Building sustainable clinical trial sites in Sub-Saharan Africa through networking, infrastructure improvement, training and conducting clinical studies: The PanACEA approach

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Key words

Capacity Development; infrastructure upgrade; networking; sub-Saharan Africa; sustainability; training

Abstract

Introduction

The Pan-African Consortium for the Evaluation of Anti-Tuberculosis Antibiotics (PanACEA) was designed to build tuberculosis (TB) trial capacity whilst conducting clinical trials on novel and existing agents to shorten and simplify TB treatment. PanACEA has now established a dynamic network of 11 sub-Saharan clinical trial sites and four European research institutions.

Objectives

In 2011, a capacity development program, funded by the European & Developing Countries Clinical Trials Partnership (EDCTP), was launched with four objectives, aiming at strengthening collaborating TB research sites to reach the ultimate goal of becoming self-sustainable institutions: networking; training; conducting clinical trials; and infrastructure scaling-up of sites.

Methods

Assessment in six sub-Saharan TB-endemic countries (Gabon, Kenya, South Africa, Tanzania, Uganda and Zambia) were performed through a structured questionnaire, site visits, discussion with the PanACEA consortium, setting of milestones and identification of priorities and followed-up with evaluations of each site. The results of this needs-based assessment were then translated into capacity development measures.

Results

In the initial phase, over a 4-year period (March 2011 – June 2014), the programme scaled-up six sites; conducted a monitoring training program for 11 participants; funded five MSc and four PhD students, fostering gender balance; conducted four epidemiological studies; supported sites to conduct five Phase II studies and formed a sustainable platform for TB research (panacea-tb.net).

Conclusion

Our experience of conducting TB clinical trials within the PanACEA programme environment of mentoring, networking and training has provided a sound platform for establishing future sustainable

research centres. Our goal of facilitating emergent clinical TB trial sites to better initiate and lead research activities has been mostly successful.

Funding Statement

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Introduction

Tuberculosis (TB) remains a global threat and continues to take an enormous and unnecessary toll of life in sub-Saharan Africa. In 2017, there were an estimated 1.6 million TB deaths worldwide. An estimated 25% of TB deaths continue to occur in the African Region (1). Despite recent progress, current treatment regimens for TB remain unacceptably long and are associated with the risk of considerable toxicity with the potential to cause irreversible disability, thereby resulting in poor compliance. Current treatment is sub-optimal, increasing the risk of relapse and the development of drug-resistant TB strains. To improve the situation, the global TB community will need to increase local site capacities to accelerate the development and implementation of new medical interventions, of which new treatments, identifying new disease biomarkers and new diagnostics are crucial. Especially, the current Covid 19 pandemic with a considerable impact on increased mortality due to decreased case detection, the urgency of this endeavour is emphasized even more (2 MC QUAID)

Performing the clinical studies needed in high-burden countries is important to further the development of new drugs and to create shortened and simplified TB treatment regimens. It is also of vital importance for TB treatment sites to gain knowledge about the disease, and to actively contribute to the research and public health agenda of their respective region or country. In order to perform

clinical trials in the affected countries, clinical sites need to be built, developed and maintained. This can only be realised by experienced clinical research trial staff, who require first basic, then advanced training in Good Clinical Practice (GCP), Good Clinical Laboratory Practice (GCLP), statistics, data management, quality control, research management, ethics in health research and national regulatory activities. Whilst these capacities are required for TB, strengthening in this context will have multiplier effects across clinical research in this setting. Specifically for TB, there is a need for specialist microbiology skills and facilities (3 KITUA).

There is considerable emphasis on capacity development from international funders although there is less information on what constitutes a successful model. The Pan-African Consortium for the Evaluation of Anti-Tuberculosis Antibiotics (PanACEA) is a network of eleven sub-Saharan clinical trial sites brought together and supported by several European research institutions (Table 1). Its main objective is to build clinical TB trial capacity by means of conducting high standard GCP-compliant clinical studies and trials to shorten and simplify treatment. From this consortium, a capacity development programme, funded by the European & Developing Countries Clinical Trials Partnership (EDCTP), was launched to build and strengthen the collaboration of research sites across Sub-Sahara Africa with diverse infrastructure and training needs.

