UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Project of the Republic of South Africa

Support to South Africa on the local production of an HIV/AIDS vaccine and active pharmaceutical ingredients (APIs)
(TE/SAF/11/003 – SAP ID 100086)

Technical Report

Programme to support the Ministry of Health of South Africa in the implementation of a national program of global response to HIV & AIDS

Assessment of the results in South Africa for: Component 1 (Strengthening of health care services – NEW) Component 2 (GMP vaccine manufacturing - UPDATED) and Component 3 (Phase II trials on HIV Tat vaccine - UPDATED)

Bernard Fourie (South Africa), Koleka Mlisana (South Africa), Alberto Saracco (Italy)*

*Members of the International Scientific Advisory Committee on the Joint Project and Monitoring and Evaluation Consultants: Health Systems Strengthening and Vaccines Manufacturing, UNIDO, Vienna

30 September 2015

UNIDO Project Manager: Juergen Reinhardt, PTC/BIT/CBU

Preamble

In May 2014, an interim report was prepared on progress with Components 2 and 3 of ISS Project Aid 8421. The report presented here by the International Scientific Advisory Committee (ISAC) constituted under the auspices of UNIDO reflects again on Components 2 and 3 one year later, at the conclusion of the project period. In addition, specific obeservations on Component 1 are included.

In its evaluation of Project Aid 8421 outcomes in July 2015, the ISAC observed that the 2014 report remains valid in its entirety, including almost all of the recommendations proposed at the time. It was therefore decided to retain the text of the 2014 report as part of the 2015 report, but to add also a chapter on Component 1 and to update all other chapters by including additional remarks where appropriate. Final recommendations have been added. Updated sections appear at the end of each chapter and are identified in the Table of Contents. The section on Remarks and Recommendations have been updated to retain only the essential statements from 2014 and to include observations for Component 1. However, the appendices to the 2014 report have been excluded from the 2015 report. We believe that its absence does not detract from the readability and validity of the narrative retained from the 2014 report.

For any enquiries regarding this report, please contact:

Dr Juergen Reinhardt
Senior Industrial Development Officer
BIT/PTC/CBU, UNIDO, POB 300, A-1400 Vienna, Austria
T: +43 1 26026 3405
E: j.reinhardt@unido.org

Executive Summary

Under an Italy–South Africa agreement, it was foreseen that a three-year project, which involves complex transfer of technology, would provide the South African government with instruments for undertaking preventive and therapeutic vaccine programmes to complement current research vaccination programmes in South Africa. The specific objectives of ISS Project Aid 8421 were to: (1) Support the development and/or the strengthening of a network of clinical sites and laboratories located in the area of intervention capable of providing quality health care, particularly in the HIV/ AIDS sector; (2) Support the development of a GMP line of production to manufacture vaccines in South Africa; and (3) Development and conduct of a Phase II therapeutic clinical trial with the Tat vaccine developed at ISS.

In Mpumalanga Province, Gauteng Province, and Eastern Cape Province, demonstration facilities were selected for implementation of health services strengthening interventions. The NDOH in South Africa has implemented national policies to enhance the quality of primary health care in the country, and the project aimed at strengthening the process (Component 1). The Biovac Institute was selected as implementing partner for Component 2, aiming at the establishment of a vaccine manufacturing capability in Cape Town. Technology transfer from Italy to TBI was successfully concluded, with a demonstration batch manufactured that met all required specifications. State-of-the-art facilities have been created in the process. As for Component 3, outstanding capability and laboratory support infrastructure was developed for the purpose of defining target populations for conduct of observational studies and for selection of candidate subjects to participate in clinical trials with Tat vaccine. Public health service delivery and HIV/AIDS clinical care in the catchment areas benefitted considerably. Two clinical research units were established, the Medunsa Clinical Trials Unit (MeCRU) and in Mthatha, the Walter Sisulu University HIV Vaccine Research Unit. MeCRU performed a Phase II trial. 200 subjects were enrolled and followed-up. The CRU in Mthatha focused on operational research capacity building, with a view to establishing vaccine trial capability in the region.

Overall, the project was deemed highly relevant, and that implementing partners proved to be efficient and effective in executing the work. However, there is a need to secure sustainability of the effort. In this respect, key actions to consider are:

1. All partners (NDOH South Africa, Italian Cooperation, and ISS) contributed significantly to the successful outcome of the project. It is essential, however, to ensure sustainability and expansion, building effectively on the investments made.
2. Experiences with roving doctor/nurse/social worker concept are promising and should be formalised, expanded and secured. Likewise, information networking is to be rolled-out wider, maintained and upgraded. Very specifically, secure data capture posts (high-risk consequences if not achieved).
3. Excellent infrastructure has been established at Biovac. Scale-up capability to be strengthened and opportunity for wider vaccine production and commercialisation into Africa to be explored. Italian companies could be encouraged to engage with Biovac in order to fully exploit the Italian government investment, in particular, partnerships representing late stage biological medicines product development and manufacturing. A long-term plan for up-scaling of infrastructure and larger-scale production of Tat vaccine (with Diathiva) is essential.
4. Expand the MeCRU model to other CRU's and network current partners. NDoH and MRC to engage in medium- to long-term planning around effective utilisation of the CRU's.
5. Conclude the ISAC evaluation process by conducting a high-level scientific workshop engaging leading scientists (local and international) to comment on the future prospects of Tat vaccine development and implementation, in particular in the context of ISS project Aid 8421. ISAC to use the collective output to guide final recommendations on future directions.

TABLE OF CONTENTS

Description of activities performed

Terms of reference – Project context and scope of the assignment

The assignment forms part of a UNIDO advisory and capacity-building intervention that supplements an ongoing bilateral technical cooperation project between Italy and South Africa and is entitled "Program to support the South African Department of Health (DOH) in the implementation of a national program of global response to HIV/AIDS in the border zones between South Africa and neighbouring countries and in selected region of development". In addition to rendering specific support for the country's local pharmaceutical production agenda, UNIDO was tasked with conducting a number of monitoring and evaluation activities pertaining to the bilateral project's progression. The present assignment relates to the latter. The bilateral, originally three-year intervention (2008-2011) that was subsequently extended twice – with August 2014 as envisaged final completion date – has focused on controlling and reducing the spread of HIV/AIDS in South Africa through three defined components:

- Component 1: Development and strengthening of healthcare services and reinforcement of the governance capacity of the healthcare system (Health Care Services),
- Component 2: Establishment of a Good Manufacturing Practices (GMP)-compliant site for the production of vaccines (Vaccine Production),
- Component 3: Start-up and conduct of phase II clinical trials in South Africa on a candidate (HIV Tat) vaccine developed by the National Institute of Health (ISS), Italy (Clinical Trials).

As a precursor to a final evaluation at the conclusion of the project in August 2014, DGCS in early 2014 requested an interim assessment of the project's results with respect to those areas where activities had largely been completed already by that time. This refers to Component 2 and to the interface between Component 1 (activities aimed at the conduct of an observational study) and Component 3 (activities on the setup and capacitating of Clinical Research Units for the conduct of clinical trials under the project). The assessment report was submitted to the 4th Meeting of the Project Steering Committee on 20 May 2014.

As stated above, the 2014 assessment only partially addressed the outcomes of the overall project (Component 1 not reviewed), with a final assessment to follow the conclusion of the project in August 2014. Important, however, is the fact that the Steering Committee at their 4th Meeting in Cape Town in May 2014 endorsed the recommendations advanced by the interim report, one of which strongly advised that the observation period on patients that participated in the Phase II trials continued to be observed and samples taken from them for further analysis for another 12 months. The project extension concluded mid-2015 with further project assessments conducted. This report, therefore, constitutes the final project report on status and related observations as at the conclusion of the project. In addition to updating observations on Components 2 and 3, a more substantial evaluation was performed on the outputs and status of Component 1, again focusing more specifically on issues of relevance, efficiency, effectiveness, sustainability and management of project interventions.

Assessment procedures

In the 2014 interim assessment exercise, two data recording tools were developed to enable the collection of data in a standardised manner on project activity and output, one specific to the manufacturing environment represented by Component 2 activities at TBI (The Biovac Institute), and the other specific to the clinical trial and observational study settings represented by Component 3 activities at the Medunsa Clinical Research Unit and the Walter Sisulu University HIV Clinical Research Unit. For assessment of Component 1, members of the ISAC, supported by several individuals from UNIDO and ISS, identified and visited 11 representative facilities in three provinces where the project was implemented in order to gather information relevant to project objectives (**Figures 1-3**).

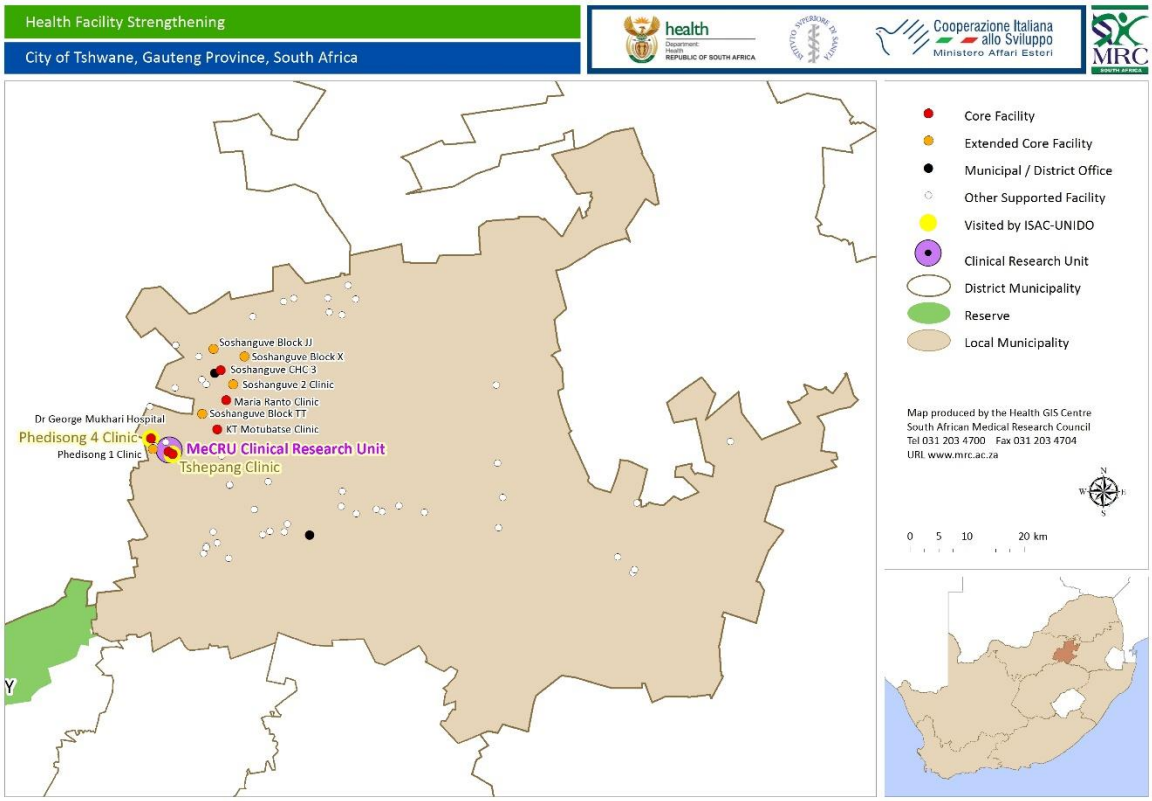

Figure 1. Health facilities visited by ISAC in Tshwane District, Gauteng Province

