IV Screening OutCome
3076	V3	CRF 10-1 Vaccine Reaction Form
3076	V4	CRF 10-1 Vaccine Reaction Form
3076	V5	CRF 10-1 Vaccine Reaction Form
3076	V6	CRF 10-1 Vaccine Reaction Form
3076	V8	CRF 10-1 Vaccine Reaction Form
3076	V9	CRF 10-1 Vaccine Reaction Form
3078	V3	CRF 10-1 Vaccine Reaction Form
3078	V4	CRF 10-1 Vaccine Reaction Form
3078	V5	CRF 10-1 Vaccine Reaction Form
3078	V6	CRF 10-1 Vaccine Reaction Form
3078	V8	CRF 10-1 Vaccine Reaction Form
3078	V9	CRF 10-1 Vaccine Reaction Form
3082	V3	CRF 10-1 Vaccine Reaction Form
3082	V4	CRF 10-1 Vaccine Reaction Form
3082	V5	CRF 10-1 Vaccine Reaction Form
3082	V6	CRF 10-1 Vaccine Reaction Form
3082	V8	CRF 10-1 Vaccine Reaction Form
3082	V9	CRF 10-1 Vaccine Reaction Form
3083	V3	CRF 10-1 Vaccine Reaction Form
3083	V4	CRF 10-1 Vaccine Reaction Form
3083	V5	CRF 10-1 Vaccine Reaction Form
3083	V6	CRF 10-1 Vaccine Reaction Form
3083	V8	CRF 10-1 Vaccine Reaction Form
3083	V9	CRF 10-1 Vaccine Reaction Form
3086	V3	CRF 10-1 Vaccine Reaction Form
3086	V4	CRF 10-1 Vaccine Reaction Form
3086	V5	CRF 10-1 Vaccine Reaction Form
3086	V6	CRF 10-1 Vaccine Reaction Form
3086	V8	CRF 10-1 Vaccine Reaction Form
3086	V9	CRF 10-1 Vaccine Reaction Form
3088	V3	CRF 10-1 Vaccine Reaction Form
3088	V4	CRF 10-1 Vaccine Reaction Form
3088	V5	CRF 10-1 Vaccine Reaction Form
3088	V6	CRF 10-1 Vaccine Reaction Form
3088	V8	CRF 10-1 Vaccine Reaction Form
3088	V9	CRF 10-1 Vaccine Reaction Form
3091	V3	CRF 10-1 Vaccine Reaction Form
3091	V4	CRF 2-III Visit Contact Form
3091	V4	CRF 3-II Physical Exam Form
3091	V4	CRF 9 - IV Haematology Form
3091	V4	CRF 9 - V Chemistry Form
3091	V4	CRF 10-1 Vaccine Reaction Form
3091	V5	CRF 10-1 Vaccine Reaction Form
3091	V6	CRF 10-1 Vaccine Reaction Form
3091	V8	CRF 10-1 Vaccine Reaction Form
3091	V9	CRF 10-1 Vaccine Reaction Form
3092	V3	CRF 10-1 Vaccine Reaction Form

3092	V4	CRF 10-1 Vaccine Reaction Form
3092	V5	CRF 10-1 Vaccine Reaction Form
3092	V6	CRF 10-1 Vaccine Reaction Form
3092	V8	CRF 10-1 Vaccine Reaction Form
3092	V9	CRF 10-1 Vaccine Reaction Form
3097	V3	CRF 9-VIII CD4 Count Form
3097	V3	CRF 10-1 Vaccine Reaction Form
3097	V4	CRF 10-1 Vaccine Reaction Form
3097	V5	CRF 10-1 Vaccine Reaction Form
3097	V6	CRF 10-1 Vaccine Reaction Form
3097	V8	CRF 10-1 Vaccine Reaction Form
3097	V9	CRF 10-1 Vaccine Reaction Form
3098	V3	CRF 9-VIII CD4 Count Form
3098	V3	CRF 10-1 Vaccine Reaction Form
3098	V4	CRF 10-1 Vaccine Reaction Form
3098	V5	CRF 10-1 Vaccine Reaction Form
3098	V6	CRF 10-1 Vaccine Reaction Form
3098	V7	CRF 9 - IV Haematology Form
3098	V7	CRF 9 - V Chemistry Form
3098	V8	CRF 10-1 Vaccine Reaction Form
3098	V9	CRF 10-1 Vaccine Reaction Form
3099	V3	CRF 9-VIII CD4 Count Form
3099	V3	CRF 10-1 Vaccine Reaction Form
3099	V4	CRF 10-1 Vaccine Reaction Form
3099	V5	CRF 10-1 Vaccine Reaction Form
3099	V6	CRF 10-1 Vaccine Reaction Form
3099	V8	CRF 10-1 Vaccine Reaction Form
3099	V9	CRF 10-1 Vaccine Reaction Form
3109	V3	CRF 10-1 Vaccine Reaction Form
3109	V4	CRF 10-1 Vaccine Reaction Form
3109	V5	CRF 10-1 Vaccine Reaction Form
3109	V6	CRF 10-1 Vaccine Reaction Form
3109	V8	CRF 10-1 Vaccine Reaction Form
3109	V9	CRF 10-1 Vaccine Reaction Form
3111	V3	CRF 10-1 Vaccine Reaction Form
3111	V4	CRF 10-1 Vaccine Reaction Form
3111	V5	CRF 10-1 Vaccine Reaction Form
3111	V6	CRF 10-1 Vaccine Reaction Form
3111	V8	CRF 10-1 Vaccine Reaction Form
3111	V9	CRF 10-1 Vaccine Reaction Form
3117	V3	CRF 5-IV Screening OutCome
3117	V3	CRF 10-1 Vaccine Reaction Form
3117	V4	CRF 10-1 Vaccine Reaction Form
3117	V5	CRF 9-I HIV Status Form
3117	V5	CRF 9-II Pregnancy Result Form
3117	V5	CRF 9 - IV Haematology Form
3117	V5	CRF 9 - V Chemistry Form
3117	V5	CRF 9-VII Urinalysis Form
3117	V5	CRF 10-1 Vaccine Reaction Form
3117	V6	CRF 10-1 Vaccine Reaction Form
3117	V8	CRF 10-1 Vaccine Reaction Form

3122	V3	CRF 10-1 Vaccine Reaction Form
3122	V4	CRF 10-1 Vaccine Reaction Form
3122	V5	CRF 10-1 Vaccine Reaction Form
3122	V6	CRF 10-1 Vaccine Reaction Form
3122	V8	CRF 10-1 Vaccine Reaction Form
3128	V3	CRF 10-1 Vaccine Reaction Form
3130	V4	CRF 10-1 Vaccine Reaction Form
3130	V5	CRF 10-1 Vaccine Reaction Form
3130	V6	CRF 10-1 Vaccine Reaction Form
3142	V3	CRF 10-1 Vaccine Reaction Form
3142	V4	CRF 9 - IV Haematology Form
3142	V4	CRF 9 - V Chemistry Form
3142	V4	CRF 10-1 Vaccine Reaction Form
3143	V1	CRF 9 - V Chemistry Form
3146	V3	CRF 10-1 Vaccine Reaction Form
3146	V4	CRF 10-1 Vaccine Reaction Form
3146	V5	CRF 10-1 Vaccine Reaction Form
3146	V6	CRF 10-1 Vaccine Reaction Form
3148	V3	CRF 10-1 Vaccine Reaction Form
3148	V4	CRF 10-1 Vaccine Reaction Form
3148	V5	CRF 10-1 Vaccine Reaction Form
3148	V6	CRF 10-1 Vaccine Reaction Form
3153	V3	CRF 10-1 Vaccine Reaction Form
3153	V4	CRF 10-1 Vaccine Reaction Form
3153	V5	CRF 10-1 Vaccine Reaction Form
3153	V6	CRF 10-1 Vaccine Reaction Form
3154	V3	CRF 10-1 Vaccine Reaction Form
3154	V4	CRF 10-1 Vaccine Reaction Form
3154	V5	CRF 10-1 Vaccine Reaction Form
3154	V6	CRF 10-1 Vaccine Reaction Form
3155	V3	CRF 10-1 Vaccine Reaction Form
3155	V4	CRF 10-1 Vaccine Reaction Form
3155	V5	CRF 10-1 Vaccine Reaction Form
3156	V1	CRF 9 - IV Haematology Form
3156	V1	CRF 9 - V Chemistry Form
3158	V3	CRF 10-1 Vaccine Reaction Form
3158	V4	CRF 10-1 Vaccine Reaction Form
3158	V5	CRF 10-1 Vaccine Reaction Form
3159	V3	CRF 9-I HIV Status Form
3159	V3	CRF 9-II Pregnancy Result Form
3159	V3	CRF 9 - IV Haematology Form
3159	V3	CRF 9 - V Chemistry Form
3159	V3	CRF 9-VII Urinalysis Form
3159	V3	CRF 9-VIII CD4 Count Form
3159	V3	CRF 10-1 Vaccine Reaction Form
3161	V3	CRF 10-1 Vaccine Reaction Form
3161	V4	CRF 10-1 Vaccine Reaction Form
3161	V5	CRF 10-1 Vaccine Reaction Form
3161	V6	CRF 10-1 Vaccine Reaction Form
3166	V3	CRF 10-1 Vaccine Reaction Form
3166	V4	CRF 10-1 Vaccine Reaction Form

3166	V5	CRF 10-1 Vaccine Reaction Form
3166	V6	CRF 10-1 Vaccine Reaction Form
3169	V3	CRF 10-1 Vaccine Reaction Form
3169	V4	CRF 10-1 Vaccine Reaction Form
3169	V5	CRF 10-1 Vaccine Reaction Form
3169	V6	CRF 10-1 Vaccine Reaction Form
3173	V3	CRF 10-1 Vaccine Reaction Form
3173	V4	CRF 10-1 Vaccine Reaction Form
3173	V5	CRF 10-1 Vaccine Reaction Form
3173	V6	CRF 10-1 Vaccine Reaction Form
3181	V1	CRF 9-II Pregnancy Result Form
3183	V3	CRF 9-VII Urinalysis Form
3183	V3	CRF 10-1 Vaccine Reaction Form
3183	V4	CRF 10-1 Vaccine Reaction Form
3185	V1	CRF 9-VII Urinalysis Form
3185	V3	CRF 10-1 Vaccine Reaction Form
3185	V4	CRF 10-1 Vaccine Reaction Form
3192	V1	CRF 9-II Pregnancy Result Form
3207	V1	CRF 2-I Visit Contact Form Screening
3207	V1	CRF 3-I Physical Exam Form Screening
3207	V1	CRF 9-I HIV Status Form
3207	V1	CRF 9-II Pregnancy Result Form
3207	V1	CRF 9 - IV Haematology Form
3207	V1	CRF 9 - V Chemistry Form
3207	V1	CRF 9 -VI Serology Form
3207	V1	CRF 9-VII Urinalysis Form

This is noted and John Mduda (IT person) has been asked to delete all missed CRFs (Vaccination reaction form (CRF 10-1) on visits V1, V2,V4,V6,V7,V9,V10,V12). All these visits are not vaccination visits. We have been assured by IT people (John Mduda and Max Kimambo) that they have already deleted those CRFsentrie during database freezing.

K. Those marked in yellow above should be resolved

Protocol violations

Not commented on since the majority of events are autogenerated deviations from the computer assigned schedule and the mechanism of generating this is under review.

K2. Present update on this.

Dr Patricia Munseri reported in the meeting held on 11th March 2011 that the clinic will generate own schedule for volunteers.

Laboratory data report

(Enclosed Appedix A is the report that dates back on Web data in Dec 15th.)

General problems identified in the earlier report

1. There are quite a number of tests that return a '0'. This should be cleaned. Only true '0' results should appear as '0'.(YELLOW) Others probably represent missing values and should be marked as such. This is true even for values that are not wanted under 2. below. Also note some clearly implausible values highlighted in YELLOW.
2. A number of variables are listed which are not outcome variables. These should be removed from the report (GREY). The exception should be Blood pressure.
3. It is not clear what normal values are used for the Upper and Lower limits (BLUE). In case of abnormal values, it would be valuable if all values could be inspected as a query. Ideally they should represent abnormal values according to the toxicity scale NB some are gender and site sensitive due to different 'normal' values. We don't need the actual values spelled out rather a marking as to the toxicity grading either as a color or as a number.
4. The list seems to include all screened, many V1. It should only contain those enrolled.
5. S-creatinine seems to exist in two formats, numerical and string? This can be true for Bilirubin Direct, heamoglobin, lymphocytes, neutrophiles, WBC too since they do not sort correctly (GREEN)

In an Report from the Makuti (ie MUHAS) database 2011-02-14, APPENDIX B, some of the concerns remain, although many seem to have been addressed. Other problems have however surfaced.

1. '0' values still appear. ***L. Review so that '0' refer to '0' and not missing data.***
2. Other changes to variables than suggested above has been made. Hemoglobin has been replaced by hematocrit. The report should contain the investigations detaile on p 49 in the protocol. Hemoglobin, WBC total, granulocytes/neutrophiles, lymphocytes, platelets, RBC. (basophiles, eosinophiles and monocytes may be omitted). ALT, total bilirubin, direct bilirubin, creatinine, blood glucose. If urinalasis is included it should be graded normal, abnormal/insignificant, abnormal/ clinically significant. ***M. Include hemoglobin.***
3. It is not clear what the normal range refers to. ***N. Present current algorithm for classification of Out of range data.***
4. Are only enrolled included? ***O. Include only enrolled.***

A comparison between the two data sets, Appendix 3, reveal that

1. Some with missing data removed ie 3003 v2 creatinine and others
2. when data appear in both data sets the numerical values are the same, but 2 decimals for some (ie lymphocytes an others) in the Dec 2010 database, and 1 in Febr 2011 database
3. some values missing in Febr 2011 data set i.e. 3048 v5 creatinine, (where range seems strange in Dec 2010 – changed reference?) and also for platelets , 3055 v4 etc, lymphocytes 3041 v4. THE OUT OF RANGE ALGORITHM NEEDS DOCOMENTATION – se above.

In APPENDIX D are abnormal labvalues per volunteer, V3 and onwards.
The magnitude of the values are modest and in those with several out of range values there is no trend to worsening with time***. Check 3148 v6 ALT***

Abbreviated MUHAS database 2011-02-14, for complete data set see APPENDIX B

P. Review YELLOW below for action; missing or clinical relevance

Participant	Visit	Field	Current Value	Lower limit	Upper limit	Unit	Responses
3076	V7	ALT	40	0	38	IUL	
…							
3148	V6	ALT	92,2	0	38	IUL	
3086	V6	Basophils	0,14	0	0,14	10^3 cells /ul	
…							
3092	V6	Basophils	0,31	0	0,14	10^3 cells /ul	
3166	V3	Bilirubin Total	32,3	0	31	umol/L	
…							
3130	V8	Bilirubin Total	61,2	0	31	umol/L	
3032	V8	Creatinine	82	40	81	umol/L	
…							
3128	V4	Creatinine	108	40	81	umol/L	
3091	V8B	Eosinophils	0	0,03	1,47	10^3 cells /ul	3.8 Entered by mistake, it is not done in this visit
3154	V6	Eosinophils	0	0,03	1,47	10^3 cells /ul	In the database and forms it read 0.17
3189	V1	Eosinophils	0	0,03	1,47	10^3 cells /ul	
…							
3130	V4	Eosinophils	1,52	0,03	1,47	10^3 cells /ul	True value in the source documents
3098	V1	Eosinophils	1,54	0,03	1,47	10^3 cells /ul	True value in the source documents
3166	V5	Eosinophils	1,54	0,03	1,47	10^3 cells /ul	True value in the source documents
3166	V1	Eosinophils	1,8	0,03	1,47	10^3 cells /ul	True value in the source documents
3069	V4	Eosinophils	1,88	0,03	1,47	10^3 cells /ul	True value in the source documents

3130	V3	Eosinophils	2,13	0,03	1,47	10^3 cells /ul	True value in the source documents
3003	V10J	Glucose	0	3,56	5,2	mmol/L	Test was not done, only came for repeat Creatinine
3003	V2K	Glucose	0	3,56	5,2	mmol/L	Not done- not from clinic
3003	V6	Glucose	0	3,56	5,2	mmol/L	Not tested in the lab
3008	V1	Glucose	0	3,56	5,2	mmol/L	This read 0(zero)
3013	V1	Glucose	0	3,56	5,2	mmol/L	This read 0(zero)
3014	V2	Glucose	0	3,56	5,2	mmol/L	Not usually done during the visit
3015	V1	Glucose	0	3,56	5,2	mmol/L	Ordered but not done, V2 it was 4.71
3016	V1	Glucose	0	3,56	5,2	mmol/L	Ordered but not done, V2 it was 4.28
3017	V1	Glucose	0	3,56	5,2	mmol/L	Ordered but not done, V2 it was 6.37
3036	V3	Glucose	0	3,56	5,2	mmol/L	Not requested
3041	V3	Glucose	0	3,56	5,2	mmol/L	Glucose not requested
3043	V3	Glucose	0	3,56	5,2	mmol/L	Glucose not requested
3044	V4	Glucose	0	3,56	5,2	mmol/L	Glucose not done but ordered
3048	V3	Glucose	0	3,56	5,2	mmol/L	Glucose not ordered
3052	V4	Glucose	0	3,56	5,2	mmol/L	Glucose not ordered
3053	V4	Glucose	0	3,56	5,2	mmol/L	Glucose not ordered
3055	V4	Glucose	0	3,56	5,2	mmol/L	Ordered by physician, cancelled by Nurse- Protocol Deviation
3076	V5	Glucose	0	3,56	5,2	mmol/L	0.04 to be repeated at V6 and it was 4.8
3091	V8B	Glucose	0	3,56	5,2	mmol/L	No Glucose collection in this visit
3145	V2	Glucose	0	3,56	5,2	mmol/L	Not done for this visit
3160	V2J	Glucose	0	3,56	5,2	mmol/L	Not done for this visit
…							
3109	V8	Glucose	10	3,56	5,2	mmol/L	
3091	V8B	Haematocrit	0	33,1	47	%	Did not perform this visit and not a protocol required test
3078	V4	Haematocrit	12,1	33,1	47	%	
…							
3009	V1	Haematocrit	64,9	33,1	47	%	
3091	V8B	Lymphocytes	0	1	3,66	10^3 cells /ul	Not a test that is requested for this visit
3154	V6	Lymphocytes	0	1	3,66	10^3 cells /ul	In the form and Database it read 2.39
3097	V1	Lymphocytes	1	1	3,66	10^3 cells /ul	
3046	V1	Lymphocytes	7,5	1	3,66	10^3 cells /ul	
3022	V1	Monocytes	0,77	0	0,76	10^3 cells /ul	
…							
3130	V1	Monocytes	1,58	0	0,76	10^3 cells /ul	
3091	V8B	Neutrophils	0	1,1	5,4	10^3 cells /ul	Not a test that is requested for this visit
3154	V6	Neutrophils	0	1,1	5,4	10^3 cells /ul	In the form and Database it read 2.91
3189	V1	Neutrophils	0	1,1	5,4	10^3 cells /ul	Test was not done by the laboratory or the machine could not run the test
3084	V1	Neutrophils	0,5	1,1	5,4	10^3 cells /ul	
…							
3070	V1	Neutrophils	8,3	1,1	5,4	10^3 cells /ul	
3045	V2J	PH	0	5	7,8	PH	Not done
3091	V8B	PH	0	5	7,8	PH	True value Entered 28th March 2011
3205	V1	PH	0	5	7,8	PH	True value Entered 28th March 2011
3014	V1	PH	8	5	7,8	PH	

…							
3127	V1	PH	9	5	7,8	PH	
3091	V8B	Platelets	0	125	425	10^3 cells /ul	Not done in this Visit
3026	V1	Platelets	45	125	425	10^3 cells /ul	
3009	V1	Platelets	64	125	425	10^3 cells /ul	
3026	V2	Platelets	67	125	425	10^3 cells /ul	
3098	V8	Platelets	95	125	425	10^3 cells /ul	
…							
3066	V1	Platelets	566	125	425	10^3 cells /ul	
3091	V8B	White blood cells	0	2,8	8,2	10 ^ 3 cells/ul	Not a required Visit
3117	V6	White blood cells	2,2	2,8	8,2	10 ^ 3 cells/ul	
…							
3046	V1	White blood cells	10,9	2,8	8,2	10 ^ 3 cells/ul	

All responses with NOT DONE or NOT REQUESTED mean that it is a true missing value.

Q. Narratives requested for

Terminated due to multiple AEs

3043
3076

3076

3142
3117

All these have been prepared now

Kindest Regards.

Report Prepared by: Dr Patricia Munseri & Mr Thomas Mwinyiheri

Counterchecked by: Prof Muhammad Bakari

14th May 2011


HIV Vaccine Immunogenicity
Study (HIVIS)
TAHSWTI HIV Programme

Notes of the
TaMoVac 01 Trial Management Group
Thursday 12th April 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS
Muhammad
Patricia
Mary
Buma

MMRP
Philipp
Bahati
Marco

NIMR

Imperial
Anna
Frances

LMU

SMI
Eric
Gunnel

MHRP
Merlin
Tina

CISPOC, Maputo
Edna
Bindiya

MRC CTU
Liz
Sheena

1. Review of notes and action points

- Liz has started coding the events extracted after the last call and will circulate when she has completed this
- Roger drafted the letter for EDCTP and this was completed and submitted
- Eric contacted Eligius who confirmed he is happy with the arrangements regarding Dermax. Cellectis has shipped to SMI and Britta is checking the shipment
- Roger to enquire whether there is interest in UK HVC in taking over the IP for Dermavax
- Sayoki to follow up with Thomas regarding errors in the earlier data reports which are probably typos

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator
- Presentation of individuals screened out if multiple reasons given – do we need to identify a primary reason?

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were updated using Edna's report circulated on 11th April, and by Philipp and Patricia on the call.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		CISPOC	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		187 (80)		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number to replace					1 (#4025)	
Eligible, not yet enrolled					4 (all female)	
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25	
Second	62/61		63/61		20	
Third	61/60		62/60		13	
Fourth	60/59		61/58		Due May12	
Fifth	58/58		61/58			
Protocol deviations:					14	
Eligibility/enrolment					1	
Vaccination schedule						
Follow-up schedule						
Procedures					13	
Clinical issues:	293 (7 ongoing)		333 (5 ongoing)		117 (25 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2259)		0	
EAEs	0				0	
Pregnancies						
HIV						
Grade 3 or 4	11 (0 ongoing)		10 (0 ongoing)		1 (#4064)	
Grade 2	55 (2 ongoing)		102 (? ongoing)		48 (8 ongoing)	
AE resolved	286		320		92	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18	54 completed		All completed		0	

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons. **Candida, are you happy with this list?**

Recruitment Issues

All trials are fully recruited!

Pharmacy Issues

Bindiya received the MVA shipment on 8th April and it is stored in the -20. She asked about the expiry date as the label refers to date of Aug2012. Ongoing stability testing supports a longer period, and Merlin will follow up with Mary for advice regarding the date. There was a discussion about the labels. At CTU we would usually relabel with the new date, and this is what happened in MucoVac2 where there was a similar issue. However, as Merlin noted, this would necessitate removal of the vials from the freezer incurring risk. It was agreed that the vials could be relabelled at the point of use. Merlin will follow up with Mary to arrange new labels.

AP Merlin to follow-up on revised expiry date for MVA and new labels

Bindiya had emailed Buma about the gauge of needle as only 21/23 gauge were available in Mozambique, not 22g. Buma agreed that 23g would be fine. Bindiya also asked about the cover used for the syringes that Beryl had given her. Buma confirmed on the call that he used the cover so that staff could not see the product in the syringe in order to maintain blinding.

Clinical issues

Regarding ongoing events at MMRP - #2160 and #2259 are both HIV positive, and were not willing to transition to the treatment centre at the last call. These events are classified as 'ongoing at the end of study', as are two grade 1 anaemias.

#2004 who exited in January had a grade 3 anaemia (Hb=8.8) at v18. Repeat was 7.4 with a hypochromic, microcytic picture. Platelets are normal. US scan had revealed a cyst on the left ovary but no fibroids. She did report heavy menses but not unusually so recently, and previous abdominal pain around the umbilicus. Iron profile is not possible, but the team will check the stool for ova, occult blood and plan to repeat the abdominal US. Arne previously suggested a trial of H2 antagonists, but she has had a good response to folic acid and iron and her Hb is now 11.4. This ppt still has haematuria which the team think is due to menses. They are recalling her for a further check.