Table 1. Sites of the PanACEA consortium

	Country	**Institutes**
African Partner Sites	**Gabon**	Centre de Recherche Médicale de Lambaréné (CERMEL) - Lambaréné Albert Schweitzer Hospital, Lambaréné (HAS) - Lambaréné
	Kenya	Kenya Medical Research Institute (KEMRI) - Nairobi
	South Africa	Aurum Institute for Health Research (AIHR) - Johannesburg University of Stellenbosch - Task Applied Science (TASK) – Cape Town University of Cape Town – The Lung Institute (UCT) – Cape Town University of the Witwatersrand (Wits) - Johannesburg
	Tanzania	Mbeya Medical Research Centre (MMRC) - Mbeya Swiss Tropical Institute & Ifakara Health Institute (IHI) - Bagamojo

		Tumaini University Kilimanjaro Christian Medical Centre (KCMC) - Moshi
	Uganda	Makerere University Mulago Hospital (MUMH) - Kampala
	Zambia	University Teaching Hospital – University of Zambia (UTH) - Lusaka
Northern Grant Holders	**Germany**	Klinikum der Universität München (KUM) - Munich
	The Netherlands	Radboud University Medical Centre (Radboudumc) - Nijmegen Amsterdam University Medical Centers - University of Amsterdam (AUMC-UvA) - Amsterdam
	United Kingdom	University College London (UCL) - London
		University of St. Andrews (USTAN) – St Andrews

Methods

All eleven selected research centres in the six sub-Saharan TB-endemic countries self-assessed their requirements for capacity development in the following fields: 1. Clinical staff availability and experience; 2. TB laboratory infrastructure and staff; 3. safety laboratory infrastructure and staff; 4. clinical site facilities and equipment; 5. pharmacy facilities and staff; 6. Information Technology (IT) facilities and staff; and 7. overall training needs of all site personnel.

Some elements were identified through a structured questionnaire, some aspects were driven by site visits and with extensive discussions with the relevant partners and ultimately within the entire PanACEA consortium. This was achieved through regular meetings of the consortium in annual meetings and calls. Thereby, priorities and milestones for implementation were set. The strength of this process was that it was a dialogue in which sites were partners and the evaluation was a vehicle for training. This process challenged the whole network to fairly distribute the allocation of material and human resources to sites and create a realistic plan of implementation.

The results of this need-based assessment were then translated into a capacity development plan. The consortium established four pillars of capacity development: 1. Networking: Fostering site

development by implementing activities and platforms to consolidate South-South and North-South collaboration 2. Enhancing infrastructure: Refurbishing of laboratory, clinical sites and improved infrastructure; 3. Training: Strengthening expertise by supporting MSc and PhD students, conducting local monitor training programmes, training of clinical, technical and administrative site personnel, and mentoring sites to ICH-GCP and GCLP standards; 4. Research: Conducting observational studies and clinical trials.

Results

Within four years of its formation, the PanACEA consortium, which started as an informal network of research collaborations, built a strongly interwoven network of state-of-the-art research centres capable of conducting clinical trials in Africa to regulatory standards. PanACEA has built a community of researchers, through providing information, guidance, resources and shared experience. In summary, all centres achieved their self-assessed goals, which were previously agreed and set by the consortium, for capacity development in the fields of networking, enhancing infrastructure, training and research.

1. Networking

Panacea established and consolidated South-South and North-South collaboration platforms. The platforms were used by all stakeholders to share their expertise, to facilitate the links between the African sites and the European researchers and also encouraged sites to share their expertise by mentoring, sharing clinical know-how, discussions and on the job training. Specifically, these networking goals were assisted by establishing a PanACEA website (4 PANACEA WEB) using a web application platform as well as annual face-to-face meetings, and by customised individual mentoring activities.

Annual meetings: The annual face-to-face meetings, held at various African sites (Tanzania, South Africa and Senegal) and in Austria, were used to discuss achievements and challenges of all collaborators and their studies. These meetings were held with the input of an EDCTP representative.

Research agendas were established and progress discussed. The participation of the sites on the consortium board was important to foster leadership development. Furthermore, PhD and MSc students were encouraged to present and discuss their research.

Mentoring programmes: Mentoring activities were performed on a regular basis, whereby clinical, scientific and administrative support was given (North-South and South-South). This support included regular calls, email reviews, on-site job shadowing, manuscript writing, laboratory visits, presentation support and trainings in GLP and GCP.

PanACEA website: The PanACEA website (4 PANACEA WEB) was widely used for communication of PanACEA's work within the consortium and towards the external community. The website comprises information about the mission and history of PanACEA, introduces the teams and the scientific network, lists facts about TB and PanACEA's clinical studies. A whole section of the webpage is dedicated to capacity development: infrastructure update, networking, internal monitoring and student training. Regular news updates and in-detail study and site descriptions are posted.