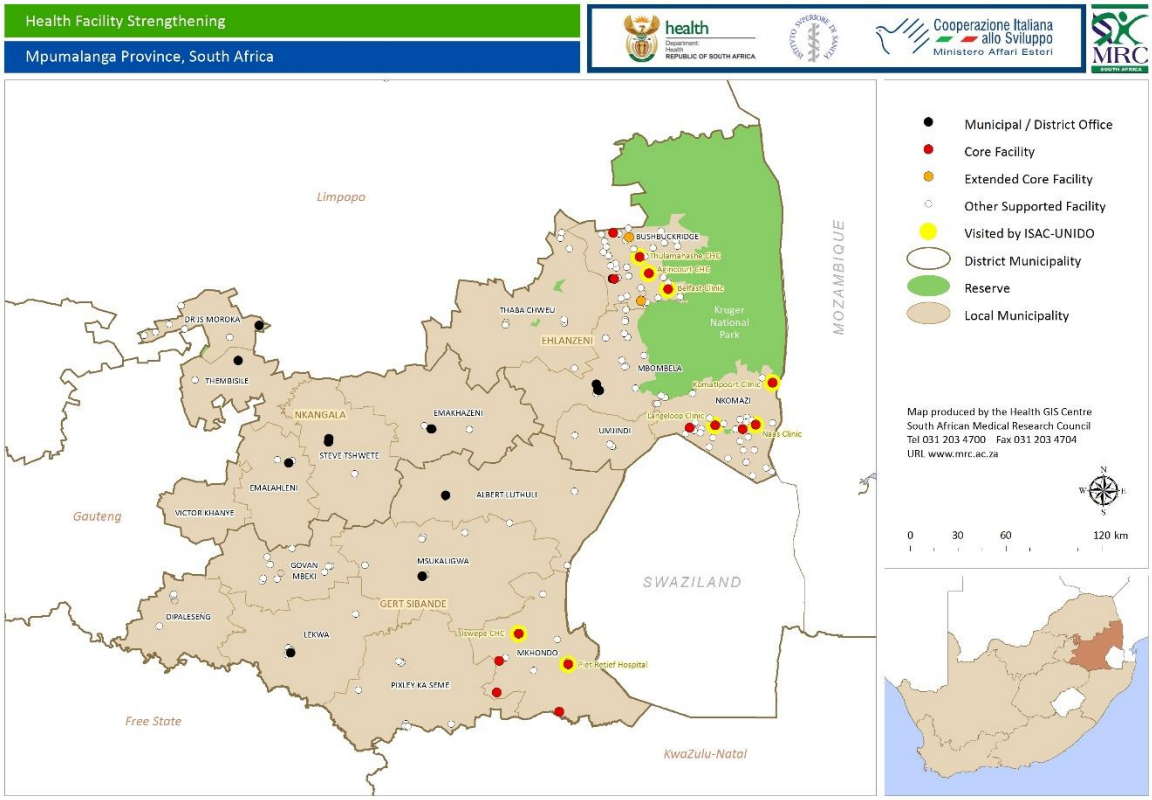

Figure 2. Health facilities visited by ISAC in Mpumalanga Province

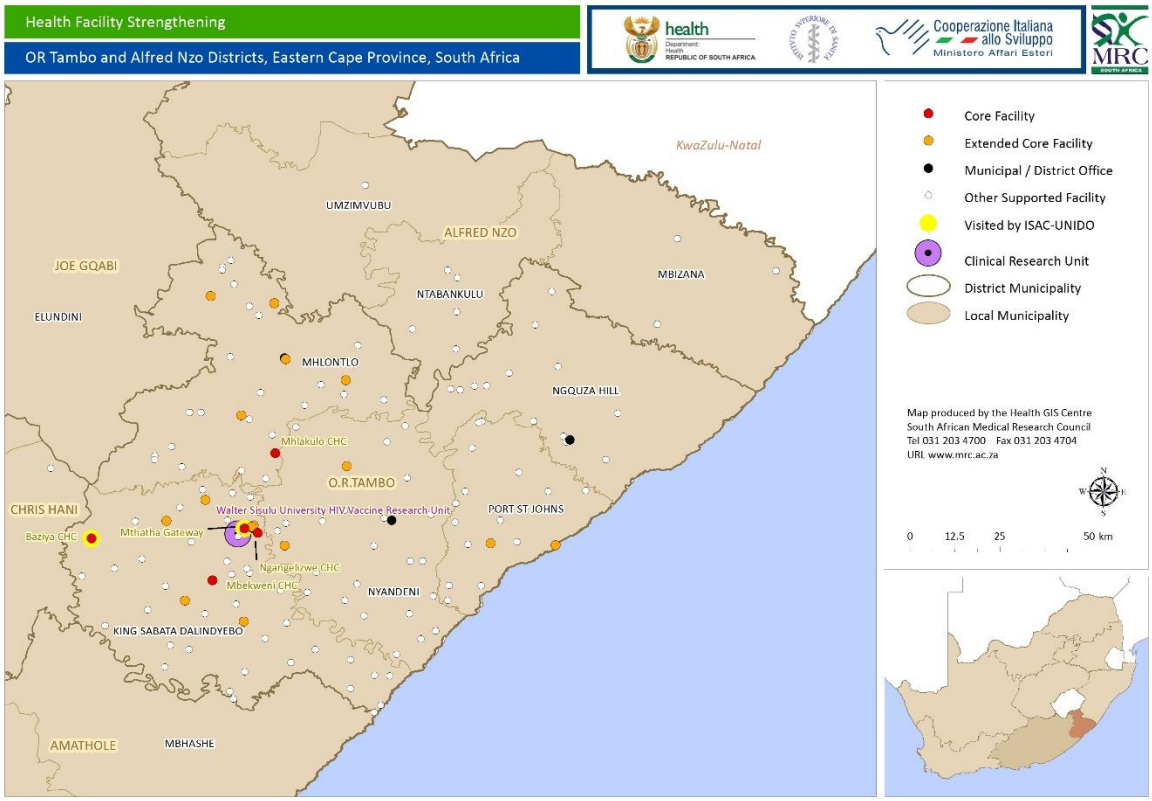

Figure 3. Health facilities visited by ISAC in Eastern Cape Province

ISAC members were tasked with providing independent opinions during each site visit on the following key performance areas:

a. Support demonstrated for the roll-out of ART with emphasis on strengthening quality of care
- NIMART training
- Roving clinical teams concept – Doctors and Social Workers
- Treatment adherence monitoring
- Provision of basic clinic equipment

b. Improving Data Collection and Management
- Training of Data capturers and placements thereof
- Placement of Computers and printers in HFs
- Placement of Filing Cabinets
- Availability and use of electronic data now fully operational

c. Information Systems Management
- Introduction of e-Health to HFs
- Training on DHIS and Tier.Net – Info Systems Officers training
- Generation of Monthly Performance Reports
- Continuous monitoring and evaluation
- Management tools for planning – Quality Improvement Plans
- Annual Performance Plans – local HF – Sub-district – District – Provincial level.

d. Pharmacy Improvement
- Training of Pharmacy Assistants and Dispensing Course for nurses
- Incorporation of pharmacovigilance training

On behalf of UNIDO, Dr Roberto Raggi (ISAC Coordinator) and Dr Robert Novak (UNIDO Country Office, Pretoria), supported by the ISS Head of Project in South Africa (Dr Paolo Monini) and several members of his staff, arranged, facilitated and attended all meetings, and provided much valued support during the course of data gathering and interpretation.

ISS Project Aid 8421

Background

Under the Italy–South Africa agreement, the Tripartate Technical Plan specifically refers to the agreement between the Italian Ministry of Foreign Affaires, Directorate General Development Cooperation (DGCS), and ISS for the technical implementation of the activities of the overall project for this three year programme. The initial budget allocated for the project was € 20,249,849.00 (as part of the overall budget under the tripartite agreement).

The specific objectives of ISS Project Aid 8421 were stated as follows:

A. Support the development and/or the strengthening of a network of clinical sites and laboratories located in the area of intervention capable of providing quality health care, particularly in the HIV/AIDS sector (Component 1)
B. Support the development of and GMP line of production to manufacture vaccines in South Africa (Component 2)
C. Development and conduct of a Phase II therapeutic clinical trial with the Tat vaccine developed at ISS (Component 3)

It was foreseen that the Project, which involves complex transfer of technology, would provide the South African government with instruments for undertaking preventive and therapeutic vaccine programmes to complement current research vaccination programmes in South Africa.

This report reflects the status of all three components at conclusion of the project (June 2015).

Project status – Strengthening of Health Care Services (Component 1)

Introduction

Under Component 1 (**C1**), the project aimed to

1. Improve health service management efficiency in the selected areas;
2. Create a multi-sector and multi-centre platform to strengthen the link between the clinical research units (CRU's) and health service facilities providing antiretroviral treatment (ARV clinics) with the aim of improving adherence to therapy and patients' traceability;
3. Develop and conduct an observational clinical study; and
4. Increase the awareness on HIV as well as TB infection through awareness campaigns and health education (community awareness).

Project strategy and specific activities

In the original project plan, supported by subsequent annual revised plans of action, it was anticipated that efficient provision of care at the peripheral and community level will be ensured by strengthening and monitoring the HIV/AIDS services in order to promote their quality. Patient's clinical management will be improved through the development of an information system for management of data related to ARV therapy. Expectations were that this system will integrate ARV clinics and CRU's as well as the local NHLS and CRU laboratories to improve patient tracking and to reinforce the capacities of health services towards population surveillance, adherence to intervention protocols and management of side effects.

Activities, goods and human resources committed under C1 are those that would be expected to have direct impact or consequences on health services provision, or that leave South Africa with a strengthened position in terms of technical knowledge, equipment or structures to the advantage of public health services. These specifically include:

1. Local staff (doctors, nurses, technicians, IT staff, administrative and support) to support and implement ARV treatment programmes (including pharmacy services), and to carry out observational and clinical studies.
2. Infrastructure improvement (e.g. facility renovation) and placement of equipment (except BIOVAC under Component 2), including software acquisition and development.
3. Activities aimed at training of staff, community education interventions, and production of educational materials.
4. Establishment of laboratory activities linked to observational studies.

In the ISAC assessment, the key areas focused on are summarised in **Table 1**. Specific comments and observations for each health facility by province can be found in **Table 2**.

It may be noted that NDOH has entrusted parts of C1 (and C3) to the MRC/SAAVI for implementation. In particular, the SAAVI-Masikhulisane educational activity (community involvement) should be noted.

C1 can be seen as an intervention cohort in support of the National and Provincial Departments of Health Strategic Plans. In particular, strengthening of efforts to fill gaps in the roll-out and management of ART programmes was identified as a priority area. Activities focused on provision of key staff and critical equipment, and in the development of staff skills. Other focus areas included the strengthening of community health care governance structures, the development and enhanced use of district health information systems (DHIS), and engagement of the communities targeted by the interventions.

Health facility performance under Component 1

General observations

Overall, the goals set for C1 have been achieved. The programme has successfully lived up to its main objective of providing support to the Ministry of Health in the implementation of a national programme of global response to HIV and AIDS. Component 1 of the programme specifically targeted one of the aims of the National Strategic Plan (2012 – 2016) that is aiming to ensure that 80% of individuals requiring ART are receiving it. With the National MoH directive to roll out antiretroviral therapy (ART) to all patients requiring treatment, critical gaps in health systems needed to be addressed in preparation. The model used in this programme has been to work very closely with the respective PDoHs, identifying gaps in the health systems and providing solutions at both facility and sub-district level.

The ISS Programme is appreciated as a critical foundational key player in health system strengthening of HFs and their surrounding communities in these 3 provinces. It played a catalyst role on which the DoH and other funders and stakeholders could build. Programmes integrated into the department's plan yielded a much broader impact as these build capacity and provide resources to the public facilities and such models, if successful, can be Impact of the programme is obvious although it cannot be individually measured as numerous stakeholders have added more resources – especially DoH and other funders.

All visited HFs were very familiar with the Programme as well as the ISS staff – implying a positive and healthy collaboration/support. Key challenge is to ensure sustainability and skills transfer as well as transitioning the operations into DoH.