There are 3 further ongoing events being followed. Contact has been made with ppts but they have not yet come back to clinic. #2259 has asymptomatic pyuria. This even is currently recorded as UTI, and it was agreed to rename the event if it was confirmed at the visit that the ppt was asymptomatic. #2255 has grade 1 elevated ALT, and #2260 grade 1 low glucose, both asymptomatic.

#3098 developed otitis media and is scheduled for specialist surgery in May when a team of US surgeons is visiting MUHAS. Patricia will review the ongoing events and email the update.

AP Patricia or Thomas to update status of ongoing events at MUHAS

#3153 and 3166 had lab error grade 4 low platelets, reported two calls ago. Following discussion about data management of these and similar events (eg pre-existing conditions that had been entered as AEs even though they were no worse than prior to the trial), Sheena wrote to Max who reported that he could delete the AE CRFs from the database if the clinical team provided him with a list. Sayoki reported that he believed Aybua could also do this, and agreed to follow-up with the team. Please note that Max is only able to do this work at the weekends at the moment, as he has started his new job and is very busy. The data team was not represented on the call.

Post-call note: Namo confirmed via Philipp that he can delete AEs. This is an example of a list that should be signed off for the Clinical Study Report.

Edna updated us on ppt #4025 who was reported on the last call to have presented with penile ulcers after having unprotected sex with a female in a province 500km away that he was visiting at the weekend. This was treated according to national guidelines for syndromic management, which almost certainly includes treatment for syphilis, although it was agreed on the call that genital herpes was the more likely diagnosis. Unforuntately two weeks later the ppt presented with fever and headache and the team suspect a seroconversion illness. They have repeated the HIV test, including PCR and this is negative. Meanwhile he contacted the female partner and advised her to be tested for HIV and other infections. He has had no sex with his regular girlfriend since she became pregnant, and therefore she has not been at risk. This is the ppt who was replaced because he was going to relocate to a rural province. Although he remains in Maputo, as he had already been replaced he will not receive any more immunizations but will complete the visit schedule.

Edna agreed that #4068 is an eligibility deviation rather than procedural. This event (neutrophils of 1.3 rather than >1.3) was circulated to the group and agreed to be of minor clinical importance. #4004 and 4009 were never enrolled but were procedural deviations in that they went on to visit 2 even though the visit 1 results made them ineligible.

Edna also reported #4064 who has a CD4 <200 which is unexpected in a HIV negative healthy individual. Total WCC was normal. The ppt will be called back for a repeat and Edna will update everyone by email.

Laboratory issues

Gunnel to report on the issue of the cryo-preserved samples. Are there any outstanding actions on this point?

An ongoing concern is the need to find funds for the CMDR peptides (see EDCTP below).

3. Update on database validation and documentation

Cleaning of AEs has been ongoing. Liz is coding the events in an additional column on the spreadsheet extracted from the webdata, and the one circulated by Edna for CISPOC.

Another issue that Eric has highlighted was that of lab AEs. Once events are coded we could look at the lab events side by side with out of range labs, and flag any that look like they might need a clinical code for checking before we sign them off as clinically insignificant.

Key event lists that merit sign off as we approach the database lock include SAEs and primary safety and immunogenicity endpoints, withdrawals/early terminations, but there may be other useful lists such as ongoing, but stable events, indicating which are under continued follow-up and which are not considered clinically significant.

A database officer (Patricia) has started at Maputo, and was present for the visit by the NIMR team. Ayuba circulated a report of the visit on the day of the call, and Edna will go through it. The team had explained that there were two types of problem, one of which could be fixed immediately, and one which needed revision of the source code and took longer. She hopes to be able to extract data directly from the database for the next TMG call.

Sayoki reported on the previous call that plans were well underway for the TaMoVac II database. Ayuba and Thomas have now visited MMRP and Maputo and completed the needs assessment. Mbazi emailed Sheena regarding the CRF workshop. It was not possible to organize this in Dar, or indeed in March in London as originally suggested. Sheena strongly recommended that the clinical and data teams get

together in Dar and go through the TM01 CRF for TMII and identify questions that had been problematic. Gail, Sheena and Liz would provide feedback by email. Eric requested that NIMR provide an update of activities against the timeline presented in Zanzibar at the annual meeting.

AP NIMR to provide update against timeline for TM II database and to organize meeting of clinic and data teams to identify CRF problems that need to be amended for TM II. Gail, Sheena and Liz to feedback by email.

Pre-existing conditions that have not worsened are not AEs and a decision about how to manage these CRFs in the database needs to be made in a similar way to the lab errors. Philipp previously queried whether dental caries could be considered a pre-existing condition if it arose during the trial, but had happened before. Sheena did not think so, as this could be a new episode due to a different tooth. Philipp has an example of this event, and of dental caries due to trauma that was a pre-existing condition that has not worsened during the trial (grade 1 throughout). He has produced a spreadsheet of pre-existing conditions that have also been reported as AEs and identified those that went up in grade (definitely AE), and those that are chronic, non-episodic conditions that did not change (not AE). There was a discussion about lab events such as low glucose at screening which reverted to normal range and then dipped again in follow-up. Merlin commented that this could be an artefact of the time from blood draw to analysis as they had noticed that putting blood on ice resulted in far fewer low glucose readings. He advised to report as AE unless there was a physiological explanation for low glucose.

Philipp completed the spreadsheet after the call and will advise the data team to delete those that are not AEs.

4. Monitoring

A draft SOP/working practice document for transfers should be included in the TaMoVac II documentation.

Gail has visited Maputo and is in transit on the way back to the US.

AOB and time of next call

TM01 AfrEVac amendment

MucoVac2: 16 enrolled. The breakdown by group of the first 14 was provided in the previous notes.

v4.1 has been submitted to IRB, and v4.0 with IRB approval submitted to TFDA. The technical agreement for the shipment has been finalized, and Roger is planning for a shipment in the week of 22nd May, subject to approvals coming through in time. We hope there is a good chance of these being received in April. Buma explained that TFDA has agreed to an accelerated review of 6 weeks which is inside this time limit, and he did not think it would be a problem that approval of v4.1 was also required from TFDA. Buma called the TFDA this week but there was no reply. He will continue to chase and circulate the TMG when he has news.

Philipp circulated the flow chart of CRFs and subject status form to all.

Monique Surette (our EDCTP officer) has confirmed that the extension is approved in principle based on the letter and preliminary budget provided, and that this is supported by Gates being willing to accept a later report. MRC CTU will have an underspend of 131,846 euros in the AfrEVac award which ended 27th March (total 158,000). TaMoVac I needs to produce a detailed workplan and budget to justify transfer of the necessary funds to support the extension and complete this important work. Gunnel reported progress in the laboratory group. There are no peptides left

now, and a decision was taken by the lab group to place the order balancing the small risk that EDCTP would not agree to this expenditure (40,000) against the bigger risk of not being able to complete the assays as it takes 12 weeks for the peptides to be processed and shipped. Costs for the functional antibody assays are still being calculated. Gunnel has investigated options including Robin Shattock's lab, and the only one is for Agricola to go to the US to the Motefiorri lab and conduct the assays there. Muhammad has identified clinic costs of 29,000 for MUHAS and is waiting to hear from MMRP. Sheena knew that Arne and Beitel were finalizing the budget, so everything should be in place regarding the detailed budget and justification within the week to return to EDCTP. Gunnel and Muhammad would see this through.

Sheena anticipated some underspend in TM II for MRC as well, as NIMR was managing the database, and there was continued support from MHRP for monitoring. She had yet to discuss this in detail with Merlin. CTU has advertised for a Clinical Project Manager, who would spend 50% of their time on TaMoVac. This individual will hopefully be in place in July. Meanwhile Livia Vivas, a clinical epidemiologist will spend part of her time on TaMoVac.

TMII protocol

The final change to the protocol was to remove Cellectis and to change the DNA groups to the following: 1) 2x0.1ml to give a total of 600μg given with Zetajet, with or 2) without Dermavax EP and 3) 1x0.1ml to give a total of 600μg given with Zetajet with Dermavax EP.

Arne and Eligius were not able to join the call, but Philipp reported on the status of the protocol which is awaiting all the signatures before submission to IRB. As IRB approval is required for submission to TFDA it was agreed to request an expedited review from TFDA which did not seem unreasonable given that the products are the same apart from the Dermavax. An expedited review does cost more - $6000 – but this was justified. Eligius is away for a family bereavement this week, but Muhammad will see him on Monday, and Gunnel may speak to him before that. Both will ask him to email an update on the progress with signatures and submission.

AIDS Vaccine 2012 abstracts

Several abstracts have been submitted to the conference – good luck! – and these could form the basis of the 21012 analysis and writing workshop in London.

The next call will be Thursday 24th May

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 26 May, 23 June Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 19th January 2012
08.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS
Eligius

MMRP
Philipp

NIMR
Sayoki

Imperial
Frances
Roger
Kylie

LMU
Arne
Chris

SMI
Eric
Gunnel

MHRP
Merlin
Gail
Beryl
Kathleen/Christine?

CISPOC, Maputo
Edna

MRC CTU
Sheena
Liz
Sarah

1. Review of notes and action points

- Max to enable comment field for out of range values to be visible via webdata
- Arne circulated the notes from the call in December 2011: main points were to resolve the way in which the CISPOC team was capturing an AE which had changed in grade (#4012 headache) to reflect that this is a single event of max grade 2 rather than 2 events.

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were taken from Edna's report attached to her email of 20th January, Philipp's report of 18th January 2012, and Thomas' of 19th January.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		INS	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	26	22
Screened out *	58 F ~~114~~ 115M		187 (80)		31 (14 Female)	
HIV positive	~~2~~ 3				1	
Pregnant	~~3~~ 4 (V1 or 2)		4 (V1 or 3)		1	
ECG	25				2 (#4016,4032), 4021*	
Number enrolled	62 (25 female)		67 (29 female)		14 (9 Female)	
Number to replace					1 (#4025)	
Eligible, not yet enrolled					3 (1 Female)	
Number immunized:	Attend/vaccinated		Attend/vaccinated			
First	62/62		67/67		14	
Second	62/61		63/61		7	
Third	61/60		62/60			
Fourth	60/59		61/58			
Fifth	58/58		61/58			
Protocol deviations:						
Eligibility/enrolment					0	
Vaccination schedule					0	
Follow-up schedule					0	
Procedures					7 (#4, 6, 9, 11, 22, 24, 40)	
Clinical issues:	283 (17 ongoing)				29 (9 ongoing)	
Reactogenicity						
SAEs	1 (#3117)				0	
EAEs	0				0	
Pregnancies					0	
HIV					0	
Grade 3	6 (0 ongoing)				0	
Grade 2	52 (2 ongoing)				13 (4 ongoing)	
AE resolved	266				20	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18			50 (11 to go)		0	

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons.

Recruitment Issues

68 volunteers have attended an informed consent seminar (41 females). 4 individuals are eligible but not yet enrolled. Progress is good, but the screen:enrol ratio remains high with 30 screened out, mainly for abnormal CBC (6), positive syphilis (6) and at risk of HIV defined as >1 partner in the last 6m (6). The team plans to accelerate efforts in order to complete enrolments by the end of February. The projected end of the trial would then be Apr 2013 which is anticipated to be acceptable to the SIDA

Programme Officer. Gunnel has been communicating with her, and she will attend the workshop in Zanzibar.

Pharmacy Issues

No pharmacy issues reported.

Clinical issues

#2160 who is HIV positive with CD4 of 214 (9.7%) in August when VL >100,000 and 177 (9.7%) in September, has NOT started ART. She attended the clinic twice but the waiting time was very long (~8hrs) and she left without treatment. The team has managed to put her on septrin prophylaxis but her CD4 is now 94. The team is doing their best to support her and persuade her of the importance of taking treatment. She does have some family support in Mbeya, and one of the TaMoVac nurses will go with her to the CTC to wait next time. Eric asked whether ART could be started in the research clinic but Philipp said that this would not be sustainable.

2246 who was previously reported with chicken pox has grade 2 anaemia.

2261 who delivered recently is well, and her grade 3 anaemia resolved. She has asymptomatic pyuria which was treated with augmentin. Nitrofurantoin was added as she developed microscopic haematuria.

2259 who received an immunization whilst HIV infected has a CD4 of 390. He is well and the team will see he transfers to the CTC for care.

The conclusion regarding # 3215 is that he did not have pericarditis. There are 2 ongoing grade 2: otitis meida (#3098) and low platelets (#3091).

Edna submitted a detailed report regarding the AEs, circulated with this agenda. There are 4 ongoing grade 2: #4006 has a UTI on microscopy and intermittent vaginal discharge, which is accompanied by a bad smell at times. Sheena wondered about Chlamydia and Eric queried TV and BV. She has been treated with ciprofloxacin, and the team will see her again in a week. Other events include an upper respiratory tract infection (#4025) and pyodermitis (#4026).

Deviations and missing CRFs

#2027 lives in Arusha and has missed v18- he is still not responding on his mobile.
#2021 has now attended v18, although out of window.

#4009 and 4004 had blood collected in error as they were not eligible. The samples had already been processed and the volunteers informed of the results.

Out of range values

No comments.

Laboratory issues

The immunology team is busy preparing for the Annual meeting when Candida will present the main result by treatment group. The last fifth immunisation visit with respect to the primary endpoint took place on 10th January, and ELISPot will be collected on 23rd January. Lotta will be in MUHAS from 26th January and Chris will be in Mbeya and both are primed to complete the last analyses and transfer to Candida for unblinding by treatment group. Sheena reminded everyone that there would be no unblinding of individuals to the clinical or laboratory teams, but investigators would be able to review the results by treatment group. Wolfgang had pointed out the need to finalise and sign-off the Statistical Analysis Plan before the main analysis

was presented at the workshop, and he had liaised with Candida on this point. It was agreed that the sign-off should be Muhammad, Candida and Lotta.

Chris reported that although the rgp140 assay was generating nice readings, the range is very narrow, and he will follow this up with Imperial. Sarah asked whether he was using the same reagents as Imperial and CLS, and pointed out that Mark (from CLS) will be attending the workshop in Zanzibar so there would be an opportunity to compare notes. Eligius reported that they have not been doing the assays in MUHAS since the wet lab training.

Gunnel noted that a laboratory meeting was planned for immediately after the investigator meeting, in order to discuss a number of things but particularly the issue of the cryo-preserved samples.

3. Update on database validation and documentation

Max explored the use of '999' for missing lab results but this would be very time consuming to do. It is relatively easy to solve this problem in the statistical programmes, and it was agreed that this was a satisfactory solution.

We need to identify the CRFs that will be used for the rgp140/GLA-AF boosts in order to let Max know what the database should expect.

AP: Arne and Philipp to advise and liaise with Max

4. Monitoring

Gail and Kathleen monitored Mozambique in the preceding week, and found everything in good order. They did not manage to get through all the files, but were impressed with those they reviewed. Gail and Christine will likely monitor MUHAS and MMRP after the meeting but the precise dates have not yet been finalised. Unforunately none of the monitors can attend the Investigator meeting.

At the previous visit, it was agreed to draft a SOP/working practice document for transfers, and this will be done after the monitoring report is completed. The report is expected in the next 3 weeks.

Philipp spent a week in Maputo and there will be a further exchange with the Mozambique team visiting Mbeya after the Zanzibar meeting. These exchanges are very useful.

AOB and time of next call

TM01 AfrEVac amendment

MucoVac2 has started, and three ppts have now been enrolled, two of whom have received rgp140/GLA-AF IM the third receiving rgp140 in chitosan IN. There have been no AE of note (indeed none at all in the firSt ppt who has received two immunizations).

Post call note: not strictly true – she had a temp of 37.8 at 10min which is 0.1 inside the grade 1 range! We heard on 23rd Jan call that the second ppt to receive rgp140/GLA-AF IM had grade 1 night sweats for 3 nights starting within 48hrs of her first immunization.

The documentation (protocol, summary of changes, IB, IMPD, copies of MHRA approval and cover note regarding the improvements in manufacture between the MucoVac2 batch and the TM 01 batch) are almost complete – the Qualified Person contracted to Imperial is finishing the IB and IMPD. Roger is aiming for 23rd January. It has been decided to ship direct to Tanzania, using World Courier. Roger explained

that the vials are packed in gel to maintain the temperature range of 2-8^{o}C for 5 days. Some concern was expressed about the viability of this - it would be important to meet the shipment and extract it promptly from the airport. Beryl pointed out that the temperature range on the labels should match the protocol and IMPD stipulations.

AP: Sheena and Roger to complete the documents with the latest MucoVac2 update, and send to Buma for submission

TMII protocol

Arne circulated the next version on 18th January with instructions to individuals to attend to various sections/supporting documents. Arne to update, and everyone to discuss whether realistic/sensible to submit prior to seeing the TM01 data by treatment group as this could impact on the decision to combine/separate the plasmids and possibly on the DNA groups. At this stage, it was agreed to wait to see the results by treatment group at the investigator meeting, but to be ready to submit quickly thereafter. Arne requested the up to date IB for each product, and that Sheena/Wolfgang look through the analysis and data management sections.

Arne pointed out that the recruitment would have to be complete within 9m at the longest (assuming start in June 2012). Is this realistic for the sample size?

AP: All those noted in Arne's email to complete review by the Investigator meeting

The next call will be Thursday 23rd February

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 26 May, 23 June Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 21st June 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS
Muhammad
Patricia
Mary

MMRP
Philipp

NIMR
Sayoki
Ayuba

Imperial

LMU
Arne
Michael (for part)

SMI
Frances
Anna
Roger

MHRP
Merlin
Gail
Tina
Shaquanda
Kathleen

CISPOC, Maputo
Edna
Ilesh
Bindiya

MRC CTU
Liz
Sarah
Sue
Livia
Sheena

1. Review of notes and action points

- Philipp followed up on TM01 database changes for boosts with Max, but needs to check current status – will do so
- Roger enquired and there is no interest in UK HVC in taking over the IP for Dermavax
- Sheena emailed Sayoki and Ayuba circulated an updated timeline for TM II database development (circulated with this agenda)
- Buma sent an SOP for transporting rgp140/GLA to Roger
- The clinical coding call has been deferred due to lack of time at CTU to prepare
- Eric to send IB to Bindiya and Arne

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator
- Presentation of individuals screened out if multiple reasons given – do we need to identify a primary reason?
- Need to review clinical AE that are laboratory events against the lab values
- Key event lists that merit sign off as we approach the database lock include SAEs and primary safety and immunogenicity endpoints, withdrawals/early terminations, but there may be other useful lists such as ongoing, but stable events, indicating which are under continued follow-up and which are not considered clinically significant.

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were updated using Edna's report of 20th June, and on the call.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		CISPOC	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		187 (80)		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25	
Second	62/61		63/61		23	
Third	61/60		62/60		22/22	
Fourth	60/59		61/58		12/22	
Fifth	58/58		61/58			
Protocol deviations:					20	
Eligibility/enrolment					3	
Vaccination schedule					2	
Follow-up schedule					2	
Procedures					13	
Clinical issues:	300 (10 ongoing)		333 (1 ongoing)		189 (21 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2259)		0	
EAEs	0				0	
Pregnancies					1 #4045	
HIV					0	
Grade 3 or 4	12 (1 ongoing)		10 (0 ongoing)		2 (0 ongoing)	
Grade 2	56 (3 ongoing)		102 (#2259 ongoing)		82 (13 ongoing)	
AE resolved	290		332		168	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18	59 completed		All completed		0	

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons. **Candida, are you happy with this list?** Wolfgang is following up with Candida re progress on analyses for CSR.

Recruitment Issues

All trials are fully recruited!

Pharmacy Issues

The MVA titres for MVA-CMDR Lot#07860210 have all been done and are with QA. Tina will issue an updated expiry note when she has the report.

Rgp140 and GLA arrived in Dar and the MMRP box was collected by Revocatus and Philipp. The temperature monitor inside the MMRP box recorded temperatures outside the recommended range, implying that the MUHAS fridge was either faulty or the door was being opened too often. The QP can sanction release of the products for use at MMRP but has requested a 7 day continuous monitoring of the MUHAS fridge temperature prior to use of product to ensure the fridge is not faulty. Muhammad explained that this would have to be purchased. Sarah J could bring when she visits in July, but we need the information as soon as possible and Michael thought that there may be monitors available at MMRP. However, Lucas was travelling from Munich to Dar on the 22nd June and Michael will make sure he brings 2 thermometers back with him that can record continuous temperature. Roger requested that these be placed in the centre of the fridge.

AP Michael to arrange for Lucas to transport 2 continuous temp monitors to Dar

Roger asked about the mixing SOP, but Buma was not on the call. Liz will send the SOP that she has for MucoVac2 from the York centre.

AP Liz to send Roger the mixing SOP for his review

Clinical issues

Sheena thanked Edna for her comprehensive report. Edna had confirmed that #4045 who had a positive pregnancy test at her visit 8, had an induced abortion (with misoprostol) on 2nd May after which there was a small amount of vaginal discharge, not bloody. She is booked for an U/S to ensure no retained products, and to see a gynaecologist. She stopped her immunizations after receiving 2 DNA.

There are 22 volunteers still in the immunization schedule. #4025 and 4063 were unable to continue due to logistic reasons (moving, and too busy respectively).

The eligibility deviations were marginally raised bilirubin (#4039 and 4061) and neutrophils of exactly 1.3 (#4068). The Trial Coordinating Committee was informed about the bilirubins in an email from Edna of 1st June 2012, and ethics, regulatory and DSMB have all been notified.

There was only 1 MMRP event that was still being followed at the time of the May call: #2259 has asymptomatic pyuria. This event is currently recorded as UTI, and it was agreed to rename the event if it was confirmed at the visit that the ppt was asymptomatic. Unfortunately this ppt who has also serocoverted for HIV has been reluctant to attend the clinic. He remains in contact with the team and may yet attend.

#3098 did not have their ear operation as the local surgeon who was collaborating with the visiting specialist was away at the time of the visit.

#3221 who had grade 3 neutropaenia has been seen by a haematologist. The fluctuation between grade 2 and 3 neutropaenia was considered to be a normal variant and did not warrant further investigation.

Sue and Livia will check the lists of adverse events that have been deleted from the database as they are not adverse events (mainly laboratory events), when they visit in July for each clinical centre. The TMG notes should provide a record of these events.

Laboratory issues

Gunnel has reported by email that Colman Schau who has spent a month at SMI doing gp140 assays will go to MMRP to do these on the MUHAS samples, with another member from the laboratory team. SMI has sent all the materials and reagents for cellular assays for the 20 volunteers at MMRP, including for cryopreservation of PBMC. The request to EDCTP for additional funding included the costs of Agricola's travel to Duke to conduct ADCC assays, and the reagents for neutralizing antibodies to be assessed at MHRP. There were no other funds for these activities. Sarah was not sure if the intention was for Agricola to analyse specimens from MMRP as well as MUHAS but she will find out.

AP Sarah to clarify that MMRP samples would also be analysed by Agricola if EDCTP funding could be obtained for her to go to the US

3. Update on database validation and documentation

CISPOC has been able to extract data from the database. There are still small residual errors including dates in the ppt calendar. The team met with the NIMR team to go through these after the CRF workshop, and Ayuba estimated that these would be fixed by the end of June.

There has been no progress on the AE coding exercise as it has not been possible for Livia to find a time in Sheena's diary (sorry) to prepare for the larger call. Sheena thought that August would be acceptable in order to be ready for the report writing in September, July ideal.
The current priority is to conclude the CRF review exercise for TM 02. John/Ayuba organized a workshop in Dar bringing the 3 clinical teams together 11-14th June, and this was very successful in identifying a number of changes. There was a lively discussion in email (unfortunately Gail and Livia were not on the list but I forwarded the comments to them). Here is a summary of the main points raised in the emails, prepared by Livia:

CRF 5-I:
- The martial or civic status question should remain or be split in two.
- "Marital Status" has been changed to "Current Marital Status" as somebody could be divorced and cohabiting (with the next partner), both.

CRF 5-IV Screening outcome:
- To delete reason No. 3 as it can be tracked from reason No. 11
- To include ECG in the table of reasons for ineligibility
- New column for primary reason added for the investigator to select

CRF 6-I Adverse Events: Discussion mainly around the Outcome box.
- Point "Continuing at protocol completion /termination was added". The terms stable and unstable deleted.
- AE status could be also commented within the comments section.
- Point 6 of outcome box: Arne queried the option "replace by another event", and Philipp explained that this was needed if, for example, what started as a fever was found to be malaria. In this example could 'fever' be crossed-out in the paper CRF and replaced by 'malaria' as the start date for the malaria is really the same as the fever? The CRF would be sent to data entry and the original term replaced. There would be an audit trail in the database.
- Was there a discussion about how to report a change in grade?