Document sharing platform: A web application platform (Sharepoint®) was used by all consortium members and by the EDCTP to share all developed study and trial documents. It is the document repository for all PanACEA activities; in addition, it is extensively used for communication and document sharing within the consortium, all vendors, investigators and trial personnel. Various useful templates, study plans and SOPs for laboratory, clinical and project management work were designed, distributed and implemented by all consortium members. These documents were created for the PanACEA studies, but can, in the future, be used as templates for further research projects by the site and by the consortium.

2. Enhancing infrastructure

An intensive means assessment was performed on the limited funding available, and contributions were allocated according to sustainability, outputs and projected academic returns. Contributions to physical infrastructure of tuberculosis clinical sites through PanACEA, included refurbished wards, clinics, laboratories (accreditation) and pharmacies of six sites in Uganda, South Africa, Tanzania

and Gabon according to needs established in their self-assessments. The sites were asked to assess their needs in the following categories: laboratories, clinical facilities, data management (infrastructure and human resources), sample repositories, information technology, library facilities, finance and administration.

3. Training of medical, technical and administrative staff

The grant contributed to the professional development of the staff employed on the project. PanACEA employed senior, mid-career and early career clinical personnel. Furthermore, PhDs and MSc students, nurses, and administrative personnel were recruited during the running time of the grant (5 – 7 MPAGAMA; ROJAS; HONEXBORNE). The majority of the 24 full-time and 13 medical staff, technical and administrative staff was local African colleagues with an equal gender balance.

To enhance the leadership platform capacity, two delegates per site attended the annual PanACEA General Assembly (GA) meetings, to obtain and to exchange knowledge, by actively participating in the meetings and discussions and network with others from the TB research community. Furthermore, various sites participated at TB research community conferences (e.g. CROI, Lung Health Meeting) where PanACEA members could present their data and could collaborate with other TB trial networks.

Post graduate training programme: In its first phase reported here, PanACEA has funded five MSc and four PhD students (in South Africa and Tanzania) at the consortium sites to fill identified institutional gaps. Five students from Tanzania, South Africa and Kenya successfully finalized their Masters programme and two PhD students from Tanzania and South Africa also finalised their PhD.

Mentoring programme: Postgraduate and postdoctoral training and attachments to key positions within the network for mentorship and career development were encouraged. Intensive mentor – mentee relationships were established N-S, S-S and within an institution.

Monitoring training programme: PanACEA conducted a monitoring training programme for eleven trainees from sites located in Gabon, South Africa, Tanzania and Zambia to teach standardized Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) procedures across the sites.

This training was performed by the African Clinical Research Organization (ACRO) in Johannesburg, South Africa, in order to establish a central monitoring pool for current and future studies. The initial step was completed with primary training of monitors. These monitors are now gaining experience to enable them to deliver the next phase: to train new monitors at their respective sites.

4. Research: Conducting studies and trials

The sites were supported to participate and design their own studies appropriate to local conditions and individual stages of development. The studies included epidemiological studies (to characterise the available TB patient populations in preparation for future studies) and GCP standard intervention trials. PanACEA conducted epidemiological studies (Table 2) to provide an understanding of the impact, incidence, prevalence, and characteristics of TB in the communities to be involved in current and future clinical trials. These aims were achieved by establishing a detailed description of the demographic, medical, sociological and nutritional characteristics of the patients.

Table 2. Epidemiological studies of the PanACEA consortium.

Epidemiological Study	Objective	Involved Sites	Publications
OEBA - Observational Early Bactericidal Activity	To evaluate the decline in sputum bacillary counts in patients with newly diagnosed, sputum smear positive pulmonary TB during the first 14 days of standard HRZE treatment following Tanzanian guidelines.	MMRC (Mbeya, TZ), KCRI (Moshi, TZ)	Honeyborne et al. 2014 (7) Bowness et al. 2015 (8)
CONFIRM – Clinical and Care Observations, Novel Findings in Radiology and Mycobacteriology of Mycobacterium tuberculosis	To determine the proportions of known TB risk factors among patients with active TB in Kampala	MHMU (Kampala, UG)	Kirenga et al. 2012 (9) Ssengooba et al. 2016 (10)

Epi Study - A study of the epidemiology and management of TB at one site in Tanzania	To establish and followed up a cohort of TB suspected individuals in close collaboration with the National TB and Leprosy Programme to provide information on epidemiological, demographic, clinical, operational and social aspects of TB in the study area.	IHI (Bagamoyo, TZ)	
PANEPI - Epidemiology of Tuberculosis in Lambaréné	To characterize the epidemiology of pulmonary TB in areas of high TB prevalence in Africa including clinical and molecular information.	CERMEL (Lambaréné, GA)	Bélard et al. 2014 (11) Janssen et al. 2014 (12) Flamen et al. 2014 (13)

PanACEA conducted and supported the sites to conduct the following clinical studies (Table 3). Through this process of working together in these large studies, the sites were not only able to identify their needs of resources and training, but to be able to independently perform clinical TB trials in the future.