Table 1. ISAC assessment focus areas

Support demonstrated for the roll-out of ART with emphasis on strengthening quality of care • NIMART training • Roving clinical teams concept – Doctors and Social Workers • Treatment adherence monitoring • Provision of basic clinic equipment
Improving Data Collection and Management • Training of Data capturers and placements thereof • Placement of Computers and printers in HFs • Placement of Filing Cabinets • Availability and use of electronic data now fully operational
Information Systems Management • Introduction of e-Health to HFs • Training on DHIS and Tier.Net – Info Systems Officers training • Generation of Monthly Performance Reports • continuous monitoring and evaluation • management tools for planning – Quality Improvement Plans • Annual Performance Plans – local HF – Sub-district – District – Provincial level.
Pharmacy Improvement • Training of Pharmacy Assistants • Dispensing Course for nurses • Incorporation of pharmacovigilance training

In **Table 2** below, a detailed summary is provided of observations on each facility visited:

Table 2. Summary of ISAC observations during field visits to core facilities (1-20 July 2015)

Component 1. Health Services Strengthening

Mpumalanga Province (6-10 July)

FACILITY	KEY OBSERVATIONS				
	HIV/AIDS services & ART roll-out	**Infrastructure and equipment support (ISS)**	**Data collection and IT management**	**Pharmacy and dispensing services**	**Other**
1. Nkomazi CHC	• Roving doctor NB, services continued • ARV management in children enhanced • Training for management of concomitant conditions, e.g helminths	• Air conditioning • Computers/printers • Filing cabinets • Equipment functional • 24hr Security available for equipment safety	• Patient files properly organised, numbered, up-to-date • Electronic data capturing	• Air conditioned, temp charts • Stock adequate, no expired items • Staff trained • Records neat and organised	• Well-managed facility
2. Naas CHC	• Training for HIV & TB integrated management • Training on adherence counselling in ART • NIMART training • Monthly reports • ART monitoring programme in place	• Air conditioning & service • Security gates • Computers/printers • Filing cabinets • Small medical equipment	• Electronic data capturing • Patient files properly organised and maintained • Regular transmission of files	• Comply with national standards • Good management of stock, no expired items • Pharmacy Assistants trained	• Good Infection Prevention and Control programme • Facility is neat, clean and gives impression of a well-organised operational routine • Manager and staff well-informed about project • Project impact is positively acknowledged by clinic management
3. Tonga District Hospital	• As for 1 & 2	• As for 1 & 2	• As for 1 & 2	• As for 1 & 2	• Data capture officer assigned to Switchboard
4. Langloop CHC	• As for 1 & 2 • Training on DHIS and Tier.Net	• As for 1 & 2 • Extra furnished room for VCT	• As for 1 & 2	• As for 1 & 2	• None

5. Belfast CHC	• Roving team provided an excellent service • MD and social workers - for the first time operating in the district thanks to the project - have not been absorbed by the health system • 70% of staff trained • Training for HIV & TB integrated management • Training of nurses revolutionised HIV management: • ART initiation • De-centralised training (previously only Regional Training Centre) allowed for wider access by personnel	• Filing cabinets supplied even to the non-designated HCF • Provision of basic clinical equipment • Air conditioning • Computers/printers • Filing cabinets • Small medical equipment • Mobile bulk filing systems	• Introduction of e-health • Information Officers training at UWC • Excellent record keeping in facilities • Electronic data capturing • Patient files properly organised and maintained • Regular transmission of files	• Good record keeping • Adequate stock and management thereof • Stock adequate • No expired items • Staff trained	• Challenges: • High staff turnover • Security gaps – stolen equipment • Non-local equipment poses maintenance challenges • ISS programme acted as a catalyst in health systems strengthening • Reported high personnel turn over
6. Agincourt CHC	• NIMART training played a critical role in increasing ART initiation • Initial pilot programmes have become national • Paediatric HIV focus area • Distance Dispensing Course	• Small medical equipment supplied, which enhanced patient management • IT equipment available	• Data capturing running smoothly and is up to date. • Patient files properly organised and maintained	• Well run pharmacy – expiry dates managed well and adequate stock • No stock outs or expired items • Regular training of pharmacy staff	• High staff turnover with currently 70% of staff being new!!! • Good working relations with the Research team
7. Thulamahashe CHC	• Impact of roving teams was very significant	• Filing system optimised, space usage is efficient • Need to improve security to maintain patient confidentiality	• Data capturing is optimal	• Very well organised pharmacy with proper systems	• Current absence of roving teams mean it's back to poor referral system • Intergration with external partners (e.g. ANOVA) has improved service and staff skills

8. Iswepe CHC	• Roving team (Dr and Social worker) exceptionally enhanced facility performance • Home visits by the Social worker improves treatment adherence • Formation of Clinic Committees ensuring community involvement • Nurses trained to dispense	• Basic clinical equipment of great value	• 100% staff training for data collection • Clinical record update done for all surrounding facilities • All facilities on Tier2 • Electronic data capturing and report generation is up to date • 100% Monthly DHIS reports submitted electronically	• Neat pharmacy with excellent records • Proper management of stock – no stock outs or expired stock	• Excellently run clinic with neatly displayed general info – Areas covered, Vision and Mission, clinic staff members, clinical statistics, etc. • Quality Improvement Plans, based on clinical data reports • District reviews are conducted regularly using generated clinical data reports • Staff turnover is a big challenge
9. Piet Retief District Hospital	• Integrating TB and HIV management • Training nurses to dispense • Mentorship programme – roving teams	• As for 1 & 2, and for other facilities visited	• Information management systems were set up successfully	• The role of pharmacists in ARV roll-out must be emphasized • Training of pharmacy assistance was critical and this needs to be sustained • Pharmacovigilance has been incorporated in managing the pharmacy – AE monitoring is active	• Absorption of roving teams into PDoH has been of great value

Eastern Cape Province (12-14 July)

FACILITY	KEY OBSERVATIONS				
	HIV/AIDS services & ART roll-out	**Infrastructure and equipment support (ISS)**	**Data collection and IT management**	**Pharmacy and dispensing services**	**Other**
10. Baziya CHC	• Permanent doctor in the facility facilitates a good referral system within the facility • ART adherence counseling • GCP training - WSU • Distance Dispensing Course & Workshop • ECG Machine Training • Paeditric HIV Management	• Medical equipment provided contributed significantly to the CHC • Challenge of non-local suppliers of consumables and equipment servicing	• Facility with 2 data capturers • Good medical record keeping • Electronic data capturing 60-70 % coverage • Regular transmission of files	• Neat pharmacy with adequate supplies	• Medical referrals are delayed because of inefficiencies in EMS services. • High staff turnover puts pressure on training efforts • Integration of services seemed to be a challenge
11. Mthatha Gateway CHC	• Nurses have been trained on the following courses: - NIMART - STIs and TB management - Dispensing course - Adherence counselling	• Medical equipment provided contributed significantly to the CHC • Challenge of non-local suppliers of consumables and equipment servicing	• Data management training has made a great positive impact in the facility • DHIS has been introduced and is operating well. • Monitoring facility performance has been enhanced by the data reports that are generated monthly. • Facility is able to manage defaulters and follow-ups using Tier.net programme	• Even with renovations, pharmacy is very well managed • Fully stocked with a good delivery system to patients • Good management of stock	• Excellent interaction with the CRU • The facility sees participating in research as empowering and educational. It improves patient care in the long run. • Good laboratory support with ability to print lab results on site

Gauteng Province (15-16 July)

FACILITY	KEY OBSERVATIONS				
	HIV/AIDS services & ART roll-out	**Infrastructure and equipment support (ISS)**	**Data collection and IT management**	**Pharmacy and dispensing services**	**Other**
12. Tshepang CHC	• A referral facility for ART patients with complications • Male Medical Circumcision has now been rolled-out in the facility • Same day ART initiation	• Computers, printers and small medical equipment supplied and functional	• Data management not fully electronic • Staff shortages is a huge challenge with huge backlog • Software migration has been a huge challenge - some of the data could not be migrated	• Trained pharmacy assistants who also assist with adherence counselling	• Challenges encountered with changing data management software – FPD programme to Tier.Net • Defaulter management is a challenge • Participating in research has impacted positively on the facility
13. Phedisong 4 CHC	• Facility running a large pre-ART clinic • Initial training of nurses was a huge catalyst for ART initiation	• Computers, printers and small medical equipment supplied and functional	• Software bridging has been a challenge here as well	• Well controlled and pharmacy staff adequately trained	• Community Health workers and the Ward Based Outreach Team are great resources in tracing defaulters

Conclusions: Component 1

Summary of key observations

- Enhanced performance in roll-out of ART and quality of care in general: The deployment of roving clinical teams (doctors and social workers) to facilitate and enhance access to clinic health services has been very successful. The action directly speaks to the Best Practices Objective under C1 in the project plan. The impact of these teams on intervention outcomes is seen in more pronounced application of best practices as per NDOH clinical guidelines, ensuring patient flow, skills strengthening, monitoring of treatment adherence and community involvement.

- Effective data collection and information systems management: Successful scale-up from paper–based to electronic data capturing; very good record-keeping and filing. Clear evidence of introduction of e-Health in almost all HFs, wider implementation of electronic data capture activities in provinces, training on DHIS and Tier.Net and generation of performance reports to aid management of services.

- Efficient pharmacy and dispensing practices: High-quality dispensing practices and pharmacy stock control were observed. The training of pharmacy assistants is given high priority, not only in terms of pharmacy practices, but also for assistants to serve as sources of information for patients on ART-related questions on treatment, adverse events, interpretation of test results, and general awareness of challenges associated with being on ART long-term. Dispensing courses for nurses and pharmacovigilance training were commonly incorporated into the training programmes. Compliance with National Core Standards in the areas of pharmacy practice is being met by all facilities.

- Positive impact on provincial health services provision: All support interventions targeted to critical needs as identified by NDoH. The implementation of project activities are targeted to core facilities, but non-project facilities also impacted. Key challenge is to ensure sustainability and skills transfer as well as transitioning of the operations within wider DoH activities. In this context, retention of trained staff is crucial, especially of data capturers.

  Particular attention to the wider implementation of the roving team concept might be beneficial to reaching provincial and national targets. Staff quality has been positively impacted, including the performance of health services coordinators and facility managers. Project methodology could serve as a model for health services intervention at the facility level. There is a general perception that facilities are well managed and maintained, patients are present even in non rush hours. Matrons show an excellent capability to run the activities and, with respect to the project, there is a general awareness of its positive effect on *day to day* work.

  At the provincial level, provision of equipment, staff training, upscaling to electronic data capturing and improving pharmacy practices under the intervention project, has led to 315 primary health care facilities in Mpumalanga Province now having data capturing capability. In 2009 (before the start of the project, such capability was only available at hospitals. Also, general training activities are being decentralized more-and-more, with courses being run locally as more trainers become available within, or at close-by facilities. In Mpumlanga, specific budget is now provided for equipment (computers, printers, scales, small medical), with decentralized ordering and servicing being allowed.

- SAAVI-Masikhulisane Community Outreach Project: Project was successfully concluded and separately assessed by the University of Stellenbosch. MRC funding three new community-based studies in Mthatha in 2015.

Specific challenges for services strengthening in health facilities

- High turnover of trained personnel might have had a negative effect on the short term, but might have had a positive effect on the health system as whole because of re-distribution of skills in non-project facilities. Nevertheless, this requires sustained attention to training activities for health facility staff as regular practice.
- The re-organization of health facilities according to the integrated chronic diseases management model, which caters for HIV/AIDS, TB, and non-communicable diseases in a single service setting, is currently resulting in long lines in waiting areas.
- Data capturing system works well where implemented (100% coverage in almost all facilities), but as there is a single operator in most settings, there is a risk of breakdown in service if the responsible person is absent for any length of time.
- Most of the activities have been completed so far, therefore some equipment provided could be obsolete. Also, it is difficult to determine the status of donated equipment, because in some cases re-allocation to other facilities in need has taken place.
- Overall, sustainability of the intervention model as established in C1 health facilities, and expansion to non-intervention facilities, is seen as the critical issue for maintaining impact in the long-term.

Project status - Vaccine manufacturing (Component 2)

NOTE: This Chapter from the 2014 Interim Report has been retained, except for minor changes to the original document and for the addition of an UPDATE at the end, reflecting the 2015 ISAC observations and conclusions.

Introduction

The primary objective of Component 2 (**C2**) of the project was to enable the transfer of technology for Tat vaccine manufacturing technology from Italy to a suitable facility in South Africa. In order to serve the broader purpose of the Tripartite Agreement, preparations for the establishment of a MCC-certified facility capable of recombinant protein production under GMP started in February 2010. The Biovac Institute was chosen for the purpose, and a Joint Development and Collaborative Framework Agreement was established between TBI and ISS, within the scope of which the overall objectives of the Production Component within the Vaccine Implementation Program (VIP) were formulated.

Three project activities were undertaken: (a) Technology transfer; (b) Facility development; and (c) Operationalisation. The VIP was described in the Programme Mandate, signed Feb 2010, and each of the projects described in a Project Definition Report. Operational aspects of the project were governed by a Project Execution Plan.

Project strategy and specific activities

The activities within Component 2 concerned a close scientific partnership between TBI and ISS through AVITECH/Diatheva (University of Urbino), and with strong institutional support from the National Department of Health in South Africa.

Strategically, Component 2 aimed at achieving the following objectives:

- Providing technical assistance towards obtaining GMP readiness for the manufacturing of recombinant proteins for future vaccine production in South Africa;

- Supporting the development of technologies and procedures at the production site (TBI), in close cooperation with AVITECH/Diatheva, that would enable the facility to be certified as a vaccine production site by the South African Medicines Control Council (MCC);

- Ensuring GMP production of the Tat vaccine at AVITECH/Diatheva for Phase II trial application in South Africa.