CRF 6-II SAEs: discussion round the grade of the Grade of SAE box
- Ayubu commented that the SAE grade is always known, so 3 or 4 is being a bit redundant but AK pointed out that this form will not be entered into the database but is meant as a report to the Sponsor, DSMB etc. who do not necessarily have all the other AE information from the AE CRF – therefore even redundant information is necessary. The grade is not necessarily 3 or 4, e.g. hospitalization for a procedure for

a grade 2 AE. Patricia suggested that the "Grade" Column be renamed "Grade of SAE" instead of "Grade 3 or 4 SAE" to solve this issue
- Another point is the need to specific if the SAE CRF is the first report or a follow-up report, or a final report so that they can be linked
- In the criteria, HIV infection is no longer included as per protocol

Discussion around boxes for dates

- the reporting format of the date needs to be clear, as people from USA, Europe and Africa will be reading this and there are different standards as to how the date is recorded across the continents (ie dd/mm/yy or mm/dd/yy). If format poses a problem, we will specify "dd/mon/yyyy" in the "Date" column

CRF-9-VI: Merging of CRF 9-VI serology and CRF 9-VII CD4.

- Arne disagrees as the CD4 report form and the serology form are submitted at different time points. If combined the form will need to be submitted twice indicating "NA" for either serology or CD4 count creating more work to change the database.
- Phillip suggests that to avoid the need to check "N/A" for serology, we can do one serology form and one CD4/Viral Load form

CRF 9-VII: merging of CRF-9-II pregnancy and CRF 9-VII urinalysis

CRF 9-IV: merging of CRF 9-IV haematology and CRF 9-V chemistry.

- Arne questioned the need for "N/A" behind all items in the haematology form and suggests to add "Not done" so you do not need a Y/N but just a tick.
- Philip's comments: Haematology does need N/A, at least for the differentials: If we e.g. follow up on anaemia and only do a normal bloodcount (i.e without differential for WBC), we need N/A for monocytes, granulocytes etc.
- Discussion around whether to add Eosinophils and Basophils into the haematology form. These are not required by the protocol for safety assessment and create extra work.
- Eric commented that % increase or decrease is not used in clinic to flag abnormal values, rather out of range which differs between the 3 centres.
- Phillip: As for CRF 9-IV, we have always been using %. If a value is out of range, the transcriber routinely makes an active note in the comments section (e.g. "High Glucose confirmed")

CRF 10-I:

- The information from the diary card used in Tamovac 1 has now been compiled into this single form
- Eric commented that the form does not address the fundamental difference between volunteer and clinician e valuation of the events. He suggested: 1. a raw transcript of the diary form as now suggested (then 'Assesment type in unnecessary) 2. a summary form indicating the clinically interpreted maximum reactivity, maximum relationship, start and end dates (or ongoing), medication.
- Livia: I agree that we need to differentiate between what the participant and clinician are reporting. I also strongly agree that a list of ongoing medications and dose should be included
- Sheena – the clinician should check the diary as the participant may have made a mistake. However, if they don't agree on the grade, then the clinician can complete a standard AE form with their assessment of grade. In the analysis we usually give precedence to the clinician grade and make a note at the bottom of the table about the ppt grade that came from the diary.

Exlcusion criteria/Risk Assessment:

- Edna proposed to quantify alcohol consumption as part of the risk assessment as it will serve as a guide to evaluate the risk for HIV infection.
- Eric was not in favour of numerical units. Any abuse (alcohol or other) that in the mind of the clinician makes participation questionable should lead to exclusion

Only a few points were discussed on the TMG call. Firstly the issue of 'replacing' an event. Everyone agreed that the need was to minimize the risk of reporting the same event twice. At the moment, this was quite fiddly, relying on being able to match the number of the events which have different names, and would appear on two lines in a statistical datafile (probably without free text comment). They would have

matching start dates and ppt numbers but it would require some programming, either at database extraction or by the statistician, and there was the risk of imperfect matching. Sheena favoured a clear annotation of the CRF and then changing the term in the database, which would mean deleting the original term and entering the new one (although this would still be visible in the audit trail on inspection). Kathleen suggested that the event could be recorded in the source notes only and a CRF completed when the diagnosis was clear. Arne was worried that events may go unreported in this model. Secondly the need to add a field on the SAE CRF to indicate whether the report was the first one, a follow-up or a final one.

It was agreed that comments be sent to Ayuba so that his team could coordinate the next version of the TM II CRF for circulation and a final round of comments. A meeting is planned for 22nd June in Dar.

Aybua circulated an updated timeline for the database from the NIMR team, circulated with this agenda. This will need further revision based on the changes to the CRF above. Sayoki noted that Ayuba said it would take one month to change the database after the CRF was finalised

4. Monitoring

A draft SOP/working practice document for transfers should be included in the TaMoVac II documentation.

Sarah and Livia will be visiting MUHAS, MMRP and NIMR in July in order to review the data management needs and progress for TM 02, and to prepare for the next analysis workshop. They will be accompanied by Sue Fleck a Clinical Project Manager and experienced monitor. Sue and Livia will focus on the data management aspects from CRFs in clinic through data entry and database documentation. Livia and Sarah also plan 1 to 1 sessions with clinical/lab teams that would like help with preparation of analyses and papers. A concept sheet will be circulated with the notes from this call, and they hope to compile the publication strategy by the end of their visit so that we can ensure the fair participation of all investigators. They expect to arrive in Dar on the 15th, transfer to Mbeya on the 18th, back to Dar on the 21st and back to the UK on the 22nd.

Eric also expects to be in Dar in July, to do the Dermavax training for both Tanzanian centres, and this will be very helpful. Cellectis expect devices to be available in Tanzania from mid-July. By good fortune Gail will also be in Dar during this period, monitoring MMRP 8-14 July and MUHAS 14-20July.

AP please complete the concept sheets and return to Sarah so that the team can prepare for the visit

5. TM01 AfrEVac amendment

MucoVac2 immunisations by group are as follows:

	Dose 1	Dose 2	Dose 3
1 IM ld	8	6	5
2 IM hd	9	9	5
3 IN	5	5	3
4 1 IM hd + 2 IVAG	8	8	6

There has been one SAE – an accidental paracetamol overdose in a ppt who had a dental procedure and then took at least the maximum number of paracetamol allowed for 2-3 days afterwards. When she felt nauseous she was worried that she might have over-dosed, went to Accident and Emergency and they treated her

accordingly which required admission. Otherwise, AEs continue to be mild-moderate only and of short duration. No-one has discontinued due to AEs (including the SAE, although she is out of schedule) and the first ppt has exited.

The MMRP IRB had expressed concern because the information on MucoVac2 reflected an earlier stage of the enrolment. Philipp has sent an update to the chair but he is now out of town, returning today or tomorrow. Philipp thought the earliest he could get an approval letter based on this new information would be Monday 25th June.

Product is in Pharmacy and the ethics approvals for v4.1 are through (apart from above), although TFDA is still awaited for this version. However, the agreements are not finalized and Roger was worried because the individuals that were familiar with them were on holiday during parts of the next 6 weeks which could lead to delay. However, the changes from the original agreement seen by IDRI, SMI and Imperial are relatively small so he is hoping to have all in place in the next 2 weeks.

Unfortunately the EDCTP office rejected the request for additional funds, principally because the sum requested was exactly the amount returned by AfrEVac. The officers (Pauline) have provided the opportunity to go back with a lower budget that reflects the actual needs and the MUHAS/MMRP teams are working on this now with some urgency. This includes the costs mentioned under Laboratory Issues. Michael recommended a no cost extension until the end of the year, but Sheena thought this would be impossible because of EDCTP's obligation to report to Gates by then and their need to review the reports and finances before sending to Gates. Michael thought it important that we make contact with EDCTP as soon as possible, and that it would be worth checking the NCE issue as this was verbal information from Monique and not in writing.

Post-call note

Sheena discussed with Roger and we think ***it's best if Muhammad writes as the Project Coordinator*** – this is the line of communication EDCTP prefers. The email should be ccd to Gunnel, Eric, Arne, Michael, Philipp, Leonard, Roger and Sheena

TMII protocol

Philipp was confident this had been submitted to local IRB as well as NIMR ethics, but was not sure about TFDA.

AIDS Vaccine 2012 abstracts

Six abstracts had been accepted, 3 immunology including Agricola's oral presentation, the ECG abstract, Patricia and Thomas's clinical and data reports of TM01. Well done to all!

The next call will be Thursday 26th July which is in the middle of IAS conference

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 21 June, 26 July, 23 August Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 22nd March 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS
Buma

MMRP
Philipp
Bahati
Marco

NIMR
Sayoki

Imperial
Frances
Roger

LMU
Arne

SMI
Eric
Gunnel

MHRP
Gail

CISPOC, Maputo
Edna
Bindiya

MRC CTU
Liz
Sarah
Sheena

1. Review of notes and action points

- Sheena contacted Max about the way to manage AEs that transpire not to be AEs but have been entered

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator
- Presentation of individuals screened out if multiple reasons given – do we need to identify a primary reason?

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were updated using Thomas' report of 15th March for MUHAS, and Edna's report circulated on 22nd March. It was noted that there are some date errors for AE onset in Thomas' report which are probably typing errors, rather than a reflection of data entry errors. Sayoki will follow up with Thomas.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		CISPOC	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		187 (80)		45 (23 Female)	
HIV positive	3				2	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2	
Number enrolled	62 (25 female)		67 (29 female)		15 (10 Female)	
Number to replace					1 (#4025)	
Eligible, not yet enrolled						
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25	
Second	62/61		63/61		14	
Third	61/60		62/60		11	
Fourth	60/59		61/58		Due May12	
Fifth	58/58		61/58			
Protocol deviations:					11	
Eligibility/enrolment						
Vaccination schedule						
Follow-up schedule						
Procedures					11	
Clinical issues:	293 (7 ongoing)		333 (13 ongoing)		81 (23 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2159)		0	
EAEs	0				0	
Pregnancies					0	
HIV					0	
Grade 3 or 4	11 (0 ongoing)		10 (0 ongoing)		0	
Grade 2	55 (2 ongoing)		102 (7 ongoing)		39 (9 ongoing)	
AE resolved	286		320		58	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18	41 completed		All completed		0	

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons. **Candida, are you happy with this list?**

Recruitment Issues

Edna reported that CISPOC is fully recruited as of this morning – well done!

Pharmacy Issues

Bindiya is expecting the MVA to be shipped from Sweden on the 2nd April and to arrive on 3rd April in Maputo. She does not anticipate any problems especially as inspection by customs is no longer required for these materials. She needs the flight details when Gunnel has them, but otherwise has all the documents required.

The -80 freezer has not yet arrived so MVA will be stored in the -20 which according to stability data should be ok for 6m. Gail will check this with Mary, and be able to report any issues on her forthcoming monitoring visit to Maputo. The cabinet for handling MVA is operational.

Clinical issues

#2160 and #2159 are both HIV positive, and were not willing to transition to the treatment centre at the last call. These events are ongoing, as represented on Philipp's report in the comment column.

#2004 who exited in January had a grade 3 anaemia (Hb=8.8) at v18. Repeat is 7.4 with a hypochromic, microcytic picture. Platelets are normal. US scan had revealed a cyst on the left ovary but no fibroids. She did report heavy menses but not unusually so recently, and previous abdominal pain around the umbilicus. Iron profile is not possible, but the team will check the stool for ova, occult blood and plan to repeat the abdominal US. Arne suggested a trial of H2 antagonists.

#3098 has developed otitis media since the last call, and is scheduled for surgery.

#3153 and 3166 had lab error grade 4 low platelets, reported on the last call. Following discussion about data management of these and similar events (eg pre-existing conditions that had been entered as AEs even though they were no worse than prior to the trial), Sheena wrote to Max who reported that he could delete the AE CRFs from the database if the clinical team provided him with a list. Sayoki reported that he believed Aybua could also do this, and agreed to follow-up with the team. Please note that Max is only able to do this work at the weekends at the moment, as he has started his new job and is very busy.

Edna reported one ppt that the team is concerned about: #4025 who has received the first DNA. He presented with penile ulcers after having unprotected sex with a female in a province 500km away that he was visiting at the weekend. This was treated according to national guidelines for syndromic management, which almost certainly includes treatment for syphilis, although it was agreed on the call that genital herpes was the more likely diagnosis. Unforuntately two weeks later the ppt presented with fever and headache and the team suspect a seroconversion illness. They have repeated the HIV test, including PCR and await the results. Meanwhile he has contacted the female partner and advised her to be tested for HIV and other infections. He has had no sex with his regular girlfriend since she became pregnant, and therefore she has not been at risk. If this is HIV infection, it is categorized as an SAE in both TaMoVac 01 protocols (but not TaMoVac II).

Deviations and missing CRFs

Out of range values

No comments.

Laboratory issues

The Statistical Analysis Plan was signed off before the main analysis was presented at the workshop. The analysis did not reveal any significant differences between separate or combined plasmids at the lower dose, or between the high and low dose of DNA. Any trends were inconsistent between the proportion of responders and the

magnitude, for example although the proportion responding to any pool at v15 is almost significantly higher in the high dose group, there is no consistent pattern across the pools in either proportion of responders or median magnitude at this timepoint. It is important to check that the proportion of female participants is balanced across the three groups, but otherwise the conclusion that there are no important differences is valid, even though the trial was underpowered.

Gunnel noted on the last call that laboratory group planned to discuss a number of things after the investigator meeting, but particularly the issue of the cryo-preserved samples. Is there feedback? Although this point was not discussed on the call, Gunnel raised the issue of ACD versus heparin tubes for collecting samples in TaMoVac II. She pointed out that the work to formally compare the two is not trivial, and that an easier solution would be to increase the volume from 3ml to 6ml. This was agreed and Arne has incorporated into the next version of the TM II protocol.

An ongoing concern is the need to find funds for the CMDR peptides for TaMoVac II.

3. Update on database validation and documentation

On the last call, we discussed the need to correct some of the spellings and clarify acronyms used to describe AEs. Liz has looked at the list that Philipp circulated the day after the last call, and thinks that the vast majority could be coded. There was some uncertainty about whether this would be useful, but Eric felt this would be valuable. Liz confirmed that she was able to extract the AEs from the webdata this morning and so agreed to add a column for code to the spreadsheet and circulate. She would also code the events in the CISPOC report from Edna.

AP Liz to MedDRA code AEs and circulate

Another issue that Eric has highlighted was that of lab AEs. Once coded we could look at the lab events side by side with out of range labs, and flag any that look like they might need a clinical code for checking before we sign them off as clinically insignificant.

On the previous call we agreed to think of ‘key event lists’ that merit sign off as we approach the database lock. Usually these are SAEs and primary safety and immunogenicity endpoints, withdrawals/early terminations, but the process can be useful for other lists. It was agreed that a list of ongoing, but stable, adverse events would be made, indicating which were under continued follow-up and which were not considered clinically significant. Thomas has added a helpful comment column in his report for these, and Philipp also circulated a list of the 13 ongoing (code ‘5’) events prior to the call. The only one of clinical concern was the grade 3 anaemia #2004 (see above).

Edna reported that a database officer has been appointed for Maputo. Thomas sent a programme enabling extract of the data from the database and Edna has successfully implemented this. There are numerous small problems, so the database does not completely reflect the data entered.

Sayoki reported that plans were well underway for the TaMoVac II database and Ayuba and Thomas were doing a needs assessment at MMRP at the moment, and planned to visit Maputo, possibly the 27th March. Sayoki will contact Edna to arrange a suitable date.

4. Monitoring

It was agreed on the last call that v18 was the final study visit, as all the investigations are collected and reported under this visit, and it is not compulsory to return for the HIV result and post test counseling. Pre-existing conditions that have not worsened are also not AEs and a decision about how to manage these CRFs in

the database needs to be made in a similar way to the lab errors noted above. Philipp queried whether dental caries could be considered a pre-existing condition if it arose during the trial, but had happened before. Sheena did not think so, as this could be a new episode due to a different tooth. The more typical pre-existing conditions that did not need reporting were hypertension and asthma, provided they had not worsened in grade.

A draft SOP/working practice document for transfers should be included in the TaMoVac II documentation.

Gail will be visiting Maputo next week for a monitoring visit and will be in Mozambique for 10d across all the MHRP projects.

AOB and time of next call

TM01 AfrEVac amendment

MucoVac2: 14 enrolled, only grade 1 clinical AE to date. Liz provided the break down by group, and the shaded cells are most relevant to the rgp140/GLA-AF boosts planned for TM01, in that all received GLA-AF with those in the high dose groups receiving the same dose of rgp140.

Immunisation	1	2	3
IM high dose	4	2	1
IM low dose	3	2	1
IM/IVAG	5 (IM hd)	2	1
IN	3	1	1
Total	15	7	4

v4.1 has been submitted to IRB, and v4.0 with IRB approval submitted to TFDA. The technical agreement for the shipment has been finalized, and Roger is planning for a shipment in the week of 22nd May, subject to approvals coming through in time. We hope there is a good chance of these being received in April. Buma explained that TFDA has agreed to an accelerated review of 6 weeks which is inside this time limit, and he did not think it would be a problem that approval of v4.1 was also required from TFDA.

Philipp circulated the flow chart of CRFs and subject status form to all.

Monique Surette (our EDCTP officer) has confirmed that Gates is willing to accept a later report, thereby allowing a NCE with activities through to the end of September 2012. This is very good news. MRC CTU will have an underspend of 131,846 euros in the AfrEVac award which ends 27th March and they are seeking permission for this to be transferred to TaMoVac I to support the clinical and lab costs for the protein boosts. Gunnel had emailed Muhammad but had not received an answer regarding how much money remained in TaMoVac I. The urgency to produce a letter with an explanation of the underspend in AfrEVac, and the requests to 1) transfer this to TaMoVac and 2) extend TaMoVac at no additional cost to September to complete this important work was recognized. Roger had spoken to Monique that morning and understood what EDCTP needed. He agreed to draft the letter and template Annexes for each partner and circulate this as a matter of urgency for completion by the end of this week. There was a discussion about the needs for the protein boost component, and acknowledgement that this could release funds in TaMoVac II which were needed for laboratory consumables such as the CMDR peptides.

AP Roger to draft letter for EDCTP and circulate

Sheena anticipated some underspend in TM II for MRC as well, as NIMR was well advanced with the database, and there was continued support from MHRP for monitoring. She had yet to discuss this with Merlin.

TMII protocol

Arne has finalized the protocol (v1.0 12 March 2012) – well done on this mammoth task! Subsequent to the last call, it was established that Vercura could produce HIVIS DNA at 6mg/ml, and it was agreed to change the DNA groups to the following: 1) 2x0.1ml to give a total of 600μg given with Zetajet, with or 2) without Dermavax EP and 3) 1x0.1ml to give a total of 600μg given with Zetajet with Dermavax EP.

Britta updated the group regarding Cellectis, the French company that manufactures Dermvax. The company no longer plans to develop Dermavax for gene therapy, and consequently is not able to provide support for servicing the machines. They have provided 3 new apparatuses and sufficient units for the trial, provided clinics use only one unit per immunization timepoint. Units are used twice to give EP to one ppt, once in each arm, in the current Swedish trial, and there are no safety or quality issues. There are other providers that can service the machines and the General Director of SMI has reviewed the situation and accepts the conditions under which Cellectis is providing the apparatus and units for TaMoVac II. Eric asked whether there was a need to assemble the Steering Committee, but this was not considered to be necessary as there were no concerns raised and ultimately this was a Sponsor decision. He suggested that this was an opportunity to take over the IP from Cellectis, perhaps by creating a limited company, and Roger agreed to make enquiries amongst the UK HVC investigators to see if there was any interest. Eric will ensure that Eligius is aware of this new information, and it was agreed that the protocol could be signed off for submission.

AP Eric to contact Eligius about Cellectis and Roger to enquire regarding IP

The next call will be Thursday 12th April

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 26 May, 23 June Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac II and 01 Trials Management Group
Thursday 22nd November 2012
08.00 EST, 13.00 UK, 14.00 CET, 15.00 Mozambique, 16.00 Tanzania

MUHAS	**NIMR**	**MMRP**	**CISPOC, Maputo**	**SMI/KI**	**MHRP**	**LMU**	**Imperial**	**MRC CTU**
Eligius	Ayuba	Philipp	Edna	Gunnel	Apols	Arne	Frances	Sue
Patricia	John	Revocatus	Ilesh	Eric		Michael	Anna	Livia
Mary	Daniel		Igor	Britta			Roger	Sarah
Candida	Thomas		Yarma					Sheena

1. Review of October notes and action points

- Enquiries were made with respect to Dr Chaitman's availability
- The proficiency panel for rgp140 assays is deferred to the lab call
- There will be training to ensure ppts print and sign their names rather than a change to the IC as MMRP IRB has stamped the form with only one line
- Tina corresponded with Bindiya and Edna re IB and will provide updated stability data
- Edna will circulate response to IRB queries, including re the short PIS
- Sarah B has written to Eligius re the Data Services budget line and EDCTP processes

EDCTP Issues

- Eligius needs to talk to Sayoki and the MUHAS Administrator re funding for the 2013 workshop and data management, and then discuss the proposal for any transfer of funds between partners with EDCTP.

- Those attending the workshop are expected to pay for their own travel and accommodation. The Mozambique team is putting together two estimates based in the location of the workshop, which impacts on whether or not they can afford to pay for meals as well as conference facilities. The cost will be higher than previously for the Tanzania teams because of the travel, which will limit numbers from Tanzania, but it will be offset to an extent by the fact that more members of the Mozambique team will be able to attend.

Potential publications

- TM 01 main paper: safety of DNA/MVA; ELISpot; 4 colour ICS; binding Ab to rgp160.
- TM01 immunology: 8-colour ICS; more detail on the binding Ab to rgp160
- TM01 boost: safety or rgp140/GLA boost; binding and quantitative rgp140 assays; ELISpot

2. Progress with the implementation of TM II

TM II Data management

The CRFs have not yet been signed off. Arne sent out a finalized version on 10th August.Subsequently there have been a small number of changes such that the database is not precisely linked to the 10th August version. Ayubu and team will circulate the CRF used for the database for Arne and Sue to check for differences. Arne and Eric will then sign these off.

The webdata will be tackled after the clinic databases are released. Release is dependent on validation sign off, which is imminent.

Version control is essential. Previously, as recommended by MHRP monitors, the CRFs were amalgamated in one pdf marked 'final'. Currently for TM II they are separate Word documents. We agreed that once Arne and Sue had completed their checks, a pdf would be created v1,0_date in November. This will match version 1.0 of the ***database***. In the event that any forms needed changing, they would be changed individually in Word, with v2.0_the appropriate date.

NIMR have drafted the meta-data and the data management plan (which includes the list of responsibilities), and CTU will comment on these documents.

Candida and Wolfgang have tested the dummy randomization list, and 6 randomization lists for the trial have been generated, stratified by centre and gender. Each list is balanced for the treatment allocation, and the lists for men and women are 80 numbers long for each of the Tanzanian centres, and 38 long for CISPOC.

Sue has identified independent help within CTU for the envelopes, which we aim to courier in the week of 3rd December.

TM II products

Britta was about to ship DNA when she learnt of the plans to have an agreement in place first. Eric is coordinating this and liaising closely with Rigmor at SMI. A table of sponsor responsibilities and the way in which these are distributed amongst the partners has been created. Eric intends to circulate to all once he has received Michael, Arne, Sheena and ELigius's comments. Eligius would like to consult with his Director of Research before sending comments, as the arrangements for co-sponsorship have changed at MUHAS.

Britta explained that the vials were in two packages, each of which contained supplies for MMRP and MUHAS. They will be sent on different flights as a precaution and she prefers that the previous procedure is followed and Buma collects both from the airport. Clearing customs is the greatest challenge. Following this method presents a challenge for the MMRP team who have to arrange internal transfer in Tanzania. There were several problems with the rgp140/GLA transfer and they wish to avoid any repetition. Britta confirmed that Buma will be getting dry ice for the transfer. Philipp and Revocatus will contact Buma, to ensure that there is a clear agreed procedure, but the more warning they have of the date, the better. It was agreed that 14th December was the latest date for shipping from Sweden.

AP Britta, Philipp, Revocatus and Buma to liaise re transport and transfer of DNA supplies

TM II initiation training for Mozambique

Eric will train on electroporation before the meeting. Site initiation visit training dates still to be clarified.

Green light for MUHAS and MMRP

CTU recommends that this is at least dependent ons:

- Final CRF (for screening)
- Database validation sign-off (for enrolment)
- DNA in pharmacy (for enrolment)

- Envelopes in pharmacy (for enrolment)

Eric that SMI gives the green light, and he will inform TMG accordingly.

Philipp will organize the back-translation from the Swahili information sheet to English. Sue confirmed this could not be someone from the trial team, but could be someone from the campus.

TM II protocol

Edna is preparing the IRB response and will circulate for comments shortly. She needs the declaration of conflict of interest from the monitors, and will circulate a template.