Table 3. Clinical trials of the PanACEA consortium.

Clinical trial	Objectives	Involved Sites	Publications
REMox TB	To determine whether a moxifloxacin-containing TB treatment regimen could reduce the time needed to treat drug-sensitive TB patients from 6 months or longer to 4 months.	54 trial sites in 9 countries worldwide	Bryant JM, et al. 2013 (14) Friedrich et al. 2013 (15) Gillespie SH, et al. 2014 (16) Gillespie SH, et al. 2015 (17) Olaru et al. 2015 (18) Phillips PP, et al. 2016 (19) Murphy ME, et al. 2017 (20) Phillips PPJ, et al. 2017 (21) Murphy ME, et al. 2018 (22) Murthy SE, et al. 2018 (23) Tweed CD, et al. 2018 (24)

SQ109 EBA	To evaluate early bactericidal activity and safety of SQ109 in the treatment of pulmonary TB.	TASK (Cape Town, RSA), UCT (Cape Town, RSA)	Kayigire et al. 2013 (25) Bowness et al. 2015 (8) Heinrich et al. 2015 (26) Olaru et al. 2015 (18) Murphy et al. 2017 (20)
MAMS - Multi-Arm Multi-Stage Trial	To identify regimens to include in a phase III trial for shorter treatment of tuberculosis	MMRC (Mbeya, TZ), KCRI (Moshi, TZ), IHI (Bagamoyo, TZ), TASK (Cape Town, RSA), UCT (Cape Town, RSA), Wits (Johannesburg, RSA), Aurum (Johannesburg, RSA)	PanACEA 2012 (27) Phillips et al. 2012 (28) Boeree et al. 2017 (29)
HighRif 1	To determine whether high dose rifampicin, in combination with other standard TB drugs, is safe and tolerable and associated with improved response.	TASK Cape Town, RSA), UCT (Cape Town, RSA)	Boeree et al. 2015 (30) Bowness et al. 2015 (8) Bruno et al. 2020 (31)
HighRif 2	To determine whether high dose rifampicin, in combination with other standard TB drugs, is safe and tolerable and associated with improved response.	KCRI (Moshi, TZ), IHI (Bagamoyo, TZ)	Tostmann 2013 (32) Aarnoutse et al. 2017 (33)

Output

By working together in epidemiological and clinical trials, the sites were not only able to identify their need for resources and training, but to develop to the level of being independently capable of performing clinical large scale TB clinical trials. For example, through the ReMoxTB study, the microbiological laboratories were brought to an international standard for safety and mycobacterial ex-

pertise, developing a laboratory and quality manual that has formed the basis of manuals in subsequent studies (34). Furthermore, through developing skill-sets related to EBA studies, sites have since attracted commercial and other grants for further studies. Through advocacy and engagement, sites in Uganda and Tanzania now receive support from their governments, thus encouraging sustainability.

Sustainability

Sustainability is the acid test of capacity development after an intervention stops. In the case of PanACEA, sustainability has been the primary agenda throughout. For example, collaborators linked together to extend the reach of their research into innovative diagnostics, developing the PANBIOME PANacea BIOMarkers Extension programme, also supported by EDCTP. In addition to performing the evaluation of a novel treatment monitoring tool, it built laboratory infrastructure for research notably in the area of molecular diagnostics (35 ALABI). It also provided PanACEA the opportunity to expand its network including Blantyre, Malawi, and Maputo, Mozambique.

PanACEA II is the second EDCTP-funded programme, where the capacity development goals of PanACEA I have been realised. Through enhancing capacity to lead research, African investigators now make up a large part of the executive group and are actively developing new concepts, which will directly be implemented in their own research centres and take the consortium forward. The evidence of our sustainability at a personal level is that four out of ten members of the study sites have come through our programme. A major goal of this new cycle of research is to move the centre of gravity to African partners, to take a role in leading the PanACEA research programmes, so that the leadership of new research consortia and networks is located in the South. Thereby, the focus will be on African researchers to gain sponsor expertise, develop and design their own trials, manage their own drugs and enhance microbiological capacities.