Transferring of technology from ISS through AVITECH/Diatheva to TBI included the implementation of a programme of exchange visits between the two sites. Local training in Italy for the transfer of knowledge, know-how, and technical expertise provided the GMP facility at TBI with qualified personnel able to manage and further develop the infrastructure at the site. The production process transferred to TBI represents the establishment of capability for the production of recombinant proteins for human use according to certified procedures that would not be limited to manufacturing of the Italian Tat vaccine.

Operationalisation, production and testing of the GMP facility at TBI

Broadly stated, Component 2 represents a technical activity that is specifically concerned with pharmaceutical technology transfer procedures. In this context, the ultimate goal was to comply with regulatory requirements as these apply to a locally manufactured vaccine product in South Africa. Therefore, assessment of project outcomes have been conducted in line with the appropriate WHO guidance on technology transfer, in particular those sections that deal with the operationalisation of the GMP facility at TBI, and the production and testing of products produced under production runs in the facility. The following observations can be highlighted:

Organisation and management

Operational preparations for initiating the project involved transfer of protocols that cover several key aspects agreed between the supply facility (Diatheva, Italy) and the recipient facility in South Africa (The Biovac Institute, RSA). The objectives, scope and key personnel and their responsibilities are detailed in the technology transfer project definition report as well as the operationalisation project execution plan.

A visit to Diatheva by the Biovac's Discipline Engineer (DE) heading up the Tat technology transfer process was conducted in April 2010 in order to ascertain equipment and facility requirements as well as documentation available for the tech transfer. Equipment specifications, material requirements and methods for the Tat process were first translated from Italian into English by Diatheva before being supplied to Biovac and a gap analysis was performed by the Biovac team, whereby the team compiled a list of questions to ask the Diatheva team both electronically and face-to-face when the Biovac scientists attended training in Fano, Italy. These activities are adequately represented in the documentation available at TBI, in which the objectives and scope of the project are described, key personnel and their responsibilities detailed, and a parallel comparison of materials, methods and equipment that have been set-up to enable the planned technology transfer have been recorded.

Documented evidence is available which shows that each critical stage has been satisfactorily accomplished before the next commenced. Included is an identification of critical control points, comprehensive experimental design and acceptance criteria for analytical methods, information on GMP vaccine production/qualification batches, and process validation, change control for any process deviations encountered, and an assessment of end-product. Critical control points and acceptance criteria for analytical methods were defined in the documentation received by Diatheva and further elaborated upon during the scientists' visit to Fano. All batches were documented in batch

manufacturing records issued prior to each batch, and final reports were compiled which were sent to Diatheva for review.

Arrangements are in place at the recipient facility, under instruction from ISS, for keeping retention samples of active ingredients, intermediates and finished products, and SOPs are available for recording of information on reference substances where applicable. Quality assurance sign-off is under the control of a qualified person with designated responsibility.

A sample of the final batch of unformulated Tat protein bulk was shipped to both ISS and Diatheva for testing to validate that the run was successful. ISS and Diatheva confirmed in writing that the final run was successful and that the Tat protein was active.

Highlight reports were submitted monthly for the ISS infrastructure investment project. A final report was compiled in the form of a powerpoint show and presented to representatives from ISS. A project close-out report is in progress.

Production: Technology transfer

Organisation structure and appointment of staff with appropriate qualifications are in place. Training provided by technology transfer partners or appointed vendors (e.g. onsite practical training at Biozeen (dedicated facility for API and cleaning, formulation and filling). Training budget was initially 10% of the salary budget; then 6% and now at 3% level. A permanent training section within QA has been established in 2013.

All equipment and related processes are qualified. Follow-up by PQ's and process validations for API upstream, and for formulation and filling. Test runs and homogeneity studies were executed satisfactorily. Sterility assurance conforms to WHO requirements.

Clean rooms conform to environmental monitoring requirements, results are within specification. Pressure cascade, temperature, humidity and particle counting are within spec at rest and during operation; 24/7 monitoring is in place.

Quality control: Analytical methods transfer

Analytical methods encompass tests of identy only. Training received (see above). SOPs are available.

Premises and equipment

Very impressive progress has been made in this respect, with only a very few final steps to be completed. The manufacturing facility covers both API and F&F, and forms part of the shared services at TBI. A Validation Master Plan and an updated Site Master Plan are available, containing all relevant information, drawings, product/materials flow, tender documents, and personnel details. Additional infrastructural facilities included the extension of the cold room storage from 200 to 400 pallet places (in progress), construction of a sampling room, construction of a new facility for viewing, labelling and cartooning, and installation of new packaging equipment.

Documentation

Key tasks have been jointly planned and performed by both the technology supply facility (Diatheva, Italy) and the recipient facility (TBI), and supporting documentation is available as follows:

- Joint Development and Collaborative Framework Agreement between Biovac and ISS.
- Starting material specifications, equipment specifications and inventory, process master instructions, site-specific cleaning SOPs
- Facility documentation
- TBI manufacturing facility personnel: Diatheva training reports Report on Diatheva witnessing final batch production at TBI

Project output and achievements

TBI has demonstrated the capacity to deliver the project as per agreed targets. Technically and operationally, the project clearly was successful, with project deliverables and outcomes fully documented.

Technology transfer and successful production of a TAT batch was completed successfully and a good working relationship was established with Diatheva and ISS.

Note: The success of the facility and operationalisation projects are ultimately dependent on the South African MCC granting Biovac a cGMP license for the manufacturing facility. The MCC has inspected the facility, but not yet issued a certificate. Two external consultants performed audits to determine cGMP readiness and Sanofi also conducted an audit. Findings were reported and actioned before the MCC audit took place.

The following capacity and capabilities were achieved:

- Manufacturing facility with API, formulation and filling capability. These are comprehensively described in the Site Master Plan, with inspection and qualification records available. All parts of the facility operate within specification. API, formulation and filling processes are adequate, and all necessary equipment installed and validations performed to specification.
- Fermentation capacity of 200L and 20L
- Formulation capacity of 50 – 200L in tanks with smaller volumes in glass bottles.
- Automated filling capacity of 5,000 vials per hour, both 2R and 6R vials with filling volumes from 0,55 ml (2R) – 7 ml (6R).
- Skills development covered staff training in all aspects of the operation, focused on specific training targeting each specialised area of the process.

It should be noted, also, that it was identified that the inclusion of ampicillin in the production of TAT posed a risk to the introduction of the TAT process into a multifunctional manufacturing facility. For this reason, an ampicillin-free working cell bank was requested and received by Biovac from Diatheva. All precautions will in future be taken to avoid the risk of introducing ampicillin into the manufacturing facility.

Value for money

The investment at Biovac is sound because it would be able to supply Tat vaccine internationally, if the product is shown to be safe and efficacious.

Sustainability of the project

The current transition plan that ensures activities continue and impact is sustained, is focused on products other than TAT. Biovac is in a position to manufacture TAT product under GMP conditions should this be required in future, but this will require a further agreement between ISS and Biovac.

Any period of inactivity might pose a risk to the investment. Consequently, in order to sustain the operation, other activities will be undertaken in the meantime.

Conclusions: Component 2

The Plans of Action for Component 2 over the project period

- A detailed description of the expectations from Component 2 of the project has been provided in the form of the original overall project agreement and by way of amended Plans

of Action. The project strategy and specific activities are well described, plausible, and convincing.

- Overall, the expected deliverables/outputs are clearly quantified and linked to the activities. The achievements that the project aimed to generate were well-defined and achievable within the budget specifications of the component. On the basis of regular monitoring and reporting, a clear description is available of how relevant data for outputs had been obtained and how the project progressed to the point of conclusion.

Execution of the project by The Biovac Institute

- The project started out with comprehensive joint planning between the Italian and South African partners, i.e. the supply facility (Diatheva, Italy) and the recipient facility (The Biovac Institute, RSA). A detailed transfer protocol was developed which complied fully with international standards of technology transfer operations, and specifically to WHO technical guidance on this issue.

- The GMP Facility at TBI has been successfully established. The intended production capacity has been reached, the necessary staff expertise developed, and site capabilities to manufacture vaccine products in general, and TAT vaccine in particular, fully achieved. The technology transfer process was successful. A demonstration batch was produced by TBI, witnessed by the supply laboratory (Diatheva).

- Facility processes, handling of API and other materials, availability and appropriateness of equipment, and qualifications of staff are confirmed. SOPs and acceptance criteria for each step in the process have been compiled. Also, detailed plans and layout of the facility, buildings, and compliance reports are available.

- By the time of the 2015 assessment, the qualification status of the facility has not yet been issued by the MCC. It is not entirely clear why this process is being delayed.

- The implementing partner (Biovac) has shown the capability to manage and deliver the project and has established strong relationships with governmental and other organisations that supported execution of the project. The PI has documented the performance and success of the organization(s) in delivering on the goals of the project. The management structure, roles, and responsibilities of all parties are well described. There are clear and appropriate governance mechanisms in place in the organisation(s). Relationships with external bodies (e.g. national government) are described and complementarities highlighted.

- The personnel involved in the project have the skills and experience to manage and deliver the project, demonstrating appropriate capacity. The specific staff members listed on the project have been appropriately chosen and appointed for their role in the execution of the project. Curriculum Vitae are provided for all key staff, together with details of the proportion of their time that were dedicated to the project.

- The project contributed to capacity building and training in the public health field appropriate to the project. Skills development, project management and vaccine manufacturing capacity development were achieved. Creating expertise in vaccine manufacturing methodologies compliant with cGMP was a focus area. The PI has provided a breakdown of capacity building targets achieved.

- There is the expectation at TBI that further support would be granted in order to ensure sustainability of activity. In particular, there is the anticipation that actual production of TAT vaccine will be contracted. However, a proposal for a plausible transition plan at the end of ISS/DGCS time-limited support that ensures activities continue and impact is sustained, is not available. This is clearly a priority to be addressed.

COMPONENT 2 UPDATE: ISAC OBSERVATIONS 2015

Summary of key observations

In addition to the comments provided above on project outcomes and achievements, the most significant activities towards achieving the final project objectives are summarized below. These activities have been completed during the execution of the Plans of Action 1 to 6, covering the project period to conclusion:

- The acquisition, testing, qualification and GMP validation of equipment at TBI have been completed. SOPs needed for the implementation of required activities for production of Tat-vaccine are in place and all SOPs pertaining to the ISS and BioVac interactive agreements are operating effectively. The transfer of technological and organizational know-how from Italian partners to Biovac has been completed successfully, including constitution and validation of the production-line, working cell production, fermentation, purification, formulation, testing, packaging, and labeling. MCC certification for TBI as a GMP facility for vaccine production is still pending, however.
- Notable is the fact that the facility improvement at TBI led to the need for special skills. TBI invested significantly in training staff to meet the demands of the GMP production line. In this context, UNIDO supported training modules for skills in vaccine production, thereby building on the ISS project investment at the TBI.
- ***ISAC is of the opinion that the development of a GMP production line for manufacture of vaccines in South Africa has been successfully established at TBI.***

Moving forward

- In order to sustain capability, TBI would be looking for strong partnerships, in particular entities that deal with mature products or late-stage developments. This creates and opportunity for especially Italian and South African companies to address the need and to build on the Italy-South Africa investment through the project.
- In the context of possible future Tat-vaccine production, TBI would naturally be the facility to undertake the task. However, it would be necessary for long-term planning to be conducted without delay, in order for scale-up capacity to be developed and production scheduling to be determined. Estimate is that Phase 3 trials would require about 1000 litre fermenting capacity. TBI would be ready to conduct due diligence as soon as a firm request is received for new production of Tat.

Project status - Phase II trials with Tat vaccine (Component 3)

NOTE: This Chapter from the 2014 Interim Report has been retained, except for minor changes to the original document and for the addition of an UPDATE at the end, reflecting the 2015 ISAC observations and conclusions.

Introduction

The main objective of Component 3 (**C3**) under Project Aid 8421 of the Italian Development Cooperation (DGCS) wass to support the start-up and conduct of Phase II clinical trials in South Africa on the candidate (HIV Tat) vaccine developed by the National Institute of Health (ISS) in Italy.

Component 3 specifically represents the clinical trial component of the Program to support the Ministry of Health of South Africa in the implementation of a national program of global response to HIV & AIDS, a project under the larger Tripartite Technical Plan between ISS, the South African Department of Health (DoH) and the Italian DGCS.