Sue is assembling a list of issues to address in the next amendment eg:

- To correct the footers with the wrong version number
- To remove the reference to MHRA and MREC and NHS (11.5)

We hope to hear from UK HVC Steering Committee in December regarding the amendment to include the rgp140/GLA. – Roger has already heard from 2 members of the SC. The results from the boosts in TM 01 are needed for the justification, and these should be ready in January. Eligius prefers not to incur the higher cost of expedited review, but it looks as if the trial will start later and we will have time (first boosts due ~May), although the late start puts pressure on the recruitment.

3. Update from clinical research centres

	TM01-Tz				**TM01-Moz**	
	MUHAS		**MMRP**		**CISPOC**	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Number screened	83	152	121	152	44	33
Screened out * **HIV positive** **Pregnant** **ECG**	58 F 115M 3 4 (V1 or 2) 25		92 F 114 M 4 (V1 or 3)		46 (24 Female) 2 (both female) 2 2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized: **First** **Second** **Third** **Fourth** **Fifth** **Sixth** **Seventh**	Attend/vaccinated 62/62 62/61 61/60 59/59 59/57 19/19 19/19		Attend/vaccinated 67/67 67/61 61/60 60/58 58/58 21/21 20/21		Attend/vaccinated 25/25 23/23 22/22 22/22 13/13 NA NA	
Protocol deviations: **Eligibility / enrolment** **Vaccination schedule** **Follow-up schedule** **Procedures** **Consent withdrawn**	 0 0 15 7		 1 5 15 50		22 3 (all labs) 2 (#4024, 4025) 3 (late visits) 15 1 (#4063)	
Clinical issues: **SAEs** **EAEs** **Pregnancies** **HIV**	302 (4 ongoing) 1 (#3117) 0		362 (11 ongoing) 2 (#2160, 2259) 1 (#2066) 2 (#2160, 2259)		353 (15 ongoing) 1 (HIV #4052) 0 2 #4045, 4038 1	

Grade 3 or 4 **Grade 2** **AE resolved** **SAE resolved**	7[1] (0 ongoing) 56 (1 ongoing) 298 1	13 (#2246 ongoing) 112 6 ongoing) 351 0	4 (1 ongoing) 135 (18 ongoing) 277 n/a
Completed v17 **Completed v18**	59 completed	All completed	Next week

[1]12 in TMG notes

In blue are the figures that cannot be derived from Thomas's data

Recruitment Issues

How did the Community meeting at the end of last month go?

Pharmacy Issues

See earlier under DNA shipment for TM II.

A Pharmacy SOP/working practice document for transfers between Tanzania centres should be included in the TaMoVac II documentation.

Clinical issues

There is nothing new to report from MucoVac2, and the further boosts are proceeding – there will be 8 in total who receive x5 rgp140/GLA.

Igor/Edna reported that the pregnant partner of the ppt that has HIV infection, who also has HIV infection is now on ART. The ppt is enrolled for care in the youth clinic and is still being followed by the study team. His last CD4 was 450. There are no other adverse events of note to report, and the last 3 MVA should be completed by mid-December, the last visit late Feb/early March.

The last rgp140/GLA follow-up was completed today – very well done to both teams!

4. Update from research laboratories

Arne reported that the 8 colour assays in MMRP are complete for v15 and v18 are now underway. Gunnel and Chriss have discussed the transfer of sera for gp160 assays to MUHAS, which will need an MTA. Gunnel reported that Lotta will be in MUHAS next week from Tuesday to establish 8 colour ICS and oversee the serology.

5. Monitoring

CTU is awaiting comments from MHRP to on the Quality Management Plan for TM II.

6. Update on analysis and publications

Livia and Candida have been working to finalise the study population including those screened, and the adverse events prior to the boost protocol. The last ppt v18 in the original protocol was 15th June 2012, but it is reasonable to include the events reported up to the first rgp140/GLA. As we have a robust datafreeze on the 22nd August 2012, we agreed that this would be the file for the main paper reporting DNA/MVA safety.

Arne asked about the suggestion that Dickens and Thomas come to CTU for training and support in analysis in order to support Candida. Sheena apologized that she had forgotten to email Muhammad and Eligius about this after speaking to Candida. She will do this next week, and also remind them about the need for a spreadsheet of planned publications.

AP Sheena to email Muhammad and Eligius re analysis training and publications

The next scheduled call will be Thursday 20th December

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
TaMoVac Trial Management Group (TMG) - **Clinical trial implementation and progress when open, clinical and lab issues, data management, monitoring, AOB**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 14.00/15.00 Mozambique, 15.00/16.00 Tz Call, agenda and notes organised by MRC CTU (Sheena)	MUHAS–Muhammad, Patricia, Thomas, Buma MMRP–Philipp, Bahati, Marco NIMR–Sayoki, Ayubu, John, Mbazi INS–Ilesh, Edna, Nelson, Bindiya, Nafissa, Igor LMU–Arne, Chriss SMI–Eric, Gunnel, Lotta MHRP–Merlin, Mary, Gail, Tina, Kathleen MRC CTU–Sheena, Sue, Sarah, Livia, Wolfgang Imperial–Frances, Anna, Roger
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, lab and other capacity building, student progress, communications with the EDCTP and finance**	?????	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**??????**	Imperial – Robin, Lea MRC CTU –Sarah LMU – Chriss MMRP - Asli, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 23rd August 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS	**NIMR**	**MMRP**	**CISPOC, Maputo**	**SMI**	**MHRP**	**LMU**	**Imperial**	**MRC CTU**
Muhammad	Sayoki	Philipp	Edna	Eric	Merlin		Roger	Patricia
Eligius	Ayubu	Revocatus	Ilesh		Gail		Frances	Candida
Buma	John	Nhamo	+?		Tina			Livia
	Thomas				Kathleen			Sue
	Daniel							Sarah
								Sheena

1. Review of July notes and action points

- Buma has been sending temperatures to Roger, the mixing SOP and contract/MTAs are finalized, and volunteers have been immunized with rgp140/GLA at both centres!
- John generated the sign off lists on 15th August
- Tina circulated the new expiry date for MVA
- The final TM II CRF has been signed off by Eric and Arne ?ELigius also
- Candida extracted data on Sunday 19th August before she flew to London
- Lab group to complete the analysis of new immunology data from visit 18 in time for Boston (not essential for the EDCTP report).
- Patricia and Sue have started to populate the CSR

EDCTP No-cost extension for TM I

Muhammad and Gunnel had a call with the EDCTP Officers Monique and Emma on the 16th August. Gunnel also attended a follow-up call with Charles Mgone and the Director of Operations. EDCTP is very inclined to approve the no cost extension and additional funds, but requires a more formal request including further justification and amendments to the budget. MUHAS is in dire straits financially because the last 10% of the grant is not transferred until 6 months after project closure. EDCTP is aware of this and suggests that a request for at least a portion of the final payment to be transferred earlier is included with the request for the no cost extension.

An updated financial report detailing expenditure between 31st March 2011 and 20th August 2012 is required from all partners, and a technical report. Muhammad has requested the template. Timelines are very tight as EDCTP wants to receive everything by 12th September. Muhammad is therefore requesting the financial and technical reports from partners by 31st August (3rd September at the latest). Sheena advised partners to forewarn their financial officers.

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were updated on the call.

	TM01-Tz				**TM01-Moz**	
	MUHAS		**MMRP**		**CISPOC**	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		187 (80)		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25/25	
Second	62/61		63/61		23/23	
Third	61/60		62/60		22/22	
Fourth	60/59		61/58		19/22	
Fifth	58/58		61/58		6/22	
Sixth	18/20		13/22			
Seventh						
Protocol deviations:					22	
Eligibility/enrolment					3 (all labs)	
Vaccination schedule					2 (#4024, 4025)	
Follow-up schedule					3 (late visits)	
Procedures					15	
Consent withdrawn					1 (#4063)	
Clinical issues:	300 (10 ongoing)		333 (1 ongoing)		245 (13 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2259)		0	
EAEs	0				0	
Pregnancies					1 #4045	
HIV					0	
Grade 3 or 4	12 (1 ongoing)		10 (0 ongoing)		2 (0 ongoing)	
Grade 2	56 (3 ongoing)		102 (#2259 ongoing)		105 (7 ongoing)	
AE resolved	290		332		211	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18	59 completed		All completed		0 expected Oct12	

Recruitment Issues

All trials are fully recruited for DNA/MVA. Volunteers in TM01 (Tz) are being enrolled for their rgp140/GLA boosts. Of 20 screened at MUHAS, 18 have enrolled. One withdrew consent on the day of immunization, and a second is now travelling and will not be able to take part in the boosting. It will take at least 10days to identify and screen more volunteers. Luckily MMRP has screened 22, and should be able to immunize 9 next week which would mean to overall total was still 40. However, this would use up all vials including spare ones at MMRP. It was suggested that additional vials could be transferred from MUHAS to MMRP.

Pharmacy Issues

There was a minor excursion of temperature for GP140 and GLA-AF in MMRP, reported by Bahati on 13th August. It fell below 1.7oC very briefly over the preceding weekend, due to a faulty compressor and consequent absence of air-conditioning confusing the fridge. Roger confirmed that this would not effect the quality of the product, and noted that the temperature were generally low. He advised that the fridge temperature be set a little higher. MUHAS also had a mild excursion.

There are no problems with the mixing, and the product appearances are satisfactory.

Clinical issues

Edna has prepared another detailed report for the TMG, circulated with the agenda. There are 22 volunteers still in the immunization schedule. She reported that #4012's girlfriend was pregnant, but unfortunately had a spontaneous abortion following a car accident. The IRB has been informed.

At the end of the DNA/MVA main trial, MMRP has 2 SAEs (HIV) that will be signed off soon and 4 stable grade 1 events (2 anaemia, one hyperopia and one elevated ALT).

MUHAS has 1 SAE (infection following head trauma requiring hospitalisation) and 3 events that are ongoing, but likely to be resolved in the near future (otitis media, anaemia which is being treated, low neutrophils).

The rgp140/GLA immunizations are going well so far and only mild adverse events have been seen.

There is nothing new to report from MucoVac2, except that we have verbal approval to give 2 further boosts (5 immunisations total) to a subset of volunteers primed with three 100 μg IM or IN doses, and hope to start these shortly.

Laboratory issues

The Lab group will determine the timeline for completing the v18 ELISpot analyses, reviewing these, finalising and signing off for the Clinical Study Report.

3. Monitoring

A draft SOP/working practice document for transfers should be included in the TaMoVac II documentation.

Eric monitored the database/CRFs whilst in Tanzania to do the Dermavax training for both Tanzanian centres, and generated queries. There are ongoing problems with the recording of lab events (see data management).

During Gail's monitoring visit she noted letters of consent for photographs to be used by a journalist and for an exposition in the files. This led to a discussion amongst the monitors about whether or not the letters should have been reviewed by ethics before being signed. The conclusion was that as these had been prepared for individuals for specific and unique purposes, there was no need for them to be submitted to ethics in advance but that the team should submit them now and see what the IRB response is. Eric's view was that the photo for the journalist's article was not a trial issue and was concerned that this could confuse the IRB. Gail reported that the article was about the trial, so not completely independent.

Gail noted that a chart note and signature would also have been satifactory.

Eric and Gail both commended the team on their efforts to ensure good clinical practice.

AP Gail to check notes correctly reflect the consensus decision amongst the monitors

***4.* Data management and database for TM01**

TM01 (timelines and responsibilities for report to EDCTP/Clinical Study Report (CSR) due end of September 2012)

20 August -	Draft the clinical study report (safety, primary immunogenicity) up to and including v18 to support Boston abstract and EDCTP activity report	Patricia/Candida with support from Sue/Livia/Wolfgang
21 September	Report for EDCTP completed	Patricia and Muhammad

We have had a good week at CTU with Candida and Patricia.

Baseline data and tables are complete, but one problem has emerged in that the pharmacy data from MMRP is one volunteer short (#2016). This will need to be corrected in the database. Philipp and Revocatus explained that #2016 was the ppt who received 2 DNA and was then replaced by # 2200. It was agreed that #2016 should still be counted in the analysis for baseline and AEs. Nhamo will look into the database and ensure any necessary corrections are made and sent onto Candida.

AP Nhamo to investigate and correct the pharmacy data entered for #2016

We agreed that the adverse events would be presented as reactogenicity events and other events. Laboratory events will be presented using the raw data to grade the events which will include all laboratory values. Candida is now writing the code for the adverse event tables, and in doing so realized that the extract she brought with her is not complete. Ayubu sent a second extract on Wednesday 22nd, and this has been successfully read by Candida this morning.

The adverse event file (from Monday) contains laboratory abnormalities that were not considered clinically significant (in that no treatment was given). These events are numerous, and deleting them is not an appropriate solution. Therefore they need to be dropped from the analysis file when Candida prepares the table. This can be done in the programming code, but it needs to be a clinical decision, and sufficiently automated to be coded as a group rather than for each individual event. To address this, we have accelerated the coding and Livia has now coded all events in MEDDra, adding the Preferred term (PT) and the System Organ Classification (SOC) as well as the numbers to the spreadsheet that Candida sent her on Monday for each centre. Those that were untreated laboratory events have been coded under the SOC “Investigations”, and Candida will be able to write a simple code to drop these from her files.

Livia has highlighted a few of the codes that she particularly wanted Patricia and Phillip to check, including the events where there are two possible codes eg malaria and headache, and urinalysis results.

Regarding the laboratory events that are ‘0’. Patricia knows that at least some of these are errors in laboratory processing eg when they all happened on the same day/week. These were to be deleted but Candida has watched John do this, and it is not possible. In earlier discussions we suggested those were all re-entered as ‘999’. A list was available for all such events up to v15, but would need to be reviewed again by the clinical teams to take account of all the visits. Eric asked John to put all these in the Queries spreadsheet which was working well, and he thanked John for his hard work on this. This exercise will need to be completed before Candida can create the laboratory event tables, which fortunately are not required for Boston.

One further issue identified is the presence of reactogenicity events prior to immunization. In previous vaccine trials, such events have been dropped if they continue at the same grade to resolution, but included if they go away and reappear within the 7 days post-immunisation. Candida is also concerned that the files created on Monday were incomplete, and will need to check these against the more recent extract sent yesterday.

Sue started the CSR, using the ICH guidance on format and content and adding information from the protocol. Patricia is checking through this and editing. The scope of the main report is up to and including v18.

Patricia has been working with Sarah on the poster and slides for Boston, incorporating the helpful suggestions that people sent. An explanation for the use of placebo will be added to the text, but these ppts will not be included in the immunogenicity tables as the purpose of the trial was to compare the DNA groups to each other. Eric reported that Lotta will send a number of different plots for presenting the magnitude of response for Patricia to chose from. He wasn’t sure when these would be sent but it is likely to be after Patricia leaves London. This is ok as Sarah can bring the poster to Boston for Patricia, and in the meantime Patricia can practice the presentation with the existing figure.

We haven’t started work on the main paper yet, but there has been plenty to do, and all of it relevant!

Muhammad wrote to EDCTP to find out whether there is a template for the final report they expect in September. He does not recall a response but will check his email.

TM01 (CISPOC)

Sayoki reported that Ayubu will travel to Mozambique on 26th August and be there for 5 days. He will be able to fix the problems in the CISPOC database for TM 01 as well as identify needs for TM II.

Boston posters

Chriss circulated Asli's draft poster and there were several comments, including to exclude the placebos in the graphs. This has been done by Candida, as the lab and clinic remain blind to individual allocation because of the ongoing rgp140/GLA boosts.

Patricia has circulated her draft and has also received comments. We need to formulate a conclusion and Wolfgang sent the key statistical tables today. There is a trend in favour of the high dose, but this is not statistically significant, meaning that it could be chance. If the difference seen is considered meaningful, then the next logical step would be to do an adequately powered trial with large enough group size to detect this size of difference/rule it out. As everyone knows, we did not decide to do that but to proceed with the low dose DNA, combined. Therefore, it makes most sense if our conclusion is as follows:

"Although there was a trend in favour of the high dose DNA, this was not considered sufficient to offset the advantage of proceeding with a lower dose of combined plasmids in the next TaMoVac trial. However, we intend to explore alternative means of boosting the response to low dose DNA, such as electroporation."

Philipp circulated his draft today – please comment!

5. Progress with implementation of TM II

TMII protocol

- Local MUHAS IRB has given approval.
- MMRP IRB will meet in the first or second week of September
- NIMR IRB approval expected shortly as a member of the ethics committee informed Eligius that the committee will give the study clearance at/after the next meeting on the 3rd September
- Submitted to TFDA on 23rd July 2012. Eligius confirmed that the payment had been received and knows that the application is proceeding.
- Comments have been received from the INS Scientific Board in Maputo, and the team has now submitted to the IRB and regulatory authority. They can expect comments in September

TM II CRF

This was finalized on 13th August although it's not clear that Eligius and Sayoki signed off. Sayoki explained that they had decided it would be better to sign off after the database was tested at which stage we could be sure there would be no further changes to the CRF.

Having reviewed the data this week at CTU, we would like to strongly recommend brief working instructions for the completion of the AE CRFs in order to avoid some of the problems we are encountering in TM01. As the coding has been completed as a matter of urgency, it may be best to include this topic in the initiation training, and to explain in the instructions why the AE CRFs need to be filled in with the final code in mind. Livia has created a Master Coding List, and each centre could use this as a reference document.

TM-II Database and data management plan

John has started work on the meta-data (the database requirements for each CRF item), although this was dependent on finalising the CRF. Ayubu has indicated that the database will be ready for user acceptance testing by 24th September and live for 21st October. NIMR has drafted a data management plan, and shared it internally. They expect to send the draft to MUHAS, MMRP and CISPOC next week. MMRP also have an internal data management plan ready.

TM II products

Shipment cannot happen until the approvals are in place. Gail noted that she would need to give 90 days notice before travel for an initiation visit, and that this timeline was rapidly approaching for an October start. Gail is in Mbeya at the end of October to initiate another study, after which she has to go on to Kenya then Nigeria.

Eric confirmed that he had informed SMI that an initiation visit was not essential prior to the first enrolment as the CRFs and procedures were so similar to TM01 and the study teams were following these well. Sheena did not disagree, but recommended refresher training via webex or the phone, as there were improvements to be made to the completion of the CRFs particularly clinical and laboratory AEs. The training could be supported by a monitoring visit shortly after screening and enrolment begins when there would be CRFs to check.

TM II Trial Master File

Eric forwards all the documents to Eva at SMI, but is not sure that she creates the Trial Master File as this is not an area of expertise for SMI. Sheena believes this responsibility was assigned to CTU in the grant application, so the TMF can be maintained there during the trial and then copies provided to SMI, MUHAS, CISPOC at the end.

AOB

Eric noted that the training for Dermovac needs to be done in Mozambique. Edna is away Oct9-Nov26, so late November, early December looks promising. Edna will consult the team and email suitable dates. Eric would prefer to do this when Edna is back, which will be late November or early December.

AP Edna to circulate dates

The next call will be Thursday 27th September

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 21 June, 26 July, 23 August Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayubu, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 23rd February 2012
08.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS
Muhammad
Patricia
Maria
Buma

MMRP
Philipp
Bahati
Marco

NIMR

Imperial
Frances

LMU
Arne

SMI
Eric
Gunnel

MHRP
Merlin

CISPOC, Maputo
Edna

MRC CTU
Liz
Nicola
Sheena

1. Review of notes and action points

- Arne and Philipp created flow chart of CRFs for rgp140 boost and amended the subject status form and circulated to Max. Philipp will circulate to the group.
- Sheena and Roger completed the documents with the latest MucoVac2 update, and sent to Buma

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator
- Presentation of individuals screened out if multiple reasons given – do we need to identify a primary reason?

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were taken from Edna's report attached to her email of 23rd February, Philipp's report of 22nd February 2012, and Thomas' of 16th February, corrected on the call by Patricia and Philipp. It was noted that the discrepancies in Thomas' report were probably typing errors, but Philipp and Patricia will follow up with him.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		INS	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	40	33
Screened out *	58 F ~~114~~ 115M		187 (80)		40 (20 Female)	
HIV positive	~~2~~ 3				2	
Pregnant	~~3~~ 4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2 (#4016,4032), 4021*	
Number enrolled	62 (25 female)		67 (29 female)		15 (10 Female)	
Number to replace					1 (#4025)	
Eligible, not yet enrolled					9 (3 Female)	
Number immunized:	Attend/vaccinated		Attend/vaccinated			
First	62/62		67/67		15	
Second	62/61		63/61		13	
Third	61/60		62/60		4	
Fourth	60/59		61/58			
Fifth	58/58		61/58			
Protocol deviations:					11	
Eligibility/enrolment						
Vaccination schedule						
Follow-up schedule						
Procedures					11	
Clinical issues:	293 (12 ongoing)		333 (13 ongoing)		58 (14 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2159)		0	
EAEs	0				0	
Pregnancies					0	
HIV					0	
Grade 3 or 4	11 (2 ongoing)		10 (0 ongoing)		0	
Grade 2	53 (3 ongoing)		102 (7 ongoing)		30 (7 ongoing)	
AE resolved	281		320			
SAE resolved	1				n/a	
Completed v17	36 completed		All completed		0	
Completed v18					0	

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons. Candida, are you happy with this list?

Recruitment Issues

92 volunteers have attended an informed consent seminar (53 females). 9 individuals were eligible on 23Feb but not yet enrolled. Abnormal CBC (9), positive syphilis (6)

and at risk of HIV defined as >1 partner in the last 6m (9) continue to be the main reasons for exclusion. Following discussion at the workshop it has been decided to change this last criteria to >2 partners in the last 6m. The team hopes to complete enrolment in the second week of March.

Pharmacy Issues

No pharmacy issues reported.

Clinical issues

#2160 who is HIV positive with CD4 of 214 (9.7%) in August when VL >100,000 and 177 (9.7%) in September, had a CD4 of 94 at the time of the last call. This is now 133. She is on Septrin but remains reluctant to start ART. She has been shown around the clinical treatment centre by one of the trial nurses, and will be seen again next week. The team will continue to follow her each month and repeat CD4, and try to work on her denial.

2261 who delivered recently is well, and her grade 3 anaemia resolved. She has asymptomatic pyuria which was treated with augmentin. Nitrofurantoin was added as she developed microscopic haematuria. Current status is 5-10 WCC/high power field, and she remains asymptomatic.

2159 who received an immunization whilst HIV infected has a CD4 of 390. He is well and the team will see he transfers to the CTC for care. He attended V18, and is the last participant to do so. He is reluctant to attend CTC, but not to the same degree as #2160.

#3153 and 3166 have both developed grade 4 low platelets since the last call. Patricia confirmed that this was a lab error and that they were normal on repeat testing. This gave rise to discussion about data management of these and similar events. One option is to delete the AE CRF but leave the lab form entries. Provided this was apparent in the database audit trail, with explanation and in the CRF this would be fine. However, it may not be that easy from a programming perspective. Another option is to change the grade on the AE CRF to 0. This may or may not be permitted. Sheena agreed to check with Max and seek his advice.

AP Sheena to check with Max re documenting these ‘non-events’ in the database

Edna provided a detailed report regarding the AEs.

Deviations and missing CRFs

Out of range values

No comments.

Laboratory issues

The Statistical Analysis Plan was signed off before the main analysis was presented at the workshop. The analysis did not reveal any significant differences between separate of combined plasmids at the lower dose, or between the high and low dose of DNA. Any trends were inconsistent between the proportion of responders and the magnitude, for example although the proportion responding to any pool at v15 is almost significantly higher in the high dose group, there is no consistent pattern across the pools in either proportion of responders or median magnitude at this timepoint. It is important to check that the proportion of female participants is balanced across the three groups, but otherwise the conclusion that there are no important differences is valid, even though the trial was underpowered.

Gunnel noted on the last call that laboratory group planned to discuss a number of things after the investigator meeting, but particularly the issue of the cryo-preserved samples. Is there feedback? Although this point was not discussed on the call, Gunnel raised the issue of ACD versus heparin tubes for collecting samples in TaMoVac II. She pointed out that the work to formally compare the two is not trivial, and that an easier solution would be to increase the volume from 3ml to 6ml. This was agreed and Arne will incorporate into the next version of the TM II protocol.

3. Update on database validation and documentation

Candida has highlighted a number of issues regarding AEs that need cleaning and the teams have been working hard to address these. At the moment we have a list of AEs as they were reported, included spelling errors etc. These only need correcting where they create uncertainty, eg hyporglycaemia could be a mistype for hypo- or hyper-, whereas flue is still clear. There are also potential issues with the use of abbreviations such as UTI/URTI, and finally some events where it looks as if two MedDRA codes are required and we need to decide if there is a single diagnosis to apply or these should be reported as two separate symptom events eg pain lips and left leg! Another example is 'menorrhagia due to polycystic ovaries' where there could be a number of options – newly diagnosed PCO, or menorrhagia that has become more of a problem since enrolment. Liz had not received the list, but is willing to code the events in MedDRA and highlight the ones that cannot be coded, or that have multiple codes and direct the clinical teams to these events.