Discussion

The United Nations Development Programme (UNPD) describes capacity development as the process through which individuals, organizations and societies obtain, strengthen and maintain the capabilities to set and achieve their own development objectives over time (36 UNPD). The programme describes supporting growth – within three different levels: the individual level (personal change), between groups (institutional change) or within institutions and lastly across societies as a whole (societal change) (37 LANGSANG). There are few models that provide an approach yielding success. The PanACEA programme has focused primarily on the first two levels: staff and institutional levels.

Personal skills improvement change: Training, employment and mentoring programmes helped building capacity on the personal level. PanACEA employed senior, mid-career, early career, PhD students, MSc students, IT specialists, monitors, clinicians, researchers and nurses. The challenge now is to ensure that they continue on their path to research leadership and that there is a well-financed career structure that motivates them to address the problems of their continent by performing locally and globally relevant research and by driving the research agenda.

Institutional change: Institutional capacity development was triggered by performing clinical studies and trials. Our experience shows that through our capacity development activities, research site staff can be supported and mentored to perform GCP-compliant clinical TB trials. This depends on sound physical infrastructure, training and strong on-site leadership qualities and commitment. We have shown that gaining experience through physically conducting clinical TB trials, monitoring and training, is the best catalyst for future self-sustainable research centres. Learning through experience reveals existing operational gaps and highlights deficiencies in infrastructure and networks. This experience builds stronger leadership on an individual and institutional level to facilitate the sites to better initiate and lead research activities.

***Societal change*:** This involves addressing national policies, governance, and regulations, as a product of the development of the personal and institutional changes. For example, with PANACEA I as one of its important partners, CERMEL in Gabon, PanACEA was able to raise the profile of TB treatment and research at the institution, region, and Gabon as a whole. As a result, the site now has a

standardised TB diagnostic laboratory with well-trained and experienced clinical and laboratory staff providing specialised and rapid TB diagnostic services. These services have improved diagnostic and treatment support to local hospitals and treatment centres in Lambaréné; as well as providing support to the Gabon National TB Control Programme (Box 1).

Box 1. - Case Vignette: Building TB diagnostic and treatment capacity by gearing up for clinical trials – CERMEL, Lambaréné, Gabon

CERMEL is a leading clinical research center in the Central African region. Whereas the core expertise and main focus, spanning more than two decades by now, lies with developing tools for malaria control from vaccines to novel drug(combination)s, the unit has expanded into many areas of contributing to the body of knowledge on epidemiology, pathophysiology, immunology, prevention, treatment and control of tropical infectious diseases and beyond. The clinical trial capacity now spans phase I – IV trials in the fields of drug and vaccine development from malaria to e.g. Ebola virus disease, helminthic infections, and others.

Up from 2009 onwards, and with EDCTP via PANACEA I as one of the principal funding bodies, the TB laboratory was developed. By now, the unit has evolved into a fully-fledged state-of-the-art TB laboratory encompassing smear microscopy, solid and liquid culture, and drug sensitivity testing; and build local staff laboratory and clinical capacity.

Following the assessment of the TB treatment situation in the country (38 KOMBILA) and Lambaréné in particular (39 STOLP), we examined the socio-anthropological aspects of TB control in Gabon (40 CREMERS) and identified overall knowledge gaps on HIV and TB in the Central African region (41 MANABE). Alongside the TB laboratory development, CERMEL partook in a first EDCTP-funded trial ('PROMPT') (40 CREMERS) and conducted the EDCTP-PANACEA I-funded PANEPI study. PANEPI provided a thorough baseline assessment of the regional TB epidemiology and lead to the identification of a massive MDR-TB outbreak in the region (42 BELARD) and to concerns regarding the quality of care for paediatric TB patients (11 JANNSEN), as well as regarding the limited access to second-line drugs

to treat drug-resistant TB (10 SSENGOOBA). With support from the National TB programme and the Government of Gabon, the identification of an urgent need to create MDR-TB treatment capacity led to the opening of a designated MDR-TB ward in the Centre Hôpitalier Georges Rawiri in Lambaréné and the training of qualified nurses and physicians under CERMEL guidance. Up from 2015, with expert input from the AMC senior partner, MDR-TB patients were treated successfully with the shortened 'Bangladesh' regimen in an ongoing observational study before WHO treatment policy was adapted and the Bangladesh regime became standard of care (43 ATEBA). Supported by CERMEL, Gabon applied for the first time to the Global fund to obtain financial backups for MDR-TB diagnostics and treatments, and the laboratory was appointed National Reference Centre for TB diagnosis. The site is now gearing up to contribute