The public health context

The HIV/AIDS pandemic has long been identified as public health problem with multi-dimensional drivers and impact. Its impact is not only confined to the health sector, but is equally felt at the socio-economic level with resultant devastating effects of immeasurable magnitude to the communities.. The need for an HIV vaccine will lead to halting a scourge that unfortunately hits the poorest communities the most.

A clinical trial that is conducted amongst those that need an HIV vaccine most will result in an element of community empowerment knowing that they contributed to the finding of the solution. It will also enable them to benefit from the education as well as the medical assessment they receive during participation. Additional benefits of this project are also to the health care facilities which provide services to the participants and this was the unique strength of this program which facilitated a great deal to the conduct of the trial.

South Africa is home to approximately 5,6 million infected individuals. The national prevalence rate in 2008 was 10.9% as reflected in the National sero-prevalence studies[1]. The majority of those infected are in the younger economically active age-groups. Therefore, unless something is done to curb this pandemic the growth and development of South Africa is facing a period in the future where there will be no economically active citizens to facilitate it.

The government of South Africa has committed resources to prevent the further spread of HIV infections by distributing free condoms (both male and female), providing free ARV medication at rolling out clinics where patient care is conducted.

The tendency of those infected to be in poor, rural and peri-urban areas where the majority of South Africans live have made the poor to be worst hit by this disease. This has increased the burden on health care in the few facilities that exist. The cost for ARV roll out as well as health care including that for co-morbidities is enormous on government.

Currently strategy of ARV minimize the disease effect of those infected and in turn should impact the burden on health care facilities. The barrier methods prevent new infections. Unfortunately these current efforts of fighting the pandemic rely on intervention that are susceptible to external

[1] Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Pillay-van-Wyk V, Mbelle N, Van Zyl J, Parker W, Zungu NP, Pezi S & the SABSSM III Implementation Team (2009). South African national HIV prevalence, incidence, behaviour and communication survey 2008: A turning tide among teenagers? Cape Town: HSRC Press

variables/factors, some of which are not necessarily of health nature, thus making it even more difficult to resolve using health intervention.

The HIV/AIDS landscape is characterised by poor access to ARV due to roll out challenges that range from infrastructure constants to lack of human resources to provide complementing services such as nutritional and psychological support, all of which are critical to adherence to ARV medication. An HIV vaccine is a long term answer to the HIV pandemic because it will not be susceptible to all these variables and the most hit communities will need a vaccine the most.

If there ever was a nation in need of an HIV vaccine, it is South Africa. In contributing to finding a solution to the problem and not marginalising the poor due to lack of resources and sufficient information, it is appropriate to test a potential vaccine in this country and the catchment area identified is even more suitable as it has been shown to be amongst the most affected. However, all preventive vaccines tested so far have shown none or modest efficacy. In the absence of a preventive vaccine, the only possible short/medium term strategy to halt the HIV pandemics in the country remains the effective implementation of the ART-Roll out DOH strategic plans.

In this context, the therapeutic vaccine tested in phase I and II trial in Italy (the Tat vaccine) has shown to increase the effectiveness of ART[2] and it thereby promises not only to make ART more effective but also to alleviate the burden of therapy compliance by limiting virus rebound associated to poor adherence.

Study sites

The **Medunsa Clinical Research Unit (MeCRU)** in Gauteng Province and the **Walter Sisulu University HIV Clinical Research Unit (WSUCRU)** in Eastern Cape Province were identified as possible sites for conducting the clinical trial, representing a deliberate act of empowerment from the leadership of the South African AIDS Vaccine Initiative (SAAVI).

[2] Ensoli B, et al. Therapeutic immunization with HIV-1 Tat reduces immune activation and loss of regulatory T-cells and improves immune function in subjects on HAART. PLoS ONE 2010;5(11):e13540.

The activities within Component 3 of the Project were implemented in close cooperation with MRC-SAAVI and the NDoH-PDoH in order to promote and guarantee an integrated particpants' management between ARV clinics and the clinical research sites. In both study sites, strong buy-in was also demonstrated by provincial health research committees.

The NHLS was engaged to perform biochemical and haematological analyses (safety testing). The Italian and South African core laboratories took responsibility for immunological and virological testing. Triclinium, a South African CRO, supported ISS in all activities related to the clinical studies.

Project strategy and specific activities

The 3rd strategic component aimed for:

- Preparation and conduct of a Phase II therapeutic clinical trial with the HIV-1 Tat vaccine in designated intervention areas;
- Assessment of Tat vaccine immunogenicity and safety in humans;
- Dissemination of results generated in the trial

The therapeutic Phase II trial aimed to enrol 200-250 HIV-infected individuals satisfying the inclusion and exclusion criteria set by the Italian and South African scientists for the trial, with the main objective to verify the immunogenicity and safety of the vaccine candidate.

In preparation of the clinical trial site, the goal was two-fold:

- To develop a clinical research site that will be able to conduct clinical trials, provide laboratory testing, develop and implement community education programs; and
- To integrate the site with all Project clinical and laboratory platforms, i.e. comprising the other Project clinical research sites engaged in the conduct of the observational clinical study (ISS OBS T-004) and the therapeutic vaccine trial foreseen by the Project.

Project description and specific objectives

A summary of the project objectives is provided in **TABLE 3.**

MeCRU eventually took full Project responsibility for the conduct of the clinical trial, after withdrawal of the Ndlela CRU in Mpumulanga and problems with start-up at **WSU HIV Research Unit**. However, **WSUCRU** participated in the observational study.

Two studies were conducted within the framework of the Project:

- **Preparatory Observational Study ISS T004**
  An observational study to assess the seroprevalence of anti-Tat antibodies in HIV-infected South African patients

- **Randomised Clinical Trial ISS T003**
  A Phase II, randomized, double-blind, placebo-controlled trial to evaluate the immunogenicity and safety of a therapeutic, recombinant, biologically active HIV-1 Tat protein vaccine in HIV-infected, anti-Tat negative, ARV-treated adult volunteers

Feasibility within the context of the logical framework

The project logical framework was established as per the main Project technical document, the Tripartite Technical Plan (TTP). The status of the actions as defined in the logical framework, including the GANTT-chart, were periodically reported. Each update was presented as an adjusted time-by-time

response to the operational and other challenges by way of semester or annual revised Project Plans of Action and Reports to the Plans of Action.

In addition to the POA provided by ISS, a local POA was also prepared for **WSUCRU**, given the special circumstances and challenges that prevailed at this site. The early stages involved infrastructure development, refurbishment and expansion. This was done interactively with ISS, according to an extensive plan for local activity. Structural changes resulted in operational activities only starting in July 2011, almost one year late.

Specific adjustments to work plans and budget were made in 2012 to accommodate the immediate needs at WSUCRU, and to accelerate the implementation of activities. Special attention was paid to the development of the laboratory. These interventions succeeded in limiting further delays in the start-up of the operational study activities.

MeCRU also had a period of difficulty in recruiting and enrolling participants at a desired rate. The team identified challenges/barriers and these were addressed with the sponsor leading to two amendments of the protocol which were done and approved by the regulatory authorities (MCC and ethics committee). This led to execution and conclusion of the study within the revised timelines. The timelines of activities and outputs were fair and accommodating, given the difficulties that clinical trials can encounter.

The Unit regularly presented to ISS quarterly reports indicating which activities were completed within a given quarter. These allowed for programmatic indicators to be measured.

Monitoring and evaluation, quality improvement

At **MeCRU**, the trial sponsor (ISS) had a monitoring plan during the implementation of the clinical trial managed by the Clinical Research Organization (CRO) Triclinium. They sent monitors on site to monitor the data capturing and trial progress and to ensure that all procedures were conducted according to the National Guide Lines and regulatory requirements. Feedback was given to the site at the end of every visit. They had a clear schedule of visits which they communicated to the site. This was important in ensuring continuous quality assurance.

ISS also sent its representatives to discuss trial progress and requested reports at every Provincial Stakeholders meeting. To prepare for these meetings, and for monitoring activities, the site held weekly meetings to evaluate the efficiency of the site and to note what progress had been made with trial implementation. These were useful in preparing staff for conducting a trial of the magnitude as required by T003. The purchasing of equipment and training of personnel were all done on a needs basis.

Extensive M&E was also carried out on the observational study T004 in both **MeCRU** and **WSUCRU**, with follow-up POAs and reports showing the gradual improvement in infrastructure and operational quality.

Project output and achievements (May 2014)

MeCRU

Specific objectives are presented in **TABLE 3**, with outputs summarised for all activities planned. More details on studies T004 and T003 are listed below:

Preparatory Observational Study ISS T004

Recruitment, Enrolment and Retention:

- 500 HIV-positive participants, 250 on ARV and 250 ARV naïve.

- KPI: Enrolment within 6 Months. Done (25 October 2010 - 11 March 2011).
- KPI: To enrol and complete follow-up visits before ISS T003 study approval and implementation.
- Retention: 482 participants of 500 came for visit 2 (96% retention rate).

Randomised Clinical Trial ISS T003

Recruitment, Enrolment and Retention:

- 200 HIV-positive participants on ARV.
- KPI: Enrolment before June 2013. Done 19 March 2012 – 27 June 2013.
- KPI: Follow-up of participant for 12 Months.
- Retention: By 27 February 2014, 200 participants were enrolled, 144 completed the study and none was recorded as lost at follow-up.

The studies used source documentation and data collection CRFs that were well structured and clear. It is the opinion of the research team that the documentation of the study was good and that data outputs were clear for all involved. Study results have not yet been unblinded for analysis.

All in-trial activities were successfully executed and by the end of the project MeCRU had over 95% retention rate for trial ISS T004. On the current T003 project, the Unit managed to have 72% of participants completing the study and anticipated to have all participants exited by the end of June 2014, which corresponds to the revised timeline for completion of the trial.

WSUCRU

Although the primary goal of the Project (development of a fully operational CRU and its integration in the Program clinical and laboratory platforms) was achieved, part of the goals for the project had to be reviewed. In particular, **due to the unforeseen delays the involvement of the CRU in the HIV Tat vaccine trial T003 was not possible, and the involvement of the research unit in the Observation study T004 was curtailed by reducing the number of participants from 200 to 31. Nevertheless, the goals as re-defined in Plan of Action (POA) V and VI have been fully achieved.**

The main activities foreseen by the Tripartite Technical Plan with reference to the conduct of the Observational Study are listed in **TABLE 4** below. These activities represent, in turn, the reference for the intervention foreseen for WSUCRU as by the last Plans of Action of the Program (POA V and VI). Each of the activities leads to a deliverable, the achievement of which by WSUCRU is also shown in **TABLE 4**.

Organisation and management

Both **MeCRU** and **WSUCRU** managed to obtain the required regulatory and ethics approval for the studies undertaken, and to recruit and retain the required staff for conduct the work. Recruitment was preceded by preparation and implementation of the community mobilization plan which emphasised on education of the community about the project in particular and clinical trials in general. Systems were put in place to liaise with health facilities and the required numbers were recruited within stipulated time for both projects.

The relationship in this project between ISS, the department of Health of South Africa, MRC-SAAVI and the research units was managed by ISS (based in the MRC office). Provincial Stakeholder meetings ensured that everyone was up to date with the progress of the rest of the project. Each of the parties knew what the other was supposed to do and understood their roles overall.

The above was a useful guide in implementing the clinical trial at **MeCRU**, including resolving misunderstandings and identifying areas of training needed for staff.

Personnel

The core team that managed **MeCRU** had an aggregate over 20 years working experience in the health sector, with skills ranging from clinical, laboratory, public health and behavioural science. Each staff member appointed had the prerequisite skills for the job. On-going training was also used to scale-up levels of competence. The success of the organisational capability in part was due to a blend of skills amongst the MeCRU team. Some of the skills represented, include:

- Business/Project management: Administration, consultation, reporting to sponsors;
- Clinical: Patient management, other services;
- Socio-Behavioural: Psycho-social (counselling and testing and support);
- Stakeholder management: Recruitment and retention;
- Coordination: Acting on monitoring queries, facilitating feedback, managing conflicts;
- Audit skills: Quality assurance.

At **WSUCRU**, care was taken to recruit staff in an open advertisement campaign, panel interviews and panel selection. Local candidates were targeted. Overall, a highly competent team was assembled, with the enthusiasm, commitment and skills to serve the project long-term.