Another issue that Eric has highlighted is that of lab AEs. Once coded we could look at the lab events side by side with out of range labs, and flag any that look like they might need a clinical code for checking before we sign them off as clinically insignificant.

It's useful to think of 'key event lists' that merit sign off as we approach the database lock. Usually these are SAEs and primary safety and immunogenicity endpoints, withdrawals/early terminations, but the process can be useful for other lists. It was agreed that a list of ongoing, but stable, adverse events would be made, indicating which were under continued follow-up and which were not considered clinically significant (mostly lab events - see below).

Looking through Thomas' report, there are a number of ongoing lab events to be closed, either through repeat test or alternative method of closing in the database as 'stable and no further clinical follow-up indicated'. Not sure what these look like in Candida's analysis files, but they are likely to generate queries, and the lists referred to above will be useful for Candida.

4. Monitoring

Gail raised a number of questions after their monitoring visits:

- visit 18/18J the final visit date?
- Pregnancy outcomes if ongoing at the final visit?
- documentation of pre-existing conditions, including labs that have not worsened during the trial

It was agreed that v18 was the final study visit, as all the investigations are collected and reported under this visit, and it is not compulsory to return for the HIV result and post test counseling. Philipp reported that there were no ongoing pregnancies at the last visit. Pre-existing conditions that have not worsened are also not AEs in a similar way to the lab errors – another question for Max.

Did a draft SOP/working practice document for transfers get done? Something to think about for TaMoVac II.

AOB and time of next call

TM01 AfrEVac amendment

MucoVac2: still no AE of note to report.

The documentation for v4.1 is with Buma for submission, and ethics approval for v4.0 has been received so submission to TFDA is expected tomorrow or Monday. Roger circulated the technical agreement for the shipment for comments and this is now final.

See action points from previous call – Philipp agreed to circulate the flow chart of CRFs and subject status form to all.

Muhammad and Sheena were on a call with Monique Surette (our EDCTP officer) in January, and she is supportive of a no cost extension to facilitate the rgp140/GLA-AF boosts. The teams are working on redistribution of the budget and the workplan for TM I. MRC is underspent on AfrEVac and these funds could be directed to the clinics, but this would have to be signed off by EDCTP before the end of March when AfrEVac ends, and may be too complicated. Monique stated on the call that the EDCTP need the final report from TM I in September to meet their obligation to the Gates Foundation. Consequently, August was the latest month for activity. Muhammad was not sure that he had understood this from the call, and so it was agreed that he would email Monique to clarify and copy partners. The question of whether or not the CMDR peptides could be purchased arose, but as these are for TM II this probably would not be possible. Sheena reported that she anticipated an underspend on TM II for MRC as well, and noted that this was in part because of the continued support of MHRP in monitoring. It may be possible to pay for travel and subsistence so continuity could be preserved and she will explore this with Merlin.

TMII protocol

Arne has been working hard to coordinate the final version, now that the design has been decided. There are a few formatting issues to resolve, and it would be valuable for someone who has not been involved to date to review for inconsistencies. Eric is happy to keep the terms Adverse Drug Reaction and Unexpected Drug Reaction, even though they don't exist specifically in the CRF, as they fit with ICH GCP definitions. The arm to be used for the MVA boosts was resolved. It was agreed to grade social harm according to the general grading for AEs and treat it in a similar way to clinical events with respect to reporting, so that only severe social harm, or social harm that led to a discontinuation of the immunisations would be reported in an expedited manner. There was a discussion about the various oversight structures. Sheena noted that the TCC had rarely met during TM01, and Eric pointed out that the TMG was filling many of these functions, whereas his understanding of the term TMG was the group overseeing day to day activities in each centre. Sheena commented that this group can be referred to as the Trial Management Team. Arne has a visions in mind for this section of the protocol and will circulate with the next version which he hopes to complete early next week. He plans to remove the majority of appendices and make these separate documents. He asked that Patricia, Bahati/Philipp and Edna check carefully through the changes to look for any impact on the information sheets.

The next call will be Thursday 22nd March

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

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TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 26 May, 23 June Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of for the
TaMoVac 01 Trial Management Group
Thursday 24th May 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS
Muhammad
Buma
Patricia, Eligius, Said (apols)

MMRP
Philipp
Bahati
Marco
Revocatus

NIMR

Imperial
Anna
Frances (apols)
Roger
Kylie

LMU
Arne

SMI
Gunnel
Eric

MHRP
Gail
Tina
Shaquanda

CISPOC, Maputo
Edna
Bindiya
Ilesh
Patricia

MRC CTU
Liz (apols)
Sheena
Livia
Sarah

1. Review of notes and action points

From previous notes:

- Liz has completed coding except for a few events that were not clear (see item 3)
- Roger to enquire whether there is interest in UK HVC in taking over the IP for Dermavax
- Errors in the earlier data reports seem to have been corrected

From April call:

- Merlin followed up re stability testing for MVA and relabeling (see agenda item 2)
- Thomas circulated a data management report on 27April
- NIMR have not yet circulated updated timeline for TM II database development

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator
- Presentation of individuals screened out if multiple reasons given – do we need to identify a primary reason?

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were updated using Thomas's report of 27th April, Edna's report of 23rd May, and Phillip's of 24th May, and updated on the call.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		CISPOC	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		187 (80)		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2 (both male)	
ECG	25				2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25	
Second	62/61		63/61		23	
Third	61/60		62/60		19	
Fourth	60/59		61/58		5	
Fifth	58/58		61/58			
Protocol deviations:					14	
Eligibility/enrolment					1	
Vaccination schedule						
Follow-up schedule						
Procedures					13	
Clinical issues:	300 (10 ongoing)		333 (2 ongoing)		170 (24 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2259)		0	
EAEs	0				0	
Pregnancies					1 #4045	
HIV						
Grade 3 or 4	12 (1 ongoing)		10 (0 ongoing)		1 (0 ongoing)	
Grade 2	56 (3 ongoing)		102 (#2259 ongoing)		75 (16 ongoing)	
AE resolved	290		331		146	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18	59 completed		All completed		0	

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons. **Candida, are you happy with this list?** Wolfgang is following up with Candida re progress on analyses for CSR.

Recruitment Issues

All trials are fully recruited!

Pharmacy Issues

Bindiya received the MVA shipment on 8th April and it is stored in the -20. Tina asked for clarification on this point, and Bindiya explained that the -80 would not be in place for 2 months, due to issues with deportation, but she has documentation that the MVA is stable at -20 for 6m. Tine thought this might now be 12m. Tina explained that the GLP laboratory had relocated to the main base, and was only just cleared for activity. MVA-CMDR Lot#07860210 vials were cracked yesterday, and the first round of MVA titres are satisfactory. It will take about 2wks to do further titres and clear with the QA group. She will inform the group and prepare the appropriate note for the file.

Roger has arranged to ship the products for the protein boost next week, leaving on the 29th May to arrive in Tanzania on the 30th May. Buma will need to be available to help clear customs, and so that World Courier get their box back! The following steps need to be in place:

- Products should be transferred from the courier box into a secure fridge 2-8 C in the pharmacy.
- Box must be visually inspected to ensure integrity by the pharmacy
- MMRP box should not be opened by MUHAS, only visually inspected before put in the fridge.
- MUHAS temptale must be collected by the courier and temp data sent to us **NOTE: Maybe Buma can download and send the data to us.**
- MMRP needs to collect its box from MUHAS ASAP. Preferably Wednesday to be confirmed when we know ETA and if no problem with custom.
- Product should be transferred from pharmacy fridge to car fridge in a container on ice ensure no direct contact with ice do not use -20 gel pack. NOT DRY ICE.
- Product should be transferred to MMRP pharmacy fridge as soon as it arrives at MMRP
- Box integrity to be checked again (look for watermark).
- Box to be open and temp tale to be removed and temperature data to be collected (not sure how yet).
- Box to be stored in a secured fridge 2-8C
- Report to be emailed ASAP.
- Product is quarantined until QA by Sue
- Product cannot be used until legal agreements in place

An SOP (23May12) has been circulated with the agenda. Buma did not have any specific questions. The transport from MUHAS to MMRP was discussed as MMRP pharmacy has not previously been responsible for transfer of materials at 2-8^{o}C, although gp140 for the Ab assays had to be transported at this temperature and Arne confirmed there is a box that can be plugged into the car to maintain this temperature. Philipp proposed that the products were transported by air on one of the daily flights as this is the shortest transit (8-10.30am); he confirmed that 2d notice is needed to book seats on these small planes. Buma has a box which can be maintained at 2-8 using ice for up to 16 hrs. Roger was concerned about the use of ice as the products must not freeze, and there is no more if something goes wrong with the shipment. He would like to see the SOP for transport, and Buma will send it. This must be sorted out in the next 2d. He reminded everyone that QA release is dependent on satisfactory temperature recordings.

AP Buma to send SOP to Roger

Clinical issues

#2004 who exited in January had a grade 3 anaemia (Hb=8.8) at v18. Repeat was 7.4 with a hypochromic, microcytic picture. Platelets are normal. US scan had revealed a cyst on the left ovary but no fibroids. She did report heavy menses but not unusually so recently, and previous abdominal pain around the umbilicus. Iron profile is not possible, but the team will check the stool for ova, occult blood and plan to repeat the abdominal US. Arne previously suggested a trial of H2 antagonists, but she has had a good response to folic acid and iron and her Hb is now 11.4. This ppt still has haematuria which the team think is due to menses. They recalled her for a further check and there is no haematuria as expected. However her abdominal pain in association with menses does continue, and a second scan revealed a cyst on the right ovary (the left had resolved). Her pain is mild to moderate, and the team have decided to report this as ongoing at the end of the study. It was agreed that this seemed sensible.

There are 3 further ongoing events being followed. Contact has been made with ppts but they have not yet come back to clinic. #2259 has asymptomatic pyuria. This event is currently recorded as UTI, and it was agreed to rename the event if it was confirmed at the visit that the ppt was asymptomatic. Unfortunately this ppt who has also serocoverted for HIV has been reluctant to attend the clinic. #2255 has grade 1 elevated ALT (asymptomatic). He has moved away and his phone number no longer belongs to him. It was agreed to close this event which is currently a very low grade 1, although it is recorded as a grade 2 event on the database as it was, at an earlier stage, grade 2. This led to a discussion about the value of reflecting the change of grade in the database by completing another AE CRF closing the grade 2 on the day that a grade 1 was opened. This would allow the line listings for the regulatory submission to be generated from the database/analysis files. Eric did not feel this was necessary as the ongoing events at the end could be described in a narrative, and the publication would only report the highest grade of event. #2260 grade 1 low glucose has resolved. The third ongoing event

#3098 developed otitis media and is scheduled for specialist surgery in May when a team of US surgeons is visiting MUHAS. This is one of the ongoing grade 2 events, the other 2 being low neutrophils.

#3221 has grade 3 neutropaenia and has been referred to a haematologist. This is probably not related to vaccine.

#3153 and 3166 had lab error grade 4 low platelets, reported two calls ago. Following discussion about data management of these and similar events (eg pre-existing conditions that had been entered as AEs even though they were no worse than prior to the trial), Sheena wrote to Max who reported that he could delete the AE CRFs from the database if the clinical team provided him with a list. Sayoki reported that he believed Aybua could also do this, and agreed to follow-up with the team. After the call, Namo confirmed that he could delete AEs. Please note that this is an important list to be signed off when it comes to the Clinical Study Report.

Edna explained that the dates were incorrect in the circulated report for #4045 as her positive pregnancy test had occurred since the last call at her visit 8, not before February as the 'post abortion status' details implied. She had an induced abortion on 2nd May after which there was a small amount of vaginal discharge, not bloody. She is booked for an U/S to ensure no retained products, and to see a gynaecologist. Has she stopped immunizations?

Edna also reported #4064 whose repeat CD4 is ~1000, so presumably there was a mix up of specimens in the lab.

#4061 has intermittent raised unconjugated Br (2.42mg at the most, and last 1.81) which is assumed to be Gilbert's. He is asymptomatic with no signs, and has continued with immunizations.

Laboratory issues

Gunnel reported that she and the MUHAS lab personnel are in close contact with the MMRP lab. Regarding the issue of the cryo-preserved samples – they decided to wait and see what the results of the ICS on fresh cells were before determining what to do on cryo-preserved samples. MUHAS has almost completed the 4 colour ICS following the second MVA and MMRP has completed the 8 colour ICS following the first MVA (this was submitted to AIDS Vaccine) and is progressing through the samples following the second MVA. The Lab group is due another call soon.

3. Update on database validation and documentation

Liz completed the coding of events in an additional column on the spreadsheet extracted from the webdata, and an earlier spreadsheet circulated by Edna for CISPOC. There are one of two that need clarification, and I suggest we pick this up be email, and then have a specific call to resolve with the clinical group. What would be good to establish on the TMG is who should attend the call. Definitely the clinicians from all 3 centres, also Eric, Merlin, Arne, plus Sheena, Livia and Liz. Would Gail and other monitors also like to attend? And anyone from NIMR? This would be a good call to discuss the issue of whether or not to change procedures to report a change in grade on the CRF in TM II. Livia will organize this call, and it would be good to have Candida and Wolfgang too.

AP Livia to organize a date and agenda for a clinical data call

Another issue that Eric has highlighted was that of lab AEs. Once events are coded we could look at the lab events side by side with out of range labs, and flag any that look like they might need a clinical code for checking before we sign them off as clinically insignificant.

Key event lists that merit sign off as we approach the database lock include SAEs and primary safety and immunogenicity endpoints, withdrawals/early terminations, but there may be other useful lists such as ongoing, but stable events, indicating which are under continued follow-up and which are not considered clinically significant.

A database officer (Patricia) has started at Maputo, and was present for the visit by the NIMR team. Ayuba circulated a report of the visit on the day of the call, and Edna will go through it. The team had explained that there were two types of problem, one of which could be fixed immediately, and one which needed revision of the source code and took longer. There has been progress, but it was not possible to extract the data for this TMG, and there are still problems. For example, the dates in the ppt calendar for visits are not correct. Patricia continues to liaise with the NIMR team.

Sayoki reported on the previous call that plans were well underway for the TaMoVac II database. Ayuba and Thomas have now visited MMRP and Maputo and completed the needs assessment. John has organized a CRF workshop in Dar for 11th June. Sheena will try and find this email and forward it to Gail. The plan is to go through the TM01 CRF for TMII and identify questions that had been problematic. Gail, Sheena, Liz and Eric will provide feedback by email, but the main point they want to comment on is the transcribing of the diary card data onto so many CRFs. It would be much better to consolidate findings on one CRF. Gail and Sheena will send Arne examples. No-one has received an updated timeline for the database from the NIMR team.

AP Sheena to email Sayoki about NIMR issues including timeline

4. Monitoring

A draft SOP/working practice document for transfers should be included in the TaMoVac II documentation.

Gail has visited Maputo and is in transit on the way back to the US. There were only minor issues – well done CISPOC!

Gail introduced Shaquanda who is in the Clinical Operations team and MHRP and interested in monitoring – she will likely accompany Gail on her next visit.

Sarah and Livia (clinical epidemiologist with laboratory experience who previously worked on malaria and HIV treatment trials) will be visiting MUHAS, MMRP and NIMR in July in order to review the data management needs and progress, and to prepare for the next analysis workshop. They may be accompanied by a Clinical Project Manager (experienced monitor), if someone is in place at MRC CTU following the interviews on the 28th May. They expect to arrive in Dar on the 15th, transfer to Mbeya on the 18th, back to Dar on the 21st and back to the UK on the 22nd.

Eric also expects to be in Dar in July, to do the Dermavax training for both Tanzanian centres. Cellectis expect devices to be available in Tanzania from mid-July.

AOB and time of next call

TM01 AfrEVac amendment

MucoVac2: 29 enrolled, with 10 randomised to the three immunizations at the same dose as TM01 boost, 5 to intranasal, 7 in each of the IM/IVAG or low dose rgp140 groups. AEs continue to be mild-moderate only and of short duration. No-one has discontinued due to AEs and the first ppt has exited.

Product will be shipped on v4.0 and ppts can be enrolled on the basis of these approvals, but will have to resign consent to v4.1 when the approvals for this come through. Is there an update on this?

Please note, no product can be administered until the legal documents are in place, and Roger is anxious about this for two reasons. Firstly the insurance provider needs to be informed so we know that the insurance covers the trial ppts through to the end of September, and secondly, the agreement between Imperial and SMI needs to be signed. Roger and Sheena have checked the clauses and Roger will indicate which ones he would recommend are checked by SMI and MUHAS for accuracy.

AP Roger to send annotated agreement

IDRI has liability for manufacture, and Imperial for shipment of product. Muhammad confirmed that MUHAS has taken out insurance to cover medical costs for ppts if they are harmed in the trial, and to cover the investigators for their liability. This is sufficient provided it's in date.

Eric thought it would be a good idea to copy Peter as well as Eva on the TMG documentation.

Philipp has circulated the flow chart of CRFs and subject status form to all. No-one knew if the database was prepared for the additional visits, but Arne confirmed that Max was employed for a small number of hours to continue to support TM01 and this would be in his remit. Philipp will check with the data management team to see if this has been taken care of, and contact Max if not.

AP Philipp to follow up on TM01 database changes for boosts

Gunnel and Muhammad have had exchanges with the EDCTP office, having submitted the documentation on behalf of MMRP and MUHAS. This included funds for Agricola to go to Vicky Polonis's lab to do neutralizing antibodies, and potentially David Montefiorri's lab to do the PBMC neutralisation, although David had not yet been

contacted. Gunnel confirmed that Colman had completed the ELISA titrations, as for the HIVIS trials, but they needed clarification of the SOP for quantitative antibody responses. Sarah reported that this was now working well in MMRP after an initial blip because the team was not following the SOP precisely and the 5min development time was important. She noted the value of performing quantitative responses because this presence of an internal control permitted comparison across trials. This would be especially helpful for the responses following rgp140 boost in order to compare to MucoVac2 and HIVIS 07/08.

TMII protocol

This is ready to submit, subject to CVs (including mine, sorry) and signatures. Buma emailed those he needs responses from on 19th May. Arne reported that submission to TFDA can go forward in parallel to IRB, although approval will not be granted without the approval of the IRB. Eric will send the updated DNA IB to Bindiya and Arne. Buma has it. The MVA IB released by MHRP is an appended pdf.

AP Eric to send IB to Bindiya and Arne

AIDS Vaccine 2012 abstracts

Several abstracts were submitted to the conference – we should start to hear from today onwards.

The next call will be Thursday 21st June

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 26 May, 23 June Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

TM01_TMG_Notes_24November2011_Final

Notes of the
TaMoVac 01 Trial Management Group
Thursday 24th November 2011
08.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS

MMRP
Philipp
Bahati
Marco

NIMR
Sayoki
Mbazi

Imperial
Frances
Anna
Roger

LMU
Arne

SMI

MHRP
Gail

INS, Maputo
Edna
Ilesh
Bindiya
Nelson
Nafissa

MRC CTU
Sheena

1. Review of notes and action points

- Max to enable comment field for out of range values to be visible via webdata
- Sheena emailed visa letters
- DSMC guidance was not required, but Candida was ready after the London workshop
- TM01 v4 and PIS completed and submitted to IRBs

Points noted for analyses

- #3043 (elective surgery reported as AE on CRF). Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM02 CRF

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Need to ensure 3 ppts that appear in the line listing of AEs but that completed the study with no AEs are not counted in the numerator

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were taken from Mbazi's report of 18th November for MUHAS, Philipp's and Edna's report of 23rd November, and updated on the call.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		INS	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	18	21
Screened out *	58 F ~~114~~ 115M		187 (80)		22 (9 Female)	
HIV positive	~~2~~ 3				0	
Pregnant	~~3~~ 4 (V1 or 2)		4 (V1 or 3)		1	
ECG	25				3 (#4016,4032, 4021)	
Number enrolled	62 (25 female)		67 (29 female)		2 (1 Female)	
Number to replace						
Eligible, not yet enrolled					12 (4 Female)	
Number immunized:	Attend/vaccinated		Attend/vaccinated			
First	62/62		67/67		2	
Second	62/61		63/61			
Third	61/60		62/60			
Fourth	60/59		61/58			
Fifth	58/52		61/58			
Protocol deviations:						
Eligibility/enrolment					0	
Vaccination schedule					0	
Follow-up schedule					0	
Procedures					2 (#0409, 4004)	
Clinical issues:	269					
Reactogenicity						
SAEs	1 (#3117)					
EAEs	0					
Pregnancies						
HIV						
Grade 3						
Grade 2						
AE resolved	260					
SAE resolved	1					
Completed v17			55			
Completed v18			22			

A note for the publication/Clinical Study Report, is the need to determine the primary reason for screen out of ppts that have multiple reasons.

Recruitment Issues

53 volunteers have attended an informed consent seminar (28 females). 12 individuals are eligible but not yet enrolled. Progress is good, but the screen:enrol ratio is high with 22 screened out, which is higher than expected. The reasons are abnormal CBC (5 either low Hb, neutrophils or lymphocytes), hepatitis B (2) syphilis positive (5), at risk of HIV defined as >1 partner in the last 6m (5), hypertension (1), and ECG (2). A third individual had tachycardia on ECG (#4021) but she also had rheumatic heart disease and high blood pressure. It was agreed that she did not

satisfy criteria 12 in the inclusion. Edna clarified that ECGs were reviewed by 2 independent cardiologists in Mozambique, and in the event that they did not agree, the tracing was referred to Dr Chaitman in the US. Finally, one individual had withdrawn consent.

The positive syphilis serology has been confirmed and is higher than expected. Ilesh suspected this was a selection bias, and speculated about why a population with past history of syphilis, and presumably higher risk behaviours, would be more likely to come forward for a HIV vaccine trial, even though Phase I.

The team is working out the schedule over the Christmas period, and is confident they can avoid deviations.

Pharmacy Issues

There are no pharmacy issues.

Clinical issues

#2160 who is HIV positive with CD4 of 214 (9.7%) in August when VL >100,000 and 177 (9.7%) in September, has successfully transferred to care and started ART. She is expected for v18 on 19th December. Unfortunately her husband has left her.

2246 who was previously reported with fever and headache and negative malaria smear, developed chicken pox as did her child. The gap between these two illnesses was 3-4weeks, too long to associate them. Her scars are now healing.

2261 who is the pregnant ppt with anaemia has responded to folic acid and iron with Hb rise to 9.6, but subsequently developed asymptomatic pyuria. The team visited to treat her and found her to be in labour. They took her to hospital but she delivered on the way a healthy baby girl 3.3kg. She has now been discharged. The team will visit her at home for v17.

#2066 attended v18 on 19Oct but PT was not done in error and when she was recalled it was positive (14Nov). She already knew this and had taken misoprostol after which she bled for 9d. PT now negative and US normal with no retained products.

2259 who received an immunization whilst HIV infected because the tests were negative at the time. This ppt is doing well with CD4 of 427 and VL of 16,000. He returns for v17 next week and the team plan to refer him to care

In Mbazi's report, there are 9 ongoing events, 7 of which are labs (5 low Hb, 1 low platelets, I low WCC). Only one of these lab events is worse than mild: #3091 has a moderately low platelet count. #3209 complained of mild coughing, and #3098 has moderate otitis media. The majority of events are considered not related, but #3169 and #3069 have low Hbs that are 'probably not related'.

3215, a 25yrold male was reported by Patricia on 9th September to have suspected pericarditis following the first MVA/placebo. 2d post immunization he had local pain, and also reported nausea, joint pain and malaise and t=38^{o}C although not recorded in his diary. This was self-limiting and he had no symptoms 2wks after immunization. However, the T wave was inverted compared to v2-4 at this visit. Tropinin I negative. There are inconsistencies between the echoes, with the first and third showing normal pericardium, and the second suggesting pericardial thickening and a small pericardial effusion. The third suggested mitral valve prolapse with regurgitation. All three were conducted by different cardiologists and unfortunately the second video was not saved. Dr Chaitman reviewed the ECG and confirmed a change (assuming the leads were on correctly), which could be non-specific. It was agreed that non-specific changes in the ECG was the most likely scenario, but as a precaution, the echoes have been sent to the US and Sweden. Samples will also be

be sent to Sweden to check for antibody titres to potentially culpable viruses such as Coxachie.

#4011 had a headache 24 hours after immunization which was mild and of short duration. #4012 had a pain at the site of injection and a headache 6d later which was mild-moderate. He had also had a sore throat starting on day 2 after immunization and lasting 3d which the team thought to be viral. He was treated with paracetamol and ibuprofen.

Deviations and missing CRFs

#2043 and #2084 attended v17 outside the window, 6 and 7 wks late respectively. on 29th August, 4d out of the window. #2027 lives in Arusha and has missed v18- he is not responding on his mobile. #2021 who is due for v18 is also not responding – friends report that he is in Dodoma.

MMRP has had several biochemistry deviations due to the machine being broken.

#4009 and 4004 had blood collected in error as they were not eligible. The samples had already been processed and the volunteers informed of the results.

Out of range values

No comments.

Laboratory issues

The pooled immunology was reviewed in London during the analysis workshop, and circulated to the team. Well done to the immunologists who worked on all the assays and interpretation and Candida who worked on the analyses!

3. Update on database validation and documentation

There has been subsequent discussion on the missing values topic and Max suggested the use of '999' for missing lab results as it is not possible to put anything other than numeric values in these fields. Mbazi reported that this has not been implemented in the database but is being used in the analysis files. There was no update on this issue.

Sayoki reported that Thomas is still sick, and that NIMR is looking for a replacement to cover his sick leave. He also reported difficulty in accessing the MMRP database, and Phlipp suggested that Namo would be the best local contact in the absence of Max.

4. Monitoring

Gail and Kathleen will monitor Mozambique in January and then travel onto the Investigators Meeting. They will likely monitor MUHAS and MMRP after the meeting but the precise dates have not yet been finalised.

At the previous visit, it was agreed to draft a SOP/working practice document for transfers, and this will be done after the monitoring report is completed. The report is expected in the next 3 weeks.

Formatted: Bullets and Numbering

~~5.~~ AOB and time of next call

TM01 AfrEVac amendment

MucoVac2 has started, and the first ppt will attend her first safety visit on 25th November. Two more are screened in York, and St George's is expected to start screening for the first IN immunization next week.

TM01 v4 was finalized for IRB submission during the London workshop and has been submitted. These documents need to be circulated to the TMG group. TFDA has informed Buma that they wanted safety data for the submission. The key question is whether safety data from one ppt is sufficient. The next MucoVac2 TMG call is the 5th December, after which Sheena will email Buma and Muhammad with the anticipated numbers.

TM01 Interim analysis and request for DSMC

After review of the pooled data, it was clear to the assembled group that TM II needed to proceed with high dose DNA and that there would be little benefit in DSMC review as there were no immunologists on the DSMC.

A preferable solution is for the investigators to review the main analysis as soon as the last ppt has passed this timepoint in the middle of January. As she is an outlier in the overall schedule, the lab could complete the vast majority of the main analysis assays by the end of the year.

TMII Design call 22nd November 2011

A call was held on 22nd November to review the statistical power provided by the parallel group and the factorial design. A factorial design sets out to answer two separate questions with each of two randomisations. This is a good way to optimize power. It has been suggested that the first randomization address the question of DNA prime, and that the second randomization address the question of schedule. Whilst there is confidence in the 3 DNA groups that should proceed in TM II there is concern about reducing the gap between MVAs any further than it is already reduced in TM01 (4m). The merits of this second question might become clear at the workshop in February when the main analysis from TM01 was reviewed and compared to the HIVIS analyses. If it was possible to write the protocol in such a way as to allow flexibility to decide whether or not to proceed with the second question without submitting an amendment this would be ideal.

Further information with respect to the power if the design was non-inferiority was requested and will be circulated.

Arne had reviewed the gap that could be managed between MVAs given the constraints of the EDCTP grant timeline which meant the trial had to finish by July 2014. He estimated that the last enrolment could be February 2013 for a 72 week follow-up which would be needed to support a 24 week gap. This would require the enrolment to be completed in 8 months, which MMRP might manage but he thought would be more challenging for MUHAS. Mozambique thought they would manage 40 in the time period. A 16 week gap would require follow-up of 64 weeks.

The next call would be Thursday 15nd December: Arne will chair

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 26 May, 23 June Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac II and 01 Trials Management Group
Thursday 26th October 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 15.00 Tanzania

MUHAS	**NIMR**	**MMRP**	**CISPOC, Maputo**	**SMI**	**MHRP**	**LMU**	**Imperial**	**MRC CTU**
Muhammad	Sayoki	Marco	Edna	Gunnel	Tina		Roger	Livia
Patricia		Bahati	Bindiya	Eric			Frances	Sheena
Candida			Igor					
Mary								
Sue								
Gail								
Buma								

1. Review of September notes and action points

- Sue circulated draft programme for initiation
- Muhammad circulated dates for workshop
- Patricia and Philipp notified TMG of TM II approvals
- Livia has checked the numbers in Thomas's latest report

EDCTP No-cost extension for TM I

Queries have been addressed and returned to EDCTP and a response if expected by the end of October approving the NCE until the end of December for MMRP and MUHAS and until end of October for CISPOC. CISPOC has SIDA funds through to the end of June 2013 with which to complete TM01.

Potential publications

As well as the main paper, which would require at least the 4-colour ICS, and possibly some indication of the binding Ab to rgp160, it was thought that a second, more detailed immunology paper could follow. This could report the 8-colour ICS and more detail on the binding Ab once there had been a chance to understand what was going on. Finally a third paper would describe the protein boosts and resultant immune responses. This would give 3 people a chance to lead (6 if jointly led) and 3 a chance to be last author which was a good thing given the size of the network and efforts of so many investigators.

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were reviewed on the call, and updated for CISPOC only. Sue will go through Thomas's Final Data Management Report when she visits NIMR on the 27th October.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		CISPOC	
	Female	Male	Female	Male	Female	Male
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		208		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25/25	
Second	62/61		67/61		23/23	
Third	61/60		61/60		22/22	
Fourth	59/59		60/58		22/22	
Fifth	59/57		58/58		13/13	
Sixth	19/19		21/21		NA	
Seventh	19/19		20/21		NA	
Protocol deviations:					22	
Eligibility/enrolment	0		1		3 (all labs)	
Vaccination schedule	0		5		2 (#4024, 4025)	
Follow-up schedule	15		15		3 (late visits)	
Procedures	7		50		15	
Consent withdrawn					1 (#4063)	
Clinical issues:	302 (4 ongoing)		362 (11 ongoing)		353 (15 ongoing)	
SAEs	1 (#3117)		2 (#2160, 2259)		1 (HIV #4052)	
EAEs	0				0	
Pregnancies			1 (#2066)		2 #4045, 4038	
HIV			2 (#2160, 2259)		1	
Grade 3 or 4	7[1] (0 ongoing)		13 (#2246 ongoing)		4 (1 ongoing)	
Grade 2	56 (1 ongoing)		112 6 ongoing)		135 (18 ongoing)	
AE resolved	298		351		277	
SAE resolved	1		0		n/a	
Completed v17					Next week	
Completed v18	59 completed		All completed			

[1] 12 in TMG notes

In blue are the figures that cannot be derived from Thomas's data

From Livia's table which was prepared from Thomas's report

Number screened	83	152	120	151	44	33
Screened out *	58 F 115M (173)		91 F 113 M (204)		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25		30		2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	

Recruitment Issues

MMRP and MUHAS completed initiation training on 22nd and 25th October respectively. The teams are starting to think about recruitment to TM II and MMRP has a CAB meeting at the end of the month to launch the trial. The aim is to start screening in November, but this depends on database release, and the randomization list being validated. One question that arose was whether Dr Chaitman would be available to review ECGs during screening in case Dr Lakatari was travelling. Eric thought Dr Chaitman was not going to be available for the foreseeable future, but Tina will find out.

AP Tina to enquire with respect to Dr Chaitman's availability

TM01 (Tz) and TM01 (Moz) are fully recruited including for the rgp140/GLA boosts.

Pharmacy Issues

The main issue to flag is the way that replacements should be handled in the pharmacy records. The recommended practice is to take the next allocation envelope for the new participant that is replacing the one that has dropped out. If, as happened in TM01, a participant is replaced and given the allocation of the subject that has dropped out, the pharmacist will know in advance what the allocation is as there is no envelope to open. The clinic staff could, theoretically also know if it had been necessary to reveal the allocation of the subject being replaced. Merlin commented that this had not been an issue in past trials. Eric noted that this would require a change in the pharmacy procedures that Beryl had drafted. Sue and Gail had monitored pharmacy in MMRP so it would be good to talk this through with them.

Clinical issues

Igor will circulate the report tomorrow. Ppt 4038 who was pregnant has decided to continue her pregnancy. Edna reported that the team had responded to the DSMB request to report the HIV sero-conversion to other ppts, by explaining that they would continue to reinforce safe sex on a 1 to 1 basis during all visits, and that reference would be made to the possibility of catching HIV at the monthly meetings because the vaccine may have no effect and ppts could be on placebo. The team will complete all the MVA immunizations in Nov12.

Patricia reported that the ppt with otitis media has decided not to have surgery and is able to tolerate their symptoms. The ppt with anaemia still has a Hb 10.4 and continues on ferrous sulphate. The low neutrophils persist and remain asymptomatic. The protein boosts are in follow-up and there were no events of note to report.

Marco reported that #2032 attended for the safety visit.

There is nothing new to report from MucoVac2, and the further boosts are proceeding – there will be 8 in total who receive x5 rgp140/GLA.

Laboratory issues

Gunnel is pleased to report that the background in the gp160 assay has only resulted in 7 samples being excluded and is an Ag issue as there were no issues in the gp140 assay. 93% are reactive.

All 4 colour assays are complete but Gunnel was not sure about the 8 colour assays in MMRP. As agreed, only the 4 colour will be included in the main paper.

The lab group held a successful call to discuss the humoral assays. Vicky Polonis and Mary has been able to join in spite of the short notice, and the group had discussed functional Ab assays and agreed that it was not worth doing these in subjects that had only received DNA/MVA but would be interesting to see in those who received all 3 immunogens. The action points for IgG are as follows:

1. Share MMRP SOP for "finalization" with collaborators.

2. Finalize a TaMoVac JOINT SOP (by end of next week)
3. SMI proficiency panel
4. Exchange of samples subset –MTAs?

Sheena queried whether Robin's lab already have a proficiency panel and thought it would be worth checking before embarking on this.

AP Sheena to check with Robin re profiency panel

3. Monitoring

A draft SOP/working practice document for transfers between Tanzania centres should be included in the TaMoVac II documentation.

Gail and Sue completed monitoring in MMRP and there were only minor issues, the most notable being an informed consent on which a ppt had only printed their name. Gail advised that for TM II two lines are created on the informed consent so that it is clear the ppt needs to print and sign.

AP Patricia/Philipp to add a second line to the informed consent

TM II monitoring

Sue has drafted a Quality Management Plan and there may have been an opportunity to review this with Gail, although they have been busy co-monitoring and with initiation training.

***4.* Data management and database for TM01**

TM01 (timelines and responsibilities for report to EDCTP/Clinical Study Report (CSR) due end of September 2012)

20 August -	Draft the clinical study report (safety, primary immunogenicity) up to and including v18 to support Boston abstract and EDCTP activity report	Patricia/Candida with support from Sue/Livia/Wolfgang
21 September	Report for EDCTP completed	Patricia and Muhammad

Livia updated the first version of the CSR, adding tables, and Sue circulated this to Patricia and Candida, and may have a chance to collect comments whilst in Tanzania.

Philipp reported that the numbers screened were correct for MMRP, but the number screened out, which he did not recall reporting before, is wrong, and should be 208. Nhamo extracts the data from the local database and runs the programme in STATA to ascertain the numbers. Philipp recommended that Thomas contact Nhamo directly. I believe this has happened, but in Thomas's latest report the total is 204 and several other numbers that should not be changing still are. Sue will investigate when she visits NIMR on the 27th October.

Livia is still waiting to hear from Patricia regarding a few of the codes that she wanted to be checked.

Post-call note: following Sue's visit to NIMR and discussion with Candida, Candida will review the numbers in Thomas's report with Thomas and resolve inconsistencies.

Regarding the laboratory events that are '0'. Patricia knows that at least some of these are errors in laboratory processing eg when they all happened on the same day/week. These were to be deleted but Candida has watched John do this, and it is not possible. In earlier discussions we suggested those were all re-entered as '999'. A list was available for all such events up to v15, but would need to be reviewed again by the clinical teams to take account of all the visits. Eric asked John to put all these in the Queries spreadsheet. This exercise will need to be completed before Candida can create the laboratory event tables.

TM01 (CISPOC)

Most of the minor problems detected by Ayubu during his visit have been fixed, but not all.

5. Progress with implementation of TM II

TMII protocol

- All Tanzanian approvals are in place and
- Edna has received 2 pages of comments from the Mozambique IRB, including a request for a separate protocol for Doreen's sub-study, a shorter simpler information sheet to support informed consent and a declaration of conflict of interest from the monitors as they are employed by one of the partner institutions. They also requested an updated IB for MVA. Tina explained that they don't usually update it if it is only stability as this is sent separately but she will look into this and correspond with Bindiya.

APs Tina to correspond with Bindiya re IB and Sheena to send Edna the short information sheet used in MDP301

TM II CRF

This was finalized on 13th August although it's not clear that Eligius signed off. Sayoki will not sign off until the database has been tested, and indeed there is definitely a more recent version with date of last vaccination on the AE form CRF 6-I!

TM-II Database, data management plan and Randomisation list

Internal testing is complete, and John is working on the meta-data (the database requirements for each CRF item) to incorporate comments collected during the MUHAS presentations.

The database will be installed at MUHAS on 29th October and user-training will continue through that week. Installation and training at MMRP is scheduled for the week of 5th November.

Post-call note: the CRF will be finalised after the user-testing is completed in case of problems

The team will tackle the webdata view next. It could be possible to see the clinic databases but the NIMR team would like to know what tables and format the data would be needed in.

The data management plan has been circulated for comment. The list of responsibilities is pending from Candida.

Post-call note: the team need to start a Tracker document to detail all changes to the database.

Candida has been working with Wolfgang on the randomization lists which we agreed would be stratified by centre and gender. It is best practice to draw up a dummy list and check this works in the database, before drawing up the real list and putting numbers into envelopes.

TM II products

Shipment to Tanzania is imminent. Britta wants to sort out the Cellectis supplies and send everything together. Gunnel and Eric will keep TMG informed.

TM II initiation training

Eric had already conducted a comprehensive initiation training with the clinic teams, but this was some time ago. Gail and Sue have been running an initiation refresher supported on the phone by Arne, Philipp (for MMRP), Patricia (MUHAS), Eric (for MUHAS), Sheena, Livia, and Sarah.

We are planning initiation refresher for Mozambique before the workshop in February which is confirmed for 8-9th February. Unfortunately Merlin and Mary are unable to attend due to a clash. Edna raised the issue of funding. Sayoki has used the network budget to support the database development as he did not have funds for this. He is meeting with Eligius shortly to discuss this, but meanwhile Sheena will check the CTU budget as she thinks there is Data Services support that has not been, and likely will not be, used that could be transferred.

AP Sheena to check Data Services budget line item

TM II amendment

An application has been submitted to UK HVC for rgp140/GLA for half the volunteers in TM II. The proposal is to amend the current design and add a second randomization after completion of the DNA immunizations to MVA with and without rgp140/GLA at the same timepoint.

The UK HVC executive group would like to discuss the design with the TaMoVac investigators, in particular to ask if a protein only randomization might be considered. The TaMoVac investigators have discussed this and cannot see the evidence to support this suggestion. On this call, it was agreed that a sensible timeline to submit the protocol would be January when we have the results from the boost in TM 01v4.1 to support the amendment, and just about enough time.

Roger is trying to coordinate a call as soon as possible involving Gunnel, Eric, Muhammad, Eligius, Ilesh, Merlin and Arne/Chriss/Michael, but the earliest date that the majority of partners would be represented is 15th November. Eric cannot make this, but he felt that Gunnel could represent his view and it was important to have the call as soon as possible. Muhammad asked Roger to resend the dates to his yahoo address rather than the MUHAS email and he will check with Eligius.

The next call will be Thursday 22nd November

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 21 June, 26 July, 23 August Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayubu, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 26th July 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS	NIMR	MMRP	CISPOC, Maputo	SMI	MHRP	LMU	Imperial	MRC CTU
Muhammed Patricia Mary Buma	Sayoki Ayubu John	Philipp Marco	Edna Ilesh Bindiya Nelson	Eric Gunnel	Merlin Gail Shaquanda	Arne	Roger Anna	Sheena Sue Livia Liz?

Our deepest condolences to the family, friends and colleagues of the receptionist at the MUHAS/HIVIS clinic who sadly passed away on the 11th July.

ACTION POINTS 26th JULY 2012

- Buma to send weekly temperature records to Roger/Sarah obatined with the new temperature monitoring device
- Buma needs to delete Roger's name as 'aprover' from the mixing SOP and include the pharmacist at the site
- Buma and Revocatus to consider dummy run of mixing SOP using saline or equivalent
- Buma to follow up with Bindiya regarding the IRB submission at Mozambique and TFDA for TM II.
- Clinical team at MUHAS to sign off lists of AEs, withdrawals/early terminations and ongoing events that NIMR has prepared.
- Tina at MHRP to follow up the details of the MVA stability data and send new expiry date.
- Eric, Philipp, Arne and Gail to review Tamovac II CRFs and circulate final versions for all to check after which Eric will present the CRFs to Eligius for sign off. Need to revisit the creation of a working instructions file for the AEs CRF.
- Candida to prepare her visit to London on 20th August (including Visa application, etc) and bring with her the database extraction file to MRC for analysis with Wolfgang
- Lab group to complete the analysis of new immunology data from visit 18 in time for Boston (not essential for the EDCTP report).
- Patricia will lead the completion of the CSR and Muhammad will ask EDCTP for a template and circulate.
- Muhammad will finalize the budget for the no-cost extension
- Roger will continue trying to get the contract/MTA ready at Imperial

1. Review of June notes and action points

- Lucas took 2 continuous temp monitors to Dar, but unfortunately not the battery pack. Sarah J took out an alternative, and meanwhile the team logged manually. Roger received the manual temperature readings,
- Liz sent Roger the mixing SOP for rgp140/GLA and he sent on to the QP, and ultimately on to Buma and Revocatus. This will be incorporated into the Pharmacy file as part of the TMF, once approved by the pharmacist at each centre.
- Gunnel clarified that MMRP samples would also be analysed by Agricola for ADCC, but that this will not now include rgp140/GLA Ab post-boost due to time constraints (her visit is planned for 6th August to 30th September).
- Philipp rechecked TM01 database status with Max (see item 3)
- Eric sent IB to Bindiya and MUHAS but has not received comments yet. He has received comments from Arne
- Sarah only received a concept sheet from Philipp re the ECG abstract.

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were not updated due to time constraints, so please see Edna's report of 25th July circulated with the agenda.

	TM01-Tz				**TM01-Moz**	
	MUHAS		**MMRP**		**CISPOC**	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Number screened	83	152	122	152	44	33
Screened out *	58 F 115M		187 (80)		46 (24 Female)	
HIV positive	3				2 (both female)	
Pregnant	4 (V1 or 2)		4 (V1 or 3)		2	
ECG	25				2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized:	Attend/vaccinated		Attend/vaccinated		Attend/vaccinated	
First	62/62		67/67		25/25	
Second	62/61		63/61		23/23	
Third	61/60		62/60		22/22	
Fourth	60/59		61/58		13/22	
Fifth	58/58		61/58			
Protocol deviations:					21	
Eligibility/enrolment					3	
Vaccination schedule					2	
Follow-up schedule					2	
Procedures					14	
Clinical issues:	300 (10 ongoing)		333 (1 ongoing)		230 (19 ongoing)	
Reactogenicity						
SAEs	1 (#3117)		2 (#2160, 2259)		0	
EAEs	0				0	
Pregnancies					1 #4045	
HIV					0	
Grade 3 or 4	12 (1 ongoing)		10 (0 ongoing)		2 (0 ongoing)	
Grade 2	56 (3 ongoing)		102 (#2259 ongoing)		82 (13 ongoing)	
AE resolved	290		332		211	
SAE resolved	1				n/a	
Completed v17					0	
Completed v18	59 completed		All completed		0	

Recruitment Issues

All trials are fully recruited!

Pharmacy Issues

The MVA titres for MVA-CMDR Lot#07860210 have all been done and are with QA. Bindiya emailed a reminder that the expiry date is approaching – is there an update? Tina could not be on the call, but is aware and will follow this up.

The GP140 and GLA-AF are stored in the fridge in one of the immunology labs (which has air conditioning) and will be transferred to the pharmacy fridges at MUHAS when needed. These vaccines need to be stored between 2-8^{o}C and the UKHVC (who supplied the products) has requested data to this effect. There are now two temperature monitors in the fridge and 24

hour recording (16-17th July) using the device from London which showed that the temperature was maintained between 5.5-6.5^{o}C during this period. The temperature has subsequently stabilised between 4.5-5^{o}C and this is due to keeping the air conditioning on continuously. The temperatures in the pharmacy fridge in Mbeya are also satisfactory. Weekly logs of the fridge will be sent to UKHVC from now on (on Fridays).

Liz sent Roger the mixing SOP for rgp140/GLA used in MucoVac2 and he sent on to the QP, and ultimately on to Buma and Revocatus. This will be incorporated into the Pharmacy file as part of the TMF, once approved by the pharmacist at each centre. Buma does not anticipate a problem. Roger suggested doing dummy-run of procedure with saline vials or equivalent.

Clinical issues

Edna sent another comprehensive report, circulated with the agenda. She highlighted a laboratory problem that arose while processing blood samples collected from #4040 on visit 13 (5th July) for PBMC storage. Blood collection was repeated on the 13th of July, a minor out of window deviation. #4045 who had a positive pregnancy test at her visit 8, had an induced abortion (with misoprostol) on 2nd May after which there was a small amount of vaginal discharge, not bloody. Her U/S is clear of retained products, and she has seen a gynaecologist who has no concerns. She stopped her immunizations after receiving 2 DNA.

There are 22 volunteers still in the immunization schedule. #4025 and 4063 were unable to continue due to logistic reasons (moving, and too busy respectively). Ethics has given permission for #4061 (who is incarcerated) to continue, provided he is willing.

The eligibility deviations are marginally raised bilirubin (#4039 and 4061) and neutrophils of exactly 1.3 (#4068). The Trial Coordinating Committee was informed about the bilirubins in an email from Edna of 1st June 2012, and ethics, regulatory and DSMB have all been notified. The team has received a letter from ethics confirming that #4061 may continue with vaccinations.

#2259 had asymptomatic pyuria at the time of the May call. This event was recorded as UTI, but the team has confirmed on the telephone that the ppt was asymptomatic. Unfortunately this ppt (who has also serocoverted for HIV) is unable to attend the clinic. Given the absence of symptoms and normal creatinine throughout it was agreed to rename this event.

At the end of the trial, MMRP has 2 SEAs (HIV) that will be sign off soon and 4 stable grade 1 events (2 anaemia, one hyperopia and one elevated ALT).

#3098 did not have their ear operation as the local surgeon who was collaborating with the visiting specialist was away at the time of the visit. The team will refer him to another hospital. Patricia will check how severe the symptoms were/are in order to provide an appropriate grade for this ongoing event at exit as he has completed the schedule now. It is probably grade 2 as he continues to work and go about his daily business in spite of the discomfort.

NIMR showed Sue and Livia the lists of AEs that have been deleted from database (mainly lab events that are not AEs) but it was not clear which events had been actually deleted as the audit trail does not differentiate small changes due to for example, spelling errors being corrected, to real deletions. NIMR is writing a program to be able to extract the deleted AEs and John Mduda will prepare a list of these after extraction. Sayoki reported that the lists of deleted AE, withdrawals/early terminations, ongoing/stable events at exit are ready for sign off by clinical team at MUHAS.

Laboratory issues

Gunnel has reported by email that Colman Schau who has spent a month at SMI doing gp140 assays will go to MMRP to do these on the MUHAS samples, with another member from the laboratory team. SMI has sent all the materials and reagents for cellular assays for the 20 volunteers at MMRP, including for cryopreservation of PBMC. Agricola will travel to Duke to conduct ADCC assays, on specimens from both clinical centres.

3. Monitoring

A draft SOP/working practice document for transfers should be included in the TaMoVac II documentation.

Eric is currently in Tanzania to do the Dermavax training for both Tanzanian centres.

Sarah, Sue and Livia have visited MUHAS, MMRP and NIMR in July and thank everyone for their hospitality. Gail and Shaquanda also visited MUHAS and MMRP and are similarly grateful for being well looked after.
Eric, do you hold the Trial Master File documentation for SMI? If not, who does, or do you rely on the clinical centre files?