TABLE 3. Specific objectives for MeCRU and status as at end of March 2014

	Specific objective/indicator	Indicator status
1	**Training research and support personnel** • Appoint the necessary research personnel • Develop capacity of different categories of research personnel	• Done 2009-2011 • GCP, GCLP, IATA conducted 2010-2013
2	**Community preparation** • Strengthen and maintain relationship with community stakeholders, including the Community Advisory Group (CAG) • Implement community education programmes	• Fully achieved. Minutes of the meetings are available • With SAAVI support: "Masikulishane" programme to promote positive attitude towards vaccine trials
3	**Procurement of equipment and furniture** • Purchase office, clinic and laboratory equipment and furniture	• Done as planned, 2009-2012
4	**Establish and reinforce support services** • Establish voluntary counselling and testing (VCT) • Establish a family planning program for the unit • Establish STI surveillance programs	• Conducted as part of performing the clinical trial • Conducted as part of performing the clinical trial • No surveillance, but STI managed as required
5	**Establishing IT system for data management** • Upgrade the current IT infrastructure. • Develop systems for data management and reporting	• Server bought, installed and maintained • Successfully developed, fully operational
6	**Infrastructural development and site expansion** • Complete the building (permanent structure), equip pharmacy with additional equipment • Renovate additional rooms to expand the PBMC laboratory and create an archive room	• Buildings complete, pharmacy equipment installed • Equipment acquired; current PBMC Lab was not extended, but equipment bought can cater for more than one working station if the need arises
7	**Conduct of the observational study** • Recruit the study participants from the surrounding ARV clinics and perform the screening and enrolment procedures as by the Study Protocol	• The target for study conduct at MeCRU was initially set at 200 participants, later revised to 500 participants after withdrawal of the planned Ndlela Clinical Research Unit in Mpumalanga
8	**Conduct of the clinical trial** • Recruit the study participants from the surrounding ARV clinics and perform the screening and enrolment procedures as by the Study Protocol.	• Target increased from 100 to 200 participants (all sites after withdrawal of Ndlela and in view of the redefinition of the Project targets for WSUHVRU, the other clinical research site)

TABLE 4. Specific objectives for WSUCRU and status as at end of March 2014

	Specific objective/indicator	Indicator status
1	**Establishment of the local centralized laboratory (Core-lab) including technology transfer**	The establishment of the South African Core-Laboratory was foreseen only for MeCRU; the MeCRU Core-laboratory was delivered in POA II. **The WSUHVRU laboratory was delivered in POA V.** All laboratory procedures including processing of blood specimens, were evaluated in five "dry runs" before the laboratory was considered operational. The product of the dry runs was tested for evaluation at the Italian Core-Laboratory (IFO).
2	**Strengthening operational capacities (structures, staff, GCP/GLP training) of clinical and research facilities in areas of intervention**	All the operational capacities have been fully achieved as assessed by the Clinical Research Organization (CRO) Triclinium. In particular, a site qualification visit was conducted at WSU by the CRO Triclinium on 15 November 2012. The **CRO rated the site as qualified for ISS OBS T-004** pending resolution of a few matters that were definitively resolved in February 2013;
3	**Development of a multi-sector and multisite study platform**	This **deliverable was fully achieved at the end of POA V** with the integration of WSUHVRU in the Program clinical multisite platform. The platform includes MeCRU and WSUHVRU as well as the public ARV clinics presents in the catchment areas of the 2 CRUs;
4	**Strengthening of the link between CRUs and ARV services**	This activity was **implemented during POA V** during in preparation of the OBS study conduct.
5	**Development of the integrated laboratory platform including local NHLS, CRU laboratories, and the centralized laboratories for immunology and virology (the Italian and South African core-labs)**	This deliverable was **achieved at the end of POA V** and tested through the dry runs; all procedures for the processing as well as shipment of the biological specimens to NHLS and the MeCRU Core Laboratory were successfully simulated. The platform includes the MeCRU Core Laboratory, the DGM NHLS at Medunsa and the NM NHLS at Mthatha, the WSHVRU laboratory and the Italian Core Laboratories (IFO and S. Orsola);
6	**Development and finalization of the SOPs required for implementation of all the activities**	The relevant **SOPs were developed** at WSUHVRU during POA V
7	**Evaluation of HIV infection and prevalence of concurrent infectious diseases in study participants**	**Completed**; Samples/data collected at WSUCRU, evaluations done at ISS
8	**Evaluation of anti-Tat antibody seroprevalence in study participants**	**Completed**; Samples/data collected at WSUCRU, evaluations done at ISS
9	**Evaluation of adherence to ART in study participants**	**Completed**; Samples/data collected at WSUCRU, evaluations done at ISS
10	**Development of the local ART databases for the improvement of adherence to treatment and patients' tracking in the context of the IT pilot study (IT-network platform)**	**Not applicable** as this TTP activity was amended

Capacity building

MeCRU: Several staff members were developed within the unit, such as training in public health whilst working on the project. Two medical technologists have participated in an exchange programme to be trained in Italy. Nurses were trained in phlebotomy, and the community liaison officer has undergone training on English language development in one of the local institutions. MeCRU also managed to recruit some of the staff members from matriculants in the nearby community of Garankuwa, Mabopane and Soshanguve, all of whom received training and exposure to clinical trial conduct in particular, and to medical research in general. Some have managed to advance to leadership and responsible positions. In addition to project specific training, the MeCRU team have also been supported and encouraged to acquire additional qualifications.

WSUCRU: Several trainings were provided which benefited the public health service, these included:

- Good Clinical Practice (GCP) open to all interested doctors and nurses at Mthatha Hospital Complex and the Health Centres;
- Dispensing Licence Course for nurses and doctors;
- Good Laboratory Practice (GLP) Course for the two Laboratory Technologists in the research unit and National Health Laboratory Service (NHLS) technologists at Mthatha Hospital Complex;
- Paediatric HIV management course for nurses and doctors;
- ECG training for nurses and doctors;
- Capacitation of the community through the Community Advisory Board (CAB) members about HIV infection in general, HIV vaccines and research;
- Capacitation of staff through mentoring by their counterparts at the Medunsa Clinical Research Unit (MeCRU).

Alignment of outputs and project goals

Project progress reports have been made available. Also, data from the observational study was assembled into a manuscript and its publication forms part of the plan for the current year. A number of posters were presented at conferences.

Public health contribution

MeCRU: General knowledge and awareness were raised on health matters relevant to the project communities. Strong emphasis was placed on VCT promotion. A visible impact on disease burden is expected to have been achieved through the project.

WSUCRU: In the short term, the community benefitted interns and service providers (doctors, nurses and health care workers), increasing their knowledge about HIV in general and emphasising current strategies for mitigating the infection. The potential for role of an effective HIV vaccine has been widely promoted. A sound understanding of the implications of introducing an HIV vaccine in a high prevalence region was created, and its acceptability shown by the enthusiasm with which the community expressed a willingness to participate research efforts. There is also a noticeable sense of anticipation and urgency in the community for the availability of a vaccine, which bodes well for the introduction of an HIV vaccine in the project region.

Value for money

ISS has been very supportive and understanding in managing the budget for the clinical trials. MeCRU has been able to implement both trials within budget. The value of the weakening local currency (ZAR) has also assisted in meeting this target. There were additional funds for some of the activities which

were forwarded to the site at intervals from ISS via MRC. Overall, the cost of establishing and executing Component 3 activities via **MeCRU** and **WSUCRU** can be seen as money well-spent, with desirable impact and sustainable infrastructure achieved. The most prominent added-value achievement to be considered in this context is that everything was done in the public sector, in public health service facilities. The enhancement of process quality in these facilities as a result of exposure to better management and operational structures that were introduced carries considerable benefit, as testified by all of the staff interviewed.

At **MeCRU**, a strong laboratory development component was also included in the list of specific objectives for the site. By the end of the project, the impression is that the allocated budget for this activity was under-spent. However, with unforeseen delays discounted (discussed below under Conclusions: Component 3), then the laboratory reagent expense in the actual period of study shows on-budget expenditure.

Through the project, a model has been created that serves as an example for establishing clinical research infrastructure, including laboratory capability, in a public service environment challenged by high burdens of communicable disease amongst lesser educated and economically constrained communities. This demonstrates considerable overall cost-benefit.

Sustaining project impact

ISS is presently raising new funds for efficacy studies of the Tat vaccine to be conducted in South Africa, including the MeCRU and WSUCRU catchment areas. Ideally, Phase III trials should start immediately after Phase II, but the ability to progress to this stage in the near future is still uncertain.

MeCRU

Capacity created within MeCRU has enabled the staff to proactively source new funding and develop new projects from scratch. This will enable it to get funding for continuing the work of research which will contribute to the public health interventions that are necessary. Expanding the areas of engagement beyond vaccines, in response to public health needs, is envisaged.

Relationships fostered with the district/regional department of health will continue as the work in MeCRU continues. Clinically, the research will need to access patients and participants from the government facilities if and when necessary.

Community engagement as an element of clinical trial implementation and therefore as part of research will continue to empower communities and foster strong relationships with the institution. This link is important for not only MeCRU but the University as a whole in order to support various departments giving research feedback to their stakeholders.

The unit is currently planning a project on Men-who-have-sex-with-Men (MSM) and it is leveraging on the relationship built with local health care facilities. The blend of the capacity developed from this project and the established skills to educate will be used to identify and coordinate specialised training to offer services (health care) to the MSM group – which is a specialised vulnerable group that continues to be neglected in most parts of the country including the MeCRU project area.

Links have already been forged with other groups focusing on health for men in the country and the staff has already been trained on an approach to men's health. Health care facilities will also be included to train local health care workers to be MSM competent. The grant proposal preparation is in progress to submit to NIH for funding.

The Unit has developed capacity in clinical trials management, which has not gone unnoticed. This will ensure that key activities are sustained beyond the current term of the project. There is also

another efficacy clinical trial (sponsored by HIV Vaccine Trials Network – HVTN) in the pipeline for 2015 and MeCRU has been assessed as a potential site.

WSUCRU

Sustainability of the project at WSU centres on the following:

- The infrastructure set up at the Clinical Research Unit is on long term basis with the hope that the research unit will continue to function beyond the ISS project. The donation of the items used for the project by ISS to WSU through the MRC is a contribution towards the sustainability of the unit. From its side, WSU has been making a contribution towards the existence of the research unit through provision of 24 hour security, maintenance of the back-up generator, connectivity i.e. telephone and internet services, building maintenance, up-keep of the compound around the building and general cleaning services.

- Human resources and financial administration services of the research unit are continuing beyond the ISS project. The university, together with the research unit, is currently working on a business plan for incorporating the research unit into the university.

- The research unit have been, and currently are being marketed aggressively through visibility at conferences. Collaboration with organisations involved in HIV Vaccine research, such as the HIV Vaccine Trials Network (HVTN), is actively being sought in order to secure engagement of the CRU as a potential site for the next HIV Vaccine Trial scheduled for Southern Africa in 2014. The International AIDS Vaccine Initiative (AIVI) and several high-profile research units in South Africa are involved in HIV vaccine or related research, and WSUCRU is eager to play a role in such collaborative efforts. Contact has also been made with organisations involved in tuberculosis research. The research unit has its own website and is also registered with Site Finder where the availability of the Unit for clinical trial purposes is promoted.

- The MRC through its Unit directing the Strategic Health Innovation Projects (SHIP), and the National and Provincial Departments of Health are considered to be major stakeholders who can contribute to the sustainability of WSUCRU.

Conclusions: Component 3

The Plans of Action for Component 3 over the project period

- A detailed description of the expectations from Component 3 of the project has been provided in the form of the original overall project agreement and by way of amended Plans of Action. The project strategy, specific activities, and correlation with human resources are well described, and feasible.

- Overall, the expected deliverables/outputs are clearly quantified and linked to the activities. The achievements that the project aimed to generate were well-defined and achievable within the budget specifications of the component. On the basis of regular monitoring and reporting, a clear description is available of how relevant data for outputs had been obtained and how the project progressed to the point of conclusion.

- Monitoring visits have been performed regularly, and provide clear insight into the progress with infrastructure development, including laboratory capabilities. Quality improvement is obvious, compared to the start of the project. Overall, targets have been reached.

Execution of the project by MeCRU

- MeCRU participated in both the observational and clinical trial study parts of the project. A laboratory development component was included. The project started late (2010 instead of

2007), but then proceeded rapidly, with infrastructure completed, staff recruited, and studies executed to conclusion as per original/revised targets. Delays occurred as a result of the Ndlela pull-out from Component 3 activities, problems with getting the Mthatha site to initiate work on time, the need to wait for the observational study to finish in order to inform the design of the RCT with Tat vaccine (e.g. setting screening criteria based on viral load), and MCC process delays.

- Overall, the Unit has performed well, on-time and within budget, despite the additional burden of covering increased participant recruitment needs for both the observational study and the clinical trial as a result of the Ndlela and Mthatha start-up problems.

- With the project coming to an end, MeCRU is in a good position to attract other funding or RCT contracts. MeCRU has demonstrated that it would be able to deliver on such commitments. The capability developed at the Unit, and the extent of development of clinic readiness and community structures, makes it possible to run more than one trial simultaneously.

- In particular, a strong resource that arose out of the Tat vaccine clinical trial conducted is the protocol team that was created. Its composition is made up of experts from ISS, the MRC, SAAVI, the site Principal Investigator, knowledgeable representatives from DOH, and independent experts from academia and otherwise. The broad range of skills represented is noticeable. Also, the level of integration reached with the NDoH in terms of buy-in on the project is a worthy achievement.

- There is a strong desire at MeCRU that further support would be granted in order to ensure sustainability of activity. In particular, there is the anticipation that actual production of Tat vaccine will be contracted to TBI and that Phase III trials will follow. However, a proposal for a plausible transition plan at the end of ISS/DGCS time-limited support that ensures activities continue and impact is sustained, is not available. This is clearly a priority to be addressed.

Execution of the project by WSUCRU

- The Unit has engaged five health centres, serving approximately half-million population around Mthatha.

- The site experienced a number of challenges delaying start-up considerably, resulting in the decision to restrict activity to the operational/demonstration study, mainly focusing on capacity building for future trials. Activities performed, nevertheless, included all the required steps for patient recruitment and community engagement, clinic preparedness and data management, and infrastructure upgrading. It excluded vaccination and pharmacy operations. ISS has been very accommodating of the difficulties at WSUCRU and allowed for special allocations and a re-designing of project plans.

- Currently, there are major uncertainties regarding the future of the Unit, mainly related to the challenges at the University level. WSU has not been as supportive as expected. Question is whether the Unit will be fully integrated into WSU. The restructuring of MRC in 2013 also meant that staff did not get supported after October 2013, although WSU did assist for a few months. This situation indicates an uncertain future.

- A funding extension specifically directed at field studies or clinical trials would be the only way to build on the investment to date. Overall, the Unit has been well-prepared for conducting similar operational studies in future and to further develop into a clinical trial site.

- Because the project has taken a different route since its inception in Mthatha, there is an opportunity to build on its current strengths. There is a strong link with the nearby HIV clinic, and it might be possible to support the clinic by involving CRU staff. Also, it might be possible

to integrate the laboratory component into WSU. These actions would allow for expanded exposure and useful application of resources created by the project. A business plan is under construction to see to what extent the Unit could be sustained as an integrated part of WSU. Other contracts could also be sought.

- It is important to recognise that the Unit is the only one of its kind in the Eastern Cape Province. A particular strength is seen in the laboratory which is the only one that can process PBMC, alongside the Unit's community research capabilities. Future projects can build on these features.

- Activities and outputs were shown earlier. These are mainly concerned with recruitment of participants for sample collection and determining sero-prevalence in the target community (in ISS labs in Italy).

- Other contributions of the Unit relate to awareness creation in the community of the value and role of an HIV vaccine, running of capacity development programmes amongst public health service providers in and around Mthatha towards improving quality of services and clinical care. Also, the University has gained visibility through the Unit.

- Networking with the CRO Triclinium resulted in better record keeping and management of clinical data for research. Interaction with the local NHLS has also been mutually beneficial.

COMPONENT 3 UPDATE: ISAC OBSERVATIONS 2015

Medunsa Clinical Research Unit

- In 2014, the Interim Assessment recommended that the follow-up of patients who completed the T003 Phase II study be continued for a further 12 months. An amended protocol was subsequently approved and ethics clearance obtained.

- Of the 200 patients enrolled in T003, seven were lost to follow-up (including one withdrawal). Of these 193 subjects, 179 completed Stage 1 follow-up and were eligible for the follow-up Stage 2. By the time of the ISAC visit in mid-July 2015, 64 have completed Stage 2 follow-up, with remained expected to complete by September 2015.

- The objectives of the follow-up were to (a) confirm reduction of viral DNA in participants; (b) determine viral load; and (c) describe the status of immune-markers in the trial population.

- Overall, the integration of the trial activities with clinic services was beneficial to the service environment. The trial has definitely contributed to raising the quality of services. The impact on quality standards of the CRO engaged in the clinical trial activities at MeCRU, positively impacted standards at participating clinics. However, electronic systems do not operate across all facilities and were not directly linked to MeCRU. This is a disadvantage that needs to be addressed.

- The integration of health services places huge demands on data management and has a major impact on record-keeping. Patient numbers at clinics have grown tremendously and result in long waiting times. Incidents have been reported of patients leaving facilities, taking their patient files home, with the intent to return the next day with their files. This leads to uncontrolled situations. Other consequences are that patients skip counselling and pill counting, opting for direct collection of medication and leaving for home. There might be a need for strengthening pharmacies by posting a counsellor at dispensing, who could also do pill counting on the spot.

- In terms of laboratory practices, training is provided to NHLS regarding cell collection and processing. NHLS has been requesting such services from the MeCRU lab component.
- In anticipation of the closure of the Study T003 and subsequent lack of activity in the CRU, other study opportunities have been explored. A number of observational studies, including studies targeting MSM, have been mooted as potential sources of additional activity and funding, but these remain uncertain.
- Challenges faced by the facility:
    - No healthy pipeline of new studies
    - The PI of the unit has been exploring a few funders for new studies without much success – needs support in this area
- It was previously emphasised that the Unit needed to improve its productivity – the data generated over the years need to be analysed and published – in order to boost the scientific standing of the Unit.
- Current activities:
    - Community engagement activities predominantly involved participating in the activities organised by stakeholders and including them in activities organised by MeCRU. At times it meant providing a health education services, other times it would mean just being present in their activities and lending that support. Key to that was the maintenance of the Community Advisory Group that provides support to MeCRU when there are on-going trials. The CAG encourages participants in trials and supports them in the event there are matters they would like to raise. Community educators from the site ensure that they keep sharing information with the community so that they are better prepared to make informed decisions about participating in clinical trials.
    - Realising the critical importance of ensuring sustainability of MeCRU, a protocol was developed for an epidemiological study in the area and this was submitted to several funders – MRC, CANSA- in MSM. This study is a collaboration between several departments in the institution. It is hoped that it will get additional funding for the laboratory consumables from a VLIR IUC/University of Limpopo/SMU collaboration project. It will include recruitment of 200 MSM participants from our local community and is anticipated to take about 6 months, September 2015 to Feb 2016. In the meantime we are in contact with other potential sponsors for studies which may start in Jan 2016. These include:
        - ISS for potential efficacy study
        - HIV Vaccine Trials Network (HVTN) sponsored by DAIDS, for another vaccine efficacy study.

      The PI has also registered the site on the data base of other pharmaceutical companies e.g. Pfizer, for consideration in their other studies even at small scale as it will assist to generate funds for MeCRU.

Walter Sisulu University HIV Clinical Research Unit

- After completion of the ISS OBS TOO4 in June 2013 activities at the Research Unit were greatly reduced. There was no new project in place. Time was spent on finishing some of the work related to the ISS OBS T004 study, re-visiting and redoing some of the Standard Operating Procedures, continuing with the link to the community through the CABs and

attendance of some of the community activities, and planning new projects. It became financially challenging to continue to employ the staff. Ultimately, the services of all the staff, except the Project Manager and the Laboratory Technologist had to be terminated at the end of January 2014. The Project Manager took another position with an NGO in Durban and left the Research Unit at the end of March 2014.

- The university has continued to support the research unit in a number of ways, ensuring that basic services (vehicle, telephone, internet, cleaning, and maintenance) are sustained, and that the Principal Investigator and the Laboratory Technologist remain available to the Unit.
- With effect from July 2014 the research unit became part of the Centre for Global Health, a Unit within the Faculty of Health Sciences which, amongst other responsibilities, has taken charge of all the externally funded projects in the faculty. The research unit is now open for use by other researchers in the Faculty, but the HIV Vaccine Research Unit still has some control over the use of the unit by other researchers.
- Current research projects include:
    - The prevalence and incidence of HIV infection in the attendants of the Health Centres in King Sabata Dalindyebo District and the associated sexual behaviour and other factors (Prof. .J Chandia)
    - TB Pericarditis study (Prof. A Awotedu)
- Marketing of the research unit nationally and internationally for projects continues. WSU sees value in the sustainability of the unit and continues to give it support as detailed above. Also, the research unit continues to enjoy the support of the community and the Provincial and National Department of Health.
- It is anticipated that other role players who have been closely associated with the research unit e.g. the MRC, ISS, European Union, HIV Vaccines Trials Network (HVTN), International AIDS Vaccine Initiative (IAVI) etc. will continue to support the research unit in whatever way possible.
- The Centre for Global Health is a University supported institution under which the HIV Vaccine research unit falls. This development is important for the sustainability of the unit. However, the CRU's relationship to CGH is still being defined. The Unit might not necessarily be incorporated.
- The continued support given by the university to the research unit and the fact that the unit now falls under one of the institutions of the University augers well for its sustainability. It is hoped that the unit will continue to attract more research projects to keep it alive.
- Challenges remaining:
    - The research unit is heavily indebted to the university for money advanced to the unit for recurrent expenses when the ISS funding was delayed. In addition there are debts related to service provision. The unit is waiting for the final tranche from ISS to settle the debts.
    - The challenge of the research unit attracting major research projects still remains. The effort to market the unit is on-going.
    - The unit has no budget specifically for running it. The unit depends on whatever support the university is able to give.

- Concluding remarks:
    - The WSUCRU has demonstrated readiness to be involved in clinical trials. The necessary infrastructure has been achieved, and although no specific trial experience has been gained, a fair degree of exposure occurred through the observational studies in which the Unit was engaged. There is no reason to believe that the Unit would not be able to contribute meaningfully to clinical trial efforts. The University has clinical trial experience in the wider context of its operations, and under the new CGH arrangement, a consolidated capacity is available to manage the requirements of larger GCP trials. The MCC, however, require CT Pi's or Co-PI's to have clinical trial experience. This means that capacity development around the Unit would need to happen before the Unit can formally launch a CT. This would require resources.
    - The Unit is unique in that it is the only one of its kind in the Eastern Cape. It is GCP certifiable as a clinical trials entity, either observational or full CT. It is also the only one with a laboratory and pharmacy specific to the purpose. It would be possible to generate further capacity around the core. Every effort should be made to sustain the facility and its capabilities established under the ISS project.
    - An important aspect to be exploited is the fact that the Unit is linked to the NHLS and to the other clinical research unit in the North, MeCRU. This provides for a strong platform for multi-centre studies, or for networking with other stakeholders. One way to do so, would be to connect the East-London and Mthatha sites of WSU in a meaningful way to the CRU, making it attractive for funders to invest in clinical trials in the Eastern Cape. For example, the CT laboratory and administrative base could be located in East London, with the field work being conducted in Mthatha.
- Future directions:
    - Close-out activities form ISS to inform communities about status need to be launched, but uncertainty about the Unit's future makes this step uncertain.
    - The prevalence studies offer the opportunity to continue the training and community awareness activities pursued under Component 1. ISS is aiming to prepare a memo on how to sustain the community dynamic overall by requesting the NDOH to institute targeted programmes in a wider selection of sites (nDOH might be able to attract donors for the purpose).
    - ART adherence studies are being discontinued.
    - A round-table discussion is being planned for NDOH/MRC/WSU in order to define the way forward on incidence studies to measure new infections vs reinfections.

Remarks and recommendations

Adequacy of resources available to reach expected goals

The allocated budget was well-spent, and the value-add in terms of community and public health benefit, networking, and capacity building was considerable.

Cost-appropriateness of activities and goods/services procured

Activities at Component 1 and 3 sites have been extensive, because of the nature of the project. Development of protocols, operational SOPs, training programmes for staff and community representatives, clinic engagement and patient recruitment, follow-up investigations, programmes to ensure patient retention, and data management over the 3-year project period all represent a major operation in the sites involved. There is no reason to suspect that resources have not been appropriately applied. Site visits to all three implementing partners confirmed that the infrastructure items, human resources, and even consumables, have actually been procured or expended. These are in all respects appropriate to the tasks being performed, and in some instances (such as at TBI) it represents state-of-the-art installations (Component 2).