4. Data management and database for TM01

TM01 (timelines and responsibilities for report to EDCTP/Clinical Study Report (CSR) due end of September 2012)

Date	Action	Who
- 6th August	Send queries in clinic database to clinics	Nhamo and team/Thomas, Gladys and team
- 6th August	Send queries/corrections to CRF to local data management teams	Philipp/Patricia
- 6th August	Resolve queries arising from monitoring visit	Philipp/Patricia/Gladys/Nhamo
- 6th August	Generate lists from clinic to sign off	Philipp/Patricia
- 6th August	Generate lists from local database to cross check against clinic list	Nhamo/Gladys, Thomas
-15 August	Send queries from combined database to local data management teams for resolution with local clinic teams	Eric and Candida Ayuba and team
16-17 August	Extract data from combined database for Candida to analyse with Wolfgang's support	Ayubu and team
20 August-?	Candida visit to London for analysis with Wolfgang.	Candida, with support from Wolfgang
20 August -	Draft the clinical study report (safety, primary immunogenicity) up to and including v18 to support Boston abstract and EDCTP activity report	Patricia/Candida with support from Sue/Livia/Wolfgang
21 September	Report for EDCTP completed	Patricia and Muhammad

Wolfgang is following up with Candida re progress on analyses for CSR. Clinic data managers are working closely with the clinical teams to ensure a clean and complete dataset for the main analysis (up to and including v18). Eric is reviewing lists generated by Candida to clean the laboratory events (eg '0' to see whether genuine or missing, out of range values) and check the quality of key data (gender, age etc). Candida will carry out the analysis of immunogenicity and safety against demographic data with Wolfgang's assistance (including combination of immunogenicity data with main database) before/during/after her visit to London (planned for the week of 20th August). Patricia will be leading the preparation of the Clinical Study Report in close conjunction with Candida, clinicians and immunologists both in MMRP and MUHAS, and may accompany Candida to London. It was noted that the main immunogenicity analysis of the primary endpoint (v15, 2wks after the last MVA) has already been cleaned, and locked and was held in Excel spreadsheets. Gunnel asked about the plan for the v18 ELISpot and it was agreed to consult the lab group, especially Lotta and Chriss, to determine a comfortable timeline to complete these analyses, review, finalise and sign off for the Clinical Study Report.

Eric suggested that Muhammad write to EDCTP to find out whether there is a template for the report they expect in September. Sheena noted that there is ICH guidance on the format and content of the Clinical Study Report format, which we would ideally work towards. There were two options for the scope of this report: 1) the main report up to and including v18 with a supplementary report describing the boosts or 2) a single report through to the final visit of the last ppt that was boosted.

Points for Candida to note for analyses

- #3043 (elective surgery reported as AE on CRF, and flagged by MRC CTU during their visit
- Data management to be detailed in the Statistical Analysis Plan, and revisited for the TM-II CRF.

NB this is not specifically addressed in the SAP v1_110512 or v2_110728 under definitions

- Nhamo to delete the AE forms for the 3 ppts that appeared in the line listing of AEs but that completed the study with no AEs to ensure they are not counted in the analysis
- Presentation of individuals screened out if multiple reasons given. A list of reasons for screen out need to be reviewed to determine how this will be presented in a CONSORT diagram – we may need to identify a hierarchy of reasons.
- Need to review clinical AE that are laboratory events against the lab values.
- Key event lists that merit sign off as we approach the database lock include SAEs and primary safety and immunogenicity endpoints, withdrawals/early terminations, but there may be other useful lists such as ongoing, but stable events, indicating which are under continued follow-up and which are not considered clinically significant. NIMR would like clarification on 'early termination' and 'stable events'.

TM01 (CISPOC)

Are the small residual errors in the CISPOC database, including dates in the ppt calendar, fixed?

TM01 v4.1 boosts

V4.1 database

Max has restructured the database to include the CRFs to support rgp140/GLA boosts. Further restructuring to add a screen out CRF will delay immunizations and therefore an alternative approach has been proposed. MMRP and MUHAS have entered v19 CRFs for the willing ppts, a small number of whom are ineligible at MUHAS.

EDCTP No-cost extension

Muhammad is waiting for a response from Michael, Gunnel and MUHAS on revisions to the personnel budget for EDCTP. Arne will chase this up but did not think any additional personnel were required for MMRP. Gunnel recommends to ask EDCTP for as little as possible in terms of personnel as the most important thing is to ask for is funding for the peptide pools which have already been paid in advance by Munich (EUR 40,000).

Sayoki asked whether travel money could be included in the budget as they are assisting the Mozambique team with the TM01 database and the first grant has finished. Muhammad did not think EDCTP would fund travel and suggested to the Mozambique team to ask EDCTP directly for a travel budget.

Contract/MTA at Imperial for Tamovac I boost amendment:

Roger is calling partners everyday. Imperial is currently checking their insurance.

MucoVac2 update

MucoVac2 immuunisations by group are as follows:

	Dose 1	Dose 2	Dose 3
1 IM ld	8	6	5
2 IM hd	9	9	5
3 IN	5	5	3
4 1 IM hd + 2 IVAG	8	8	6

There have been two SAEs – 1) an accidental paracetamol overdose in a ppt who had a dental procedure and then took at least the maximum number of paracetamol allowed for 2-3 days afterwards. When she felt nauseous she was worried that she might have over-dosed, went to Accident and Emergency and they treated her accordingly which required admission; 2) 1 participant on the low dose IM rgp140 developed an labial abscess (vulval) and had to be admitted for drainage. Otherwise, AEs continue to be mild-moderate only and of short duration. No-one has discontinued due to AEs (including the SAEs).

The amended TM01 v4.1 protocol received approval from the MUHAS IRB and TFDA, but still waiting for response from the MMRP IRB. Meanwhile, MMRP can screen on v4.0. MMRP have

carried out 1st and 2nd data entries which went well except for the visit 19 contact form. The MMRP IRB had expressed concern because the information on MucoVac2 reflected an earlier stage of the enrolment. Philipp has sent an update to the chair but he has been out of town. Product is in Pharmacy. However, the agreements are not finalized and Roger was worried because the individuals that were familiar with them were on holiday during parts of the period that followed the last call. Please can we have an update?
Unfortunately the EDCTP office rejected the request for additional funds, principally because the sum requested was exactly the amount returned by AfrEVac. The officers (Pauline) have provided the opportunity to go back with a lower budget that reflects the actual needs and the MUHAS/MMRP teams are working on this now with some urgency. This includes the costs mentioned under Laboratory Issues. Michael recommended a no cost extension until the end of the year, but Sheena thought this would be impossible because of EDCTP's obligation to report to Gates by then and their need to review the reports and finances before sending to Gates. Michael made contact with EDCTP who are supportive. I met Hager at AIDS 2012 and she confirmed the need to report to Gates at the end of December and their need for reports to review by the end of September. After the last call, a draft was circulated to go to ECTP, and further work was done on the budgets. Do we have an update?

5. Progress with implementation of TM II

TMII protocol

- Submitted to local MUHAS IRB without IB and got approval.
- MMRP IRB has not approved protocol yet and NIMR IRB will discuss it on 27th July.
- Maputo IRB: translation to Portuguese done and protocol submitted on 17th July.
- Submitted to TFDA on 23rd July 2012 by Buma which according to Eligius, was an expedited submission which should take approx. 45 days. The IB was included.
- Hopefully all approvals ready by September. Buma to follow up with Bindiya regarding Mozambique regulatory submission.
- Database might actually go live by October

TM II CRF

Regarding the CRF review exercise for TM II: changes proposed during the CRF harmonization meeting and afterwards including in the last TMG notes, have been incorporated and CRFs sent to a group that included Eric and Arne on 23rd July. Eric noted that some points had not been changed, CRF-10 is not in the final form yet, because it doesn't not leave room for the clinical evaluation. Gail asked if she could also be copied in as she has comments based on errors noted during monitoring visits. Sue Fleck will review against changes noted in the June TMG notes. Eric, Philipp, Gail and Arne will review again and Arne will collate comments into the next, hopefully final, version. Eligius Lyamuya will sign off as main PI and it was agreed that Eric and Sayoki should also sign off. The "No AEs throughout study" info will not be entered in the list of AEs in database as it created problems in Tamovac 1 and MMRP proposed that the same should apply to the Previous conditions CRF and Concomitant medications which have a similar "No previous conditions identified throughout the entire study" and "No concomitant Medications identified throughout the entire study". Sayoki noted that it will take a month of programming to make the changes, assuming they are relatively minor.

Sites do not feel they need a working file with instructions on how to fill the AE CRF as CRF footnotes are clear and also there is the MOP. MRC and MHRP monitors still think this would be advisable to achieve consistency across three clinical centres. This can be discussed further on the clinical coding call planned for August, after Livia returns from holiday on the 16th.

Two points were discussed on the TMG call. Firstly the issue of 'replacing' an event. During the visit (see item 4) the clinical teams were clear that the AE should only be replaced if there is a change in diagnosis but not a change in grade. CRF 10 now includes all the diary cards but diary cards will still be in the form of a booklet for each day post-vaccination.

MEDdra coding will be done for TM II and MRC will assist with this.

TM-II Database and data managemet plan

Aybua will continue to update the timeline for the database, which NIMR expects to be ready by early September for user acceptance tests and live by October. NIMR has drafted a data

management plan, and will send this to MMRP and CISPOC. MMRP also have an internal data management plan ready. Ayuba planned to visit Maputo on 21st July to help set up the database, but there was a lack of clarity about how this visit would be funded.

NIMR have drafted a data management plan

TM II products

Shipment cannot happen until the approvals are in place. Gail noted that she would need to give 90 days notice before travel for an initiation visit, and that this timeline was rapidly approaching for an October start. It might not be necessary to have a full and formal initiation, as it will be the same personnel and similar CRFs. It could potentially be done by web or phone, supported by a monitoring visit shortly after screening and enrolment begins.

The next call will be Thursday 27th September

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

Committees/Groups	Teleconference schedule (as a general rule)	Membership (main participants) Full membership lists are available on demand
AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 21 June, 26 July, 23 August Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayuba, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

Notes of the
TaMoVac 01 Trial Management Group
Thursday 27th September 2012
09.00 EST, 13.00 UK, 14.00 CET and Mozambique, 16.00 Tanzania

MUHAS	**NIMR**	**MMRP**	**CISPOC, Maputo**	**SMI**	**MHRP**	**LMU**	**Imperial**	**MRC CTU**
Muhammad	Ayubu	Philipp	Edna	Gunnel	Gail	Arne	Roger	Livia
Patricia	Thomas		Ilesh		Kathleen		Frances	Sue
	John		Igor				Anna	Sheena

Edna requested that Igor, Khosa and Naisa (the clinicians) be added to the TMG email list. Igor will be presenting while she is away.

1. Review of August notes and action points

- Lab group to complete the analysis of new immunology data from visit 18 in time for Boston (not essential for the EDCTP report) – see Laboratory Issues.
- Gail checked August notes and these are satisfactory re ppt letters
- Nhamo checked pharmacy data for #2016 and this is now correct
- Edna discussed dates for Maputo visit with Eric and they agreed the first week in December

EDCTP No-cost extension for TM I

Muhammad confirmed that the financial reports had been submitted and that he was now dealing with queries, and collecting responses from the collaborators which he was compiling. The good news was that EDCTP had released the final 5% payment so that MUHAS was no longer in dire straits. He anticipated the full response regarding the no cost extension will come in time. Arne queried how the Maputo TM 01 trial would complete as the NCE only went to the end of December and Muhammad explained that they would use their co-funding from SIDA.

2. Update from clinical research centres

Community/Clinic/Pharmacy issues

The following numbers were updated on the call.

	TM01-Tz				TM01-Moz	
	MUHAS		MMRP		CISPOC	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Number screened	83	152	122	152	44	33
Screened out * **HIV positive** **Pregnant** **ECG**	58 F 115M 3 4 (V1 or 2) 25		~~187 (80)~~ 208 4 (V1 or 3)		46 (24 Female) 2 (both female) 2 2 (both male)	
Number enrolled	62 (25 female)		67 (29 female)		25 (14 Female)	
Number replaced					1 (#4025)	
Eligible, not yet enrolled					1 (out of window)	
Number immunized: **First** **Second** **Third** **Fourth** **Fifth** **Sixth** **Seventh**	Attend/vaccinated 62/62 62/61 61/60 60/59 58/58 19/19 19/19		Attend/vaccinated 67/67 63/61 62/60 61/58 61/58 21/21 20/21		Attend/vaccinated 25/25 23/23 22/22 22/22 12/12 NA NA	
Protocol deviations: **Eligibility/enrolment** **Vaccination schedule** **Follow-up schedule** **Procedures** **Consent withdrawn**	2 2		13		22 3 (all labs) 2 (#4024, 4025) 3 (late visits) 15 1 (#4063)	
Clinical issues: **Reactogenicity** **SAEs** **EAEs** **Pregnancies** **HIV** **Grade 3 or 4** **Grade 2** **AE resolved** **SAE resolved**	302 (4 ongoing) 1 (#3117) 0 7[1] (0 ongoing) 56 (3 ongoing) 290 1		362 (11 ongoing) 2 (#2160, 2259) 2 (#2160, 2259) 13 (#2246 ongoing) 102 (#2259 ongoing) 332 0		296 (19 ongoing) 1 (HIV #4052) 0 2 #4045, 4038 1 4 (1 ongoing) 135 (18 ongoing) 277 n/a	
Completed v17 **Completed v18**	59 completed		All completed		0 0 expected Oct12	

[1] 12 in TMG notes

Recruitment Issues

All trials are fully recruited for DNA/MVA, and the protein boost. The protein boosts are completed at MUHAS but the last one is delayed and may not take place at MMRP if the ppt is confirmed to be pregnant on monday.

Pharmacy Issues

There was no pharmacy representative on this call due to problems with the land lines.

Clinical issues

Since the last call, Edna had reported two events. Firstly ppt 4038 whose urinary pregnancy test was positive at visit 14 and whose vaccination regimen has been discontinued. She was unsure about continuing with the pregnancy. The team has counseled her, and is awaiting her decision. Her phone was switched off this week, but they will continue to try and contact her and support her. Secondly ppt 4052 who is now confirmed HIV positive (case report circulated with agenda). Edna reported that the team had been looking at the algorithm for HIV testing and in future would use RNA PCR at an earlier stage, especially if there was clinical suspicion of seroconversion. Edna informed the TMG that their DSMB had asked the investigators what they would tell other ppts about this event, and she asked how best she should respond to this question. There was a discussion that followed noting the GCP principle that information shared with ppts needs to be sanctioned by the local IRB, and the potential for controversy which needed to be handled in a manner appropriate to the local environment. Frances asked what one would do if a ppt asked directly, and Sheena responded that she would remind ppts that everything collected and recorded was in confidence and therefore could not be shared broadly, but that HIV seroconversions had occurred in other HIV vaccine trials for two reasons – the vaccine did not reduce risk, and because the trials have included a placebo group. Muhammad still favoured a more open approach with the ppts, because being transparent minimized the risk of controversy. The danger of this for CISPOC is the small number of volunteers, many of whom will know each other from the trial. Kathleen encouraged PIs to have a good relationship with local media, in case of controversy, and Muhammad pointed out that the media could be unpredictable – everyone agreed. As a minimum, the event should be shared with the trial team and the importance of undertaking risk reduction counseling at every visit emphasized, together with reminders to ppts that there was a placebo group in the trial and that no-one knows whether this vaccine regimen will reduce risk.

At the end of the DNA/MVA main trial, MMRP had 2 SAEs (HIV) and 4 stable grade 1 events (2 anaemia, one hyperopia and one elevated ALT). MUHAS had 1 SAE (infection following head trauma requiring hospitalisation) and 3 events that are ongoing, but likely to be resolved in the near future (otitis media, anaemia which is being treated, low neutrophils).

To date, the rgp140/GLA immunizations have been well tolerated with no memoral adverse events. Philipp recall one ppt with moderate pain at the injection site, and moderate headache but otherwise only mild events. He reported ppt #2066 whose urinary PT was negative when read at the recommended timepoint, but which turned positive a few minutes later. The team checked serum HCG and this was also positive, so they did not proceed with her second immunization but asked her to reattend. They have not yet reported this pregnancy to the IRB as it is not confirmed, and indeed she is not pregnant according to the technical interpretation of the UPT. One further ppt, #2032, will be 2d outside the visit window for her safety visit following the second immunization as she was out of Mbeya. She was fine at the telephone check, and still fine when she telephoned in the information that she would not be able to attend.

There is nothing new to report from MucoVac2, and the further boosts are proceeding.

Laboratory issues

Gunnel reported that the Lab group has had a number of discussions in Boston. Lotta spent the last 10d in MUHAS, and the v18 ELISpot and 4-colour ICS are all complete. Analyses will be completed in the next 2 weeks. The MMRP team has also made good progress but as they are doing 8-colour ICS, it has taken longer. Arne reported that Chriss and co were also well advanced. Arne asked about the binding Ab. Gunnel informed the TMG that there was a problem with the latter that would require further investigation in that the background activity in specimens tested to date was very high in 25%. This was unexpected based on the preceding trials, in which background was low and the lab team in Stockholm would be focusing on this issue next week. The plan for Colman to analyse the remaining specimens in MUHAS was slightly on hold pending the result of further investigation and discussion.

There was also a discussion regarding publications. As well as the main paper, which would require at least the 4-colour ICS, and possibly some indication of the binding Ab to rgp160, it was thought that a second, more detailed immunology paper could follow. This could report the 8-colour ICS and more detail on the binding Ab once there had been a chance to

understand what was going on. Finally a third paper would describe the protein boosts and resultant immune responses. This would give 3 people a chance to lead (6 if jointly led) and 3 a chance to be last author which was a good thing given the size of the network and efforts of so many investigators.

3. Monitoring

A draft SOP/working practice document for transfers between Tanzania centres should be included in the TaMoVac II documentation.

TM II monitoring

Sue has drafted a Quality Management Plan. MHRP will comment, after which it will go to Eric and Eligius, and then to the TMG for comment.

***4.* Data management and database for TM01**

TM01 (timelines and responsibilities for report to EDCTP/Clinical Study Report (CSR) due end of September 2012)

20 August -	Draft the clinical study report (safety, primary immunogenicity) up to and including v18 to support Boston abstract and EDCTP activity report	Patricia/Candida with support from Sue/Livia/Wolfgang
21 September	Report for EDCTP completed	Patricia and Muhammad

Livia updated the first version of the CSR, adding tables, and Sue circulated this to Patricia and Candida.

Muhammad circulated a draft technical report for EDCTP on 25 Sep, and Arne has amended this. NB MRC address is incorrect.

There remain issues with inconsistencies across the tables derived from the data. The tables are populated as follows:

- by the clinical teams on the calls using the clinic records, although this is not true for all data items, some of which are populated from Thomas's regular reports
- by Thomas ?how
- by Candida and Wolfgang after Candida/? extract data from the combined database

Philipp reported that the numbers screened were correct for MMRP, but the number screened out, which he did not recall reporting before, is wrong, and should be 208. Nhamo extracts the data from the local database and runs the programme in STATA to ascertain the numbers. Philipp recommended that Thomas contact Nhamo directly. The pharmacy database is now correct for #2016, and all the numbers for each immunization correct so it is difficult to explain how Thomas retrieved a different number this morning to yesterday. Unfortunately although the NIMR team were on the call, at least in part, the line was too poor to hear them.

When Candida was with us in London she and Wolfgang were working with the extract form 22nd August to populate the safety table for the poster. We were happy that the numbers were correct in the baseline tables, although there was the one inconsistency between the main tables and the pharmacy tables to resolve at MMRP (#2016 the ppt who received 2 DNA and was then replaced by # 2200). This dataset is the last freeze before the boosts, and as such precious.

The database is still 'live' to support the protein boosts and therefore things could have changed, but the number of grade 3 and 4 events cannot go down – unless the excess is the lab events that we deleted because the platelet machine was faulty. Thomas sent an email this morning saying that the numbers all match now.

AP CTU to pick up email trail with Thomas

Livia has highlighted a few of the codes that she particularly wanted Patricia and Phillip to check, including the events where there are two possible codes eg malaria and headache, and urinalysis results.

Regarding the laboratory events that are '0'. Patricia knows that at least some of these are errors in laboratory processing eg when they all happened on the same day/week. These

were to be deleted but Candida has watched John do this, and it is not possible. In earlier discussions we suggested those were all re-entered as '999'. A list was available for all such events up to v15, but would need to be reviewed again by the clinical teams to take account of all the visits. Eric asked John to put all these in the Queries spreadsheet. This exercise will need to be completed before Candida can create the laboratory event tables.

One further issue identified is the presence of reactogenicity events prior to immunization. In previous vaccine trials, such events have been dropped if they continue at the same grade to resolution, but included if they go away and reappear within the 7 days post-immunisation.

TM01 (CISPOC)

Ayubu travelled to Mozambique on 26th August for 5 days. He is fixing minor problems detected during his visit with the current database. He did a needs assessment for TM II. The server will be fine and he installed Windows Server 2003.

Boston posters/oral

Well done Patricia, Philipp and Asli (and Chriss)!

5. Progress with implementation of TM II

TMII protocol

- Local MUHAS IRB has given approval.
- MMRP IRB – may have met in September but the coordinator is out of Mbeya this week. Philipp will contact him on monday
- NIMR IRB has give approval.
- TFDA have not yet, and Buma sent an email yesterday as the time for expedited review is almost at an end. The Director responded to indicate that he would facilitate a speedy response
- Mozambique IRB and regulatory authority – not so urgent as CISPOC does not plan to start before February

TM II CRF

This was finalized on 13th August although it's not clear that Eligius signed off. Sayoki will not sign off until the database has been tested.

TM-II Database and data management plan

The CRF questions are in the database, and testing will start next week. John has started work on the meta-data (the database requirements for each CRF item) and will continue with this. There is a Tracker to document all changes made to the database. They are only a week behind the timeline, implying the database will be ready for use by 28th October, and they plan to make it available through the website. NIMR has drafted a data management plan, and shared it internally, and with MMRP who have sent comments back. MMRP also have an internal data management plan ready.

TM II products

Shipment cannot happen until the approvals are in place. Gunnel confirmed that the vials were ready to ship.

TM II initiation training

CTU and MHRP strongly recommend initiation training to ensure the clinical and data management teams are clear about the differences between the preceding trial and TM II, and to avoid some of the problems we have encountered in TM01. This could be done on the phone using slide sets (protocol review, pharmacy and product administration issues, CRF completion, AE and SAE reporting) but we know that Gail will be in Tanzania 21-27th October and that Sue can join her, and having someone on the ground to do face to face training would make a big difference. Arne confirmed his willingness to cover the protocol and highlight differences between TM 01 and TM II. It was hoped that Eric would also cover Pharmacy issues. Sue will draft a programme and assign names for presentations and circulate for comment. Patricia will let TMG know as soon as TFDA approve. Philipp will let

TMG know as soon as local IRB approve. We will work towards 21st Oct training as the early December date is too late for Tanzania, but would be good for Mozambique. Indeed, training around the time of the investigator workshop, which it is hoped will be in Mozambique, could also work very well. It was noted that Gail would need to book her travel by 1st November. Muhammad will circulate dates for the workshop.

AP Sue to circulate draft programme for initiation; Muhammad to circulate dates for workshop; Patricia and Philipp to notify TMG of approvals

TM II amendment

An application has been submitted to UK HVC for rgp140/GLA for half the volunteers in TM II. The proposal is to amend the current design and add a second randomization after completion of the DNA immunizations to MVA with and without rgp140/GLA at the same timepoint. There was email discussion regarding the pros and cons of factorial design. The main risk is that we have to analyse the groups as 6 separate groups and have insufficient power to draw any conclusion from the comparison.

In general this was well received, The UK HVC executive group would like to discuss the design with the TaMoVac investigators, in particular to ask if a protein only randomization might be considered. Sheena will work with Roger to coordinate a call as soon as possible involving Gunnel, Eric, Muhammad, Eligius, Ilesh, Merlin and Arne/Chriss/Michael. Roger reminded the group that it takes ~25 days (timelines on p1 of the application) as the application goes from the core group to the Steering Committee.

AP Roger and Sheena to organize joint call to discuss design

The next call will be Thursday 25th October

Calendar of meetings – AfrEVacc / TaMoVac / UK HVC

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AfrEVAcc Disciplinary Team Group (DTG) - **Updates on site activity and monitor of progress across the project** - **EDCTP communications and finance**	**Monthly:** 1st Thursday of the month, 12-1pm UK 2 June, 7 July, 4 Aug etc. [Dates set in advance for the year]	Representation from all partners (PI, social science, clinical, other operational staff). Imperial, MRC CTU, CHUV, Wits RHRI (Jburg), Wits CLS (Jburg), Africa Centre (UKZN), CISM Manhica (Moz), UCM Beira (Moz), LMU, MMRP (Tanz), University of Amsterdam (link with Beira site), FRCB (link with Manhica)
TaMoVac Trial Management Group (TMG) - **Clinical trial progress, clinical and lab issues, data management, database validation, monitoring, AOB including update from PSC on protocol amendment, EDCTP communications, project implementation in Mozambique**	**Monthly:** Tend to be 4th Thursday of the month, 08.00 EST, 13.00 UK, 14.00 CET, 15.00 Tz 21 June, 26 July, 23 August Call, agenda and notes organised by MRC CTU (Sheena) for MUHAS (Muhammad), MMRP (Leonard) and INS (Ilesh)	MUHAS – Muhammad, Patricia, Thomas, Buma MMRP – Philipp, Bahati, Marco NIMR – Sayoki, Ayubu, John, Mbazi INS – Ilesh, Edna, Nelson, Bindiya, Nafissa LMU – Arne, Max SMI – Eric, Gunnel, Lotta MHRP – Merlin, Mary, Gail, Beryl, Kathleen MRC CTU – Sheena, Liz, Sarah Imperial – Frances, Anna, Roger, Kylie
TaMoVac Project Steering Committee (PSC) - **Progress against workplans, cohort studies, update from TMG on trial progress, protocol development, lab capacity building, student progress, communications with the EDCTP and finance**	**6 weekly:** Wednesdays? 1-2pm 29/30 June (tbc), 10 Aug (tbc), 14 Sept (tbc), 26 Oct (tbc), 7 Dec (tbc), etc. Call, agenda and notes organised by Imperial (Kylie) for MUHAS (Muhammad and Eligius)	MUHAS – Muhammad, Eligius (joint chairs), Hassan MMRP – Leonard NIMR – Sayoki INS – Ilesh LMU – Michael, Arne SMI – Eric, Gunnel, Britta MHRP – Merlin, Mary MRC CTU – Sheena Imperial – Frances, Kylie
TaMoVac Lab eGroup **Lab endpoints, assays, training issues**	**Ad hoc calls to support email discussion** Call, agenda and notes organized by SMI (Gunnel/Lotta)	MUHAS – Said, Eligius, Agricola MMRP – Lilly INS – Nelson LMU – Christof, Michael SMI – Gunnel, Lotta MHRP – Merlin, Mary MRC CTU – Sarah Imperial – Frances, Anna, [Lea, Robin]
Rgp140 assay eGroup - **Follow on from wet lab training in Tanzania, Feb 2011** - **discussion of assay results, assay set up at sites, problems with running assays**	**6 weekly:** Tuesdays 11am-12pm UK 12 May, 14 June, 26 July, 6 Sept, 18 Oct, 29 Nov, 17 Jan 2012, 21 Feb 2012, 3 Apr 2012 Call, agenda and notes organized by Imperial (Lea, Nicola and Kylie)	Staff who attended wet lab training in Tanzania, Feb 2011 Imperial – Nicola, Lea, Anna, Kylie (minutes) MRC CTU –Sarah LMU – Christof MMRP - Lilly, Connie, Onesmo, Christina MUHAS – Agricola, Fauster, Colman (Said) NIMR – Nelson CISM Manhica – Nilsa (AfrEVAcc) SMI – Gunnel, Lotta

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First round of queries for the final technical report for TaMoVac-01

Dear Prof Bakari,

Thank you again for submitting your final technical and financial reports for your EDCTP project entitled "HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA priming and MVA boosting strategies (TaMoVac-01)"

The reviewers felt that "*considerable achievements were made in a step-wise capacity building approach to conduct HIV clinical vaccine trial from HIVIS-01 through to Tamo-vac-01 work packages*".

1. **Overall comments**
   The report was well written. Great care was taken to present the information in a clear, concise manner. This was much appreciated. I note your comment that the final report template should be provided at the beginning of the project. Usually this is the case but the re-design of the template was done quite recently, which is why it was sent to you so late. I am sorry for the extra work that this caused you.

2. **Immunology results**
   a. Immunogenicity was demonstrated in the HIVIS study as per the vaccine publication, though the statement in the report that the Nab assessment was ADCC dependent was not explicit in the paper. It will be technically important to clarify this result.

   b. Preliminary analyses of TaMoVac-01 WP2 should provide information on the immunogenicity of either Env and gag separately and when used as pooled immunogen; if these results are still being analysed, an indication of any improved magnitude of response compared to what was earlier obtained in the HIVS-03 will be useful.

   c. It is noted that in section 2.4, you have found that 3 years post-immunization, immunogenicity has waned amongst volunteers of the HIVIS03 continuation study. What are the implications of this?

3. **Publications**
   Most of the publications cited do not acknowledge EDCTP as the funder (with the exception of the Bakari *et al.* Vaccine 2011 paper). Can you please clarify whether these publications have data from TaMoVac-01? If so, why was EDCTP not acknowledged?

4. **Sub-studies**
   a. In section 2.4 (page 5), there is a list of sub-studies mentioned. Were these part of TaMoVac-01? (i.e. were TaMoVac-01 funds that were used to conduct these studies?). Could you indicate for each sub-study the source of funding

5. **Clinical trials (section 3, pages 9 – 16)**
   a. It is noted that 2 clinical trials have been registered under PACTR (WP1 and WP2), one under clinicaltrials.gov (WP3), and one under controlled-trials (WP1).

	Registration numbers (final report)		***Possible other numbers***
WP1	ISRCTN90053831	ATMR2009040001075080	PACTR2009040001075080
WP2	PACTR2010050002122368		PACTR201106000304583
WP3	PACTR2010050002122368		NCT01407497

We have found other registration numbers associated with the three clinical trials. The PACTR registration under number ATMR_080 for WP1 could not be found. Could it be under PACTR_080?

For WP2, we have found two entries. The first one, PACTR_368 is the trial before the addition of the rpg140. The other registration, PACTR_583 has the rpg140. Are these trials considered to be separate?

For WP3, the same PACTR number was reported than the WP2 trial. Is there a PACTR number for this trial? We also found a clinicaltrials.gov registration number. Can you verify if this is correct?

We have noted that all of these registries are out-of-date (for example, WP1 is still listed as in follow-up, WP2 trials are still recruiting, the last update from the WP3 trial was on October 2012). Can you please update these registries?

b. Youth trial – recruitment was projected to end in March 2013. Has this occurred?

c. Neonate feasibility study
Given that only 36 respondents participated in the survey, it is difficult to make any strong assertions about willingness to participate. Do you have any plans to extend the study or how does this finding compare with results elsewhere?

d. Can you please provide the close-out monitoring reports?

6. **Capacity building**
   a. Development of infrastructure was attained through this grant but an indication of how clinical trial unit was developed in Mozambique was lacking. According to the report, *Regulatory capacity has been strengthened as witnessed by the approval process for TaMoVac II. This is particularly true in Mozambique*. Could you explain how this was achieved – was any support provided to improve the standard of Ethics in Mozambique to circumvent the slow Ethical process?

   b. With this successful trial experience, one would expect some form of phase development in GCLP and GCP accreditation and it will be important to clarify what

the report means by 'GCP certification'. How many Clinical trial coordinators were trained to develop the clinical trial units in Tanzania and Mozambique?

7. **Postgraduate students**
   a. The reviewers considered that the output of the PhD students' work for TaMoVac-01 should be summarised, as they have produced a lot of work (though the question was raised whether the publications they have produced are from TaMoVac-01 data).

   b. According to the postgraduate training table (section 4.4, page 17), Nelson Tembe is due to start his PhD in May 2013. However, this grant ended in December 2012. As he is starting his degree after the grant has ended, we cannot see how he can be listed as a graduate student under TaMoVac-01. Can you please clarify?

8. **Networking**
   The team made major strides in creating a network for HIV vaccine trial. The monthly TMG meetings were impressive. Was the development of a TaMoVac specific website and intranet communication tool aimed to strengthen and sustain this important network?

   According to your report, *There were administratively difficult negotiations with collaborators in another EDCTP funded project that were aimed at utilizing the vaccination investment in TaMoVac-01 to have participants receive subsequent boosting with a novel rgp140 and with a novel adjuvant (GLA)* – could elaborate on this comment and indicate what if anything could be done to overcome these challenges.

If you have any questions, please do not hesitate to contact me.

Yours sincerely,

Dr Monique Rijks-Surette
Project Officer
EDCTP

Cc: Dr Pauline Beattie, Operations Manager, EDCTP
Dr Thomas Nyirenda, South-South Networking and Capacity Development Manager
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Dear Monique,

Subject: 1st round of queries for the final technical report for TaMoVac-01

Please find our responses to the first round of queries for the final technical report for the project based on the final technical report that we had submitted:

Report section	Quries	Responses
1. Overall comments	The report was well written. Great care was taken to present the information in a clear, concise manner. This was much appreciated. I note your comment that the final report template should be provided at the beginning of the project. Usually this is the case but the re-design of the template was done quite recently, which is why it was sent to you so late. I am sorry for the extra work that this caused you.	Thank you very much for the compliments and your elaboration on the reporting form
2. Immunology Results	a. Immunogenicity was demonstrated in the HIVIS study as per the vaccine publication, though the statement in the report that the Nab assessment was ADCC dependent was not explicit in the paper. It will be technically important to clarify this result.	The PhD student Agricola Joachim has reported results of assessment of neutralizing and ADCC antibodies in the HIVIS03 trial in an oral presentation at the AIDS vaccine conference in Boston, USA in September 2012. These studies will also be reported in a scientific

		publication which will be included in her PhD thesis (see the list of anticipated additional publications).
	b. Preliminary analyses of TaMoVac-01 WP2 should provide information on the immunogenicity of either Env and gag separately and when used as pooled immunogen; if these results are still being analysed, an indication of any improved magnitude of response compared to what was earlier obtained in the HIVS-03 will be useful.	In the TaMovac I trial a simplified regimen was compared to a standard regimen. Two pools of DNA plasmids were used (pool 1 envABC + revB, pool 2 gagAB + RTB) boosted with MVA CMDR envE, gagA, polA. Volunteers were randomized in three groups of 40 each, primed with either two injections of 300ug, one in each arm, (total 600ug) of DNA with combined plasmids (group IA) or two injections of 300ug with one pool in each arm (total 600ug) of DNA (group IIA) "simplified regimens" or five injections, 2 (pool 1) and 3 (pool 2) injections in the right and left arm respectively (total 1000ug) DNA (IIIA) "standard regimen". DNA/Placebo priming was administered by a needle free (Biojector) device at weeks 0, 4 and 12. All volunteers were boosted intramuscularly with 10^8 pfu of recombinant MVA/placebo at weeks 30 and 46. The primary end point was the number of ELISpot responders to gag and env, 2 weeks post the last vaccination. The response rate to gag and/or env were 27/32 (84%) in group IA vs 31/33 (94%) in group IIA (p=0.26). The response rate to gag and/or env when comparing the 'simplified regimens' (group IA and IIA) vs 'standard regimen was 58/65 (89%) vs 32/32 (100%) p=0.09. In responders the median magnitude (IQR) response to Gag was 165 (100,365) vs 210 (120,320), p=0.46 while the magnitude for Env was 150 (92,225) vs 110 (80,160) p=0.17 for the 'simplified' vs 'standard' regimens. Please note that TaMoVac I data was not expected to show increased magnitudes of immunological responses as compared to HIVIS-03 as we used lower doses and partially

		combined plasmid pool. The objective was therefore to show the feasibility and immunogenicty of a simplified DNA vaccine regimen. The overall lower responses in the comparative arm in TaMoVac I as compared to HIVIS are currently discussed.
	c. It is noted that in section 2.4, you have found that 3 years post-immunization, immunogenicity has waned amongst volunteers of the HIVIS03 continuation study. What are the implications of this?	*The long term immune protection of HIV preventive vaccines is a neglected subject. All trials have dealt with very short term immunogenicity data. In the only succesful efficacy trial, RV 144 trial, it is probable that the protection only lasted one year. Thus our conclusion of the very preliminary data is that our immunogens/regimen induces a surprisingly high immune response at 3 years and the efficient boosting is possible with the same MVA used before in spite of potential vaccinia immunity.* *Additionally, this calls for systematic approaches towards informing the comunity and health care workers on presence of such individuals in the community with vaccine-induced seropositivity (VIS). Consequently, guidelines have to be developed on the best way of handling them in the health care setting. We have already made a communication to the Minsitry of Health and Social Welfare to this effect.*
3. Publications	Most of the publications cited do not acknowledge EDCTP as the funder (with the exception of the Bakari *et al.* Vaccine 2011 paper). Can you please clarify whether these publications have data from TaMoVac-01? If so, why was EDCTP not acknowledged?	We tried as much as possible to always acknowledge EDCTP in our publications. In some instances where this did not stand out clearly then this was an oversight and we sincerely apologise for that. I will also request that the publication Aboud et al. In Clinical and Vaccine Immunology 2010 be deleted from the list. It did not include data from HIVIS03 or TaMoVac 01.
4. Sub-studies	a. In section 2.4 (page 5), there is a list of sub-studies mentioned. Were these	

	part of TaMoVac-01? (i.e. were TaMoVac-01 funds that were used to conduct these studies?). Could you indicate for each sub-study the source of funding	
5. Clinical trials (section 3, pages 9 – 16)	a. It is noted that 2 clinical trials have been registered under PACTR (WP1 and WP2), one under clinicaltrials.gov (WP3), and one under controlled-trials (WP1). ***Registration numbers (final report)*** ***Possibl*** **WP1** ISRCTN90053831 ATMR20 **WP2** PACTR2010050002122368 **WP3** PACTR2010050002122368 We have found other registration numbers associated with the three clinical trials. The PACTR registration under number ATMR_080 for WP1 could not be found. Could it be under PACTR_080? For WP2, we have found two entries. The first one, PACTR_368 is the trial before the addition of the rpg140. The other registration, PACTR_583 has the rpg140. Are these trials considered to be separate? For WP3, the same PACTR number was reported than the WP2 trial. Is there a PACTR number for this trial? We also found a clinicaltrials.gov registration number. Can you verify if this is correct? We have noted that all of these registries are out-of-date (for example, WP1 is still listed as in follow-up, WP2 trials are still recruiting, the last update from the WP3 trial was on October 2012). Can you please update these registries?	WP1 the HIVIS 03 trial is registered under the trial number ISRCTN90053831 The TaMoVac-01 WP-2 amendment to include rgp140/GLA has the same trial registration number of PACTR20100050002122368. The clinical trials.gov registration for the trial in Maputo-WP3 is NCT01407497. The PACTR registry for the TaMoVac-01 study with trial registration PACTR20100050002122368 has been updated accordingly .
	b. Youth trial – recruitment was projected to end in March 2013. Has this occurred?	The recruitment of volunteers for the TaMoVac trial in Mozambique ended in March 2012. The follow-up of the volunteers was projected to end in March 2013 and this occurred according to the projections. The last protocol study visit took place in March 2013.
	c. Neonate feasibility study Given that only 36 respondents participated in the survey, it is difficult to make any strong assertions about	The 36 respondents have participated in the pilot study in 2011. During 2012, 149 respondents have participated in the neonate

	willingness to participate. Do you have any plans to extend the study or how does this finding compare with results elsewhere?	feasibility study. Preliminary results have shown good acceptability to participate in HIV vaccine trials in neonates. The concept of "vaccines" is still questionable within the study population since a vast number of respondents do interpret vaccines on the cultural context of treatment and not prevention.
	d. Can you please provide the close-out monitoring reports?	The close-out monitoring reports are yet to be received from the External Monitor. These will be submitted as soon as they are received. The Sponsor Representative is currently organising for a visit to carry out the close-out monitoring. Once available these will also be submitted promptly
6. Capacity building	a. Development of infrastructure was attained through this grant but an indication of how clinical trial unit was developed in Mozambique was lacking. According to the report, *Regulatory capacity has been strengthened as witnessed by the approval process for TaMoVac II. This is particularly true in Mozambique*. Could you explain how this was achieved – was any support provided to improve the standard of Ethics in Mozambique to circumvent the slow Ethical process?	Through EDCTP funding the Regulatory capacity strengthening in Mozambique was achieved by supporting Regulatory Authorities with an exchange visit to the Tanzania Food and Drug Authorities (TFDA) in Dar-es-Salam, Tanzania. The aim of this visit was to expose the Mozambican authorities to other regulatory authorities that have more experience in HIV vaccine trials field in order to improve capacity to evaluate the conduct of future HIV vaccine clinical trials and vaccine candidate products in the country
	b. With this successful trial experience, one would expect some form of phase development in GCLP and GCP accreditation and it will be important to clarify what the report means by 'GCP certification'. How many Clinical trial coordinators were trained to develop the clinical trial units in Tanzania and Mozambique?	At MMRP, a total of 35 members of staff have been trained as per attachment For MUHAS 17 members had undergone GCP/GCLP trianing. In Mozambique, the GCP and GCLP certifications were obtained through a training of the trainers courses that took place in Maputo, in 2011. These courses were administered by the certified Quali Lab, Lda, South Africa. The aim of these courses was to qualify study investigators to give local GCP and GCLP trainings. For

		the GCP and GCLP courses, 09 and 11 investigators, respectively, received the training of the trainers course and were certified to reproduce GCP and GCLP trainings in house. These investigators were able to do 4 in-house trainings with a total of 60 treinees.
7. Postgraduate students	a. The reviewers considered that the output of the PhD students' work for TaMoVac-01 should be summarised, as they have produced a lot of work (though the question was raised whether the publications they have produced are from TaMoVac-01 data).	The nature of PhD projects is that they are long term and don't necessarily coincide exactly with specific grants. TaMoVac-01 has contributed to the finished PhD training of Edith Mroso, and is also the back bone of Patricia Munseri's PhD which is hopefully defended this year. TMV-01 is contributing to the the on-going PhD work by Theodora Mbunda and has resulted in one publication of the PhD student originally planned for the the study, Joel Francis. The publication in Vaccine 2011 by Bakari M, Aboud S et al. about the HIVIS-03 trial was included in Said Aboud´s PhD thesis. Additional studies of immune responses in the HIVIS03 trial as well as in the TaMoVac I trial in Tanzania will be reported in publications to be included in Agricola Joachim´s PhD thesis
	b. According to the postgraduate training table (section 4.4, page 17), Nelson Tembe is due to start his PhD in May 2013. However, this grant ended in December 2012. As he is starting his degree after the grant has ended, we cannot see how he can be listed as a graduate student under TaMoVac-01. Can you please clarify?	Nelson Tembe was enrolled 2011 as a PhD student into the Bilateral research program between Sweden and Mozambique coordinated by Universidade Eduardo Mondlane and funded by Sida. The current funding period runs from 2011 until 2015. He was scheduled to register at the Karolinska Institutet, Department of Microbiology, Tumor and Cell biology, and held his registration seminar in May 2012. However, due to administrative matters outside our control the registration was not effectuated. He will be registered at Karolinska Insitutet, Department of

		Laboratory Medicine on May 7th, 2013. He has been the laboratory coordinator for the TaMoVac I project. His PhD thesis will be based on findings in the HIV incidence and STI prevalence study funded by Sida and the TaMoVac-01 trial.
8. Networking	The team made major strides in creating a network for HIV vaccine trial. The monthly TMG meetings were impressive. Was the development of a TaMoVac specific website and intranet communication tool aimed to strengthen and sustain this important network? According to your report, *There were administratively difficult negotiations with collaborators in another EDCTP funded project that were aimed at utilizing the vaccination investment in TaMoVac-01 to have participants receive subsequent boosting with a novel rgp140 and with a novel adjuvant (GLA)* – could elaborate on this comment and indicate what if anything could be done to overcome these challenges.	The TaMoVac websites and internet communication aimed at strengthening the network, and also allowing for other interested individuals, intitutions or networks to acess our network information and updates. We were also able to network with East African Consortium for Clinical Research (EACCR), Kenya AIDS Vaccine Initiative and African Malaria Network Trust (AMANET) in conducting GCP and GCLP traninng. Otherwise the negotiations were related to the provision of rgp 140 boost as a collaborative effort with the AfreVacc. Provision of the protein and adjuvant (GLA-AF) involved a lot of legal and administrative undertakings. It was an entirely new experience, and perhaps strengthening of administrative and legal capacities of institutions in the developing countries could be of use here.

Yours sincerely,

Prof Muhammad Bakari
TaMoVac-01 Project Co-ordinator

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Second round of queries for the final technical report for TaMoVac-01

Dear Prof Bakari,

Thank you for providing your answers on 2 May 2013 to the first round of queries sent 16 April 2013 on the TaMoVac-01 final technical report.

There are a few follow-up queries/impressions which you can find below:

1. **Publications**
   EDCTP requires all of our grantees to acknowledge us in all publications that involve data from their EDCTP-funded study. Can you please contact the various publishers to get this amended? This of course should be possible with the electronic versions of the papers. We note that the Aboud et al 2010 paper should be removed from the publication list.

2. **Sub-studies**
   a. This section is missing an answer. This is the original question:
   "In section 2.4 (page 5), there is a list of sub-studies mentioned. Were these part of TaMoVac-01? (i.e. were TaMoVac-01 funds that were used to conduct these studies?). Could you indicate for each sub-study the source of funding"

3. **Capacity building**
   a. Your exchange visits with the TFDA is a very praiseworthy activity for capacity building and in the future, should be emphasized in any reports.

We look forward hearing from you shortly.

If you have any questions, please do not hesitate to contact me.

Yours sincerely,

Dr Monique Rijks-Surette
Project Officer
EDCTP

Cc: Dr Pauline Beattie, Operations Manager, EDCTP
Dr Thomas Nyirenda, South-South Networking and Capacity Development Manager
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Dear Monique,

Subject: 2nd round of queries for the final technical report for TaMoVac-01

Please find our responses to the second round of queries for the final technical report for the project based on the final technical report that we had submitted:

Report section	Quries	Responses
1. **Publications**	EDCTP requires all of our grantees to acknowledge us in all publications that involve data from their EDCTP-funded study. Can you please contact the various publishers to get this amended? This should be possible with the electronic versions of the papers. We note that the Aboud et al 2010 paper should be removed from the publication list.	On further scrutiny it is apparent that most of the supposedly "forgotten publications" were actually not directly funded by EDCTP, rather the work had a close relationship with the main trial which was funded by EDCTP. The contribution of EDCTP has otherwise been acknowledged in the publication of the main work (Bakari. et al. Vaccine, 2011). Additionally, please remove the publication "*Francis JM, et al. Tanzania Journal of Health Research. January 2012; Volume 14, Number 1".* as this was entirely supported by Sida through the PhD training of Patricia Munseri. I apologise for this.
2. **Sub-studies**	a. In section 2.4 (page 5), there is a list of sub-studies mentioned. Were these part of TaMoVac-01? (i.e. were TaMoVac-01 funds that were used to conduct these studies?). Could you indicate for each sub-study the source	

	of funding. This project has led to a number of associated projects as detailed below. Funding source is mentioned on the respective row:	
	I. The HIVIS03/TaMoVac-01 (WP1). This was by analysing the immune response 3 years after the last immunization (PI Said Aboud)	This was funded by Swedish Embassy in Tanzania
	II. The HIVIS 06 project (PI Patricia Munseri)	This was funded by Swedish Embassy in Tanzania
	III. Immunological sub-studies at MMRP to address fundamental properties of the vaccines.	Immunological studies are per se no sub studies but part of the TaMoVac I protocol. Different immunological tests have been performed and are currently prepared as different publication as approved by the TaMoVac Steering Committee. They will be submitted for publication after publication of the main TaMoVac I paper. There is no other funding source
	IV. Socio-demographic studies to address the issues of recruitment of volunteers as well as the experiences of study volunteers.	These were mostly funded by the Sida support at MUHAS related to the training of PhD students, Dr Edith Tarimo
	V. Male circumcision study to address this in the Dar es Salaam study population.	This was funded by the Sida support at MUHAS related to the training of PhD student, Dr Patricia Munseri
	VI. Sub-study on ECG abnormalities.	ECG procedures have been part of the TaMoVac I screening and safety procedures. As some unique ECG features have been detected we plan to submit a separte poublication. However, this is not per se a sub study and there is no other funding source
	VII. Troponin I sub-study as an indicator for myocardial disease	This was funded by Capacity Strengthening aspect of Sida support at MUHAS
3. **Capacity building**	a. Your exchange visits with the TFDA is a very praiseworthy activity for capacity building and in the future, should be emphasized in any reports.	Thank you very much for the comment. This will be emphasized in future reports.

Yours sincerely,

Prof Muhammad Bakari
TaMoVac-01 Project Co-ordinator