Adequacy of project achievements in relation to field benchmarks/standards

Achievements of the project may be judged against a number of benchmarks/standards.

For Component 1, the benchmark standards would be national policies and guidelines for provision of primary health care. As shown in this report, impressive advances have been instituted in project sites, serving as a model for expansion to other similar sites in all provinces.

For Component 2 (vaccine manufacturing), certification by a stringent regulatory authority as a manufacturing site, would apply as a standard. The South African MCC is in process to issue such certification to TBI. In addition, TBI holds responsibility for the importation of bulk product, filling, packaging and distribution a number of licensed biological medicines in South Africa, which is an indication of the standards to which the Institute operates. Furthermore, as indicated above, the manufacturing suite which is the result of the DGCS investment, complies fully with WHO guidance on technology transfer.

Under Component 3, the MeCRU laboratory achieved South African National Accreditation Standard (SANAS) certification, valid until 2016. This is a clear indication of systems quality, not easily obtained in many cases. WSUCRU has also been networking closely with MeCRU and the NHLS. In this context, it can be seen as operating on a validated platform.

Summary of key evaluation criteria

Relevance

What is the public health problem to be addressed and why is it significant?

It is commonplace to refer to the HIV epidemic in sub-Saharan Africa as the most severe in the world. Furthermore, its strong association with tuberculosis aggravates the situation considerably. In this context, a project to address the HIV/AIDS epidemic in a way that will reduce the incidence of new infections or overt disease has high relevance.

South Africa has the highest incidence of both HIV/AIDS and tuberculosis in the world[3] and an effective vaccine intervention would impact significantly on the epidemic. Also, other interventions related to informing vulnerable communities, encouraging testing and facilitating ART, will assist with reducing rates of morbidity and mortality. In this regard, all the components of the ISS project contributed significantly, without doubt.

Efficiency

Were the Plan of Action well-conceived and its execution shown to be feasible in the hands of the implementing partner?

The establishment of a GMP vaccine manufacturing facility at The Biovac Institute in Cape Town was a resounding success. The transfer of technology from Diatheva to TBI was conducted according to strict and well-controlled pharmaceutical principles. It was successfully concluded with the production of a demonstration batch of the vaccine that passed all necessary control criteria, witnessed by Diatheva. TBI is ready to produce the Tat vaccine at scale for international distribution, if required.

In the field sites where primary health care strengthening, observational studies and clinical trials were conducted, challenges with implementation and output were experienced, however. These were not totally insurmountable, but posed risks to the project initially. ISS very effectively met the challenge in opting for an adaptive approach to the Plan of Action, with regular updates which responded very adequately to specific project needs as pointed out by active monitoring and interaction with project partners. In particular, the gradual improvement of quality of care at primary health care facilities through targeted interventions aimed at providing training, equipment and improved data management have impacted these in critical sectors of health care service delivery very significantly.

The Medunsa Clinical Research Unit managed to fully absorb the responsibilities that have been shifted to them from two other project sites in Limpopo and Eastern Cape, and completed with great efficiency the observational study and Phase II clinical trial with Tat vaccine within the available time and on-budget.

Also, despite major challenges with initiating activities in Mthatha, the Walter Sisulu University HIV Vaccine Research Unit established all procedures necessary to expand into specific trial requirements, and demonstrated these in the observational study aimed at capacity building via conduct of a Tat seroprevalence study in the target population.

Effectiveness

Have the implementing partners demonstrated the capacity and capability to deliver the project as per agreed targets?

Sites were carefully selected according to their potential for leading the implementation efforts under Components 1, 2 and 3 of the project. In this respect, the guidance of the National Department of Health and of the Medical Research Council (SAAVI) played an important role. As shown in the preceding section above, sites generally performed well. The cost-effectiveness of the project in the hands of TBI and MeCRU is not in question since clear value for money has been demonstrated. For the WSUCRU, however, cost-effectiveness is more difficult to judge. Plans were specially adapted to suit the challenges and needs experienced by the site, and it required additional budget. Furthermore, it did not operate in a highly enabling environment. Its output is also limited, although it demonstrated a commendable level of capacity development to the benefit of the local academic and public health service communities.

In all cases, however, the quality and quantity of scientific output is low, given the fact that the project, as conceived and implemented, is based on technical (TBI) and operational research (MeCRU,

[3] World Health Organization: *Global Tuberculosis Report 2013*. World Health Organization, Geneva: 2013.

WSUCRU) principles. The opportunity to produce scientific output from the project is high, but has not been adequately utilised. Only one manuscript is in preparation (MeCRU), with a number of conference contributions that should have been developed further towards formal publication.

Sustainability

Are the outcomes achieved durable and likely to be sustained as an intervention at the national/regional levels?

Sustainability is directly linked to the continuous and rational use of competent and capable resources/infrastructure. Such an environment has been created through the project. The most sustainable part of project is certainly the enhancements observed in the primary health care facilities under Component 1 of the project. Most of these efforts already have been adopted into common practice in the participating provinces. However, attention must be drawn to the vulnerability of the effort in certain respects, in particular the continuation of roving health teams and ensuring that data capturing capability is conserved.

There is, unfortunately, no clarity as to whether the vaccine manufacturing facility in Cape Town will actually be used for the purpose in the short or medium term. Likewise, there is no certainty as to the future of the clinical research units. Some of the activity might integrate with academic environments, or function as capacity development facilities for public health purposes. All of these uses have been demonstrated as desirable during the course of the project. Ideally, however, the infrastructure and operational platforms should be applied towards serving the purpose for which it had been primarily developed. All hinges on the demonstration of Tat as an efficacious therapeutic HIV vaccine.

The Biovac Institute has plans to accommodate the development or production of other biological medicines in the manufacturing facility in Cape Town, as an alternative option. This has the potential to serve a long-term purpose nationally and internationally.

In both MeCRU and WSUCRU sites, the capability to culture peripheral blood and for freezing and storing cells is a major achievement of the project and a significant benefit to the associated university environments. This is internationally a requirement for studies where sero-prevalence and immunogenicity studies are performed. Also, in the university associated setting, the laboratories can act as training facilities, a value-add from the project. Finally, the clinical sites have put plans in operation to attract funding and trials relevant to these environments. So far, none has definitely been contracted, but the potential is high. From a public health perspective, the clinical sites have played a major role in establishing quality procedures in their areas of operation, which have benefit to the NDoH/PDoH and service delivery to high-burden communities. But, it is not clear to what extent funding would be forthcoming for the purpose.

Recommendations 2014

It can be safely stated that the project has been successfully implemented and concluded, and that the financial resources expended have been worthwhile. There is, nevertheless, a need to secure sustainability of the effort and to ensure that maximum benefit is derived. The following key recommendations might be offered in this regard:

1. Consider the continuation of the clinical development of Tat vaccine in South Africa, initially by extending the period of follow-up observation on the Phase II study group at MeCRU, and then by expanding the study into a multi-centre Phase III effort if safety and efficacy is obvious from the results still to be analysed by ISS. As regards funding the extension of the Phase II follow-up period, it is recommended that consideration be given to the possible use of budgetary savings deriving from the favourable EUR to ZAR currency rate of exchange during the past year of operation.

2. Actively pursue manufacturing opportunities at TBI, if not for Tat vaccine immediately, then for other suitable candidate biological entities developed in Italy that might have a need for scale-up manufacturing. This opportunity should be exploited fully.

3. Encourage the publication in high-profile journals of experiences in the project. The project is unique in many ways and the operational research models are worthy of sharing in this manner. It would also lend scientific credibility to the implementing partners and their capacity to attract external projects and funding. Not everything should wait for the outcome of the clinical trial, and its publication. One possible mechanism of achieving this goal, would be for ISS to participate in SANAC symposia by way of a special session, providing an opportunity for presentation of project outcomes by PIs and other invited speakers, and to publish the proceedings of the session in a recognised public health journal. This will create visibility and credibility with the scientific and public health communities.

4. Owing to the South African per-head income, the Italian Cooperation is not considering cost-extensions of on-going Programs in this country. It should be emphasized, however, that the poorest African Countries, not just South Africa, are the obvious beneficiaries of an effective therapeutic vaccine against HIV/ASIDS. On the other hand, and thanks also to this Program, South Africa offers the core infrastructural setting that, upon further capacity building, would allow for large vaccine efficacy testing in the public sector. Against this background, therefore, it is recommended that the assignment of a time-limited bridging budget that will support active engagement of ISS in assisting at least the clinical sites with recruitment of external or alternative funding in order to sustain operations without interruption, be considered (also see point 1 above regarding accessing budgetary savings). The joint development with NDoH/PDoH of a business plan and funding for optimal use of these capabilities should be further negotiated. Ideally, the plan would provide for both field and laboratory operations developed by the project to be fully integrated into routine service, whilst at the same time operating as model platforms for conducting quality operational research.

Summary of key observations 2015

Component 1 – Health services strengthening

• Enhanced performance in roll-out of ART and quality of care in general
  - NIMART training; roving clinical teams (doctors and social workers)
  - Treatment adherence monitoring
• Effective data collection and information systems management
  - Scale-up to electronic data capturing; very good record-keeping and filing
  - Introduction of e-Health to HFs; training on DHIS and Tier.Net
  - Generation of performance reports to aid management of services
• Efficient pharmacy and dispensing practices
  - High-quality dispensing practices and pharmacy stock control
  - Training of pharmacy assistants; dispensing course for nurses
  - Incorporation of pharmacovigilance training

Component 2 – Vaccine manufacturing
• Biovac infrastructure in place and readiness for manufacturing is evident • Only way to sustain capability is to engage in partnerships that move mature products or late stage developments forward into full-scale manufacturing • Timely notification of intent to advance into Tat vaccine manufacturing is necessary; currently scheduled activities already running well into the future • Biovac would need to plan for expansion soon if scale-up of volume is anticipated • Biovac invested significantly in training staff to meet demands of the GMP production line. • UNIDO supports training modules for production, building on the ISS investment

Component 3 - Clinical Research
• Sustainability of the CRU's will depend on writing and attracting grants • There are capabilities at both sites, but they might need additional support to retain and expand these • WSUHRU has launched a new observational study on HIV prevalence and incidence, but is not involved in another three MRC-associated studies also involving WSU – opportunity for engagement? The Centre for Global Health at WSU seems to be the new administrative home for the Unit, allowing for sourcing of wider expertise. Questions remain about whether this is the best way to go. ISS/NDOH/MRC/WSU round-table planned • MeCRU is active and closing-out on the Tat Trial 003 follow-up. Uncertainty as to sustainability of the staff and activities. Efforts have been made to attract grants or collaborations. So far, no clear commitments.

Recommendations 2015

All recommendations of 2014 remain relevant, although in some instances, the recommendations have been actioned and completed. Remaining funds have been re-allocated as bridging funds in order to conduct follow-up studies of participants in the clinical trials and to secure the infrastructure and staff at the CRU's. However, the 2014 recommendations did not consider Component 1 of the project. Following the 2015 assessment, the following are seen as priority areas to be pursued in order to fully exploit the investment by the project:

6. Very good examples of the beneficial interaction between Italy and SA (implementation partners ISS and DOH) on strengthening service delivery to PLWHA (clinic management, data capturing, pharmacy services, basic equipment) have been demonstrated – the relationship was very beneficial to the South African primary health care system, and in particular to the delivery of ARV care and strengthening of the implementation of national policies. All parties contributed significantly to the successful outcome. It is essential to ensure sustainability and expansion, building effectively on the investments made.

7. Experiences with roving doctor/nurse/social worker concept are promising and should be formalised, expanded and secured. Likewise, information networking is to be rolled-out wider, maintained and upgraded. Very specifically, secure data capture posts (high-risk consequences if not achieved).

8. Excellent infrastructure has been established at Biovac. Scale-up capability to be strengthened and opportunity for wider vaccine production and commercialisation into Africa to be explored. Italian companies could be encouraged to engage with Biovac in order to fully exploit the Italian government investment, in particular, partnerships representing late stage biological medicines product development and manufacturing. A long-term plan for up-scaling of infrastructure and larger-scale production of Tat vaccine (with Diathiva) is essential.

9. MeCRU successful, expand the model to other CRU's and network current partners. NDoH and MRC to engage in medium- to long-term planning around effective utilisation of the CRU's.

10. Conclude the ISAC evaluation process by conducting a high-level scientific workshop on the future prospects of therapeutic HIV vaccines, engaging leading scientists (local and international) in the field, and using the collective output to guide the process of multi-centre Phase III trials with Tat.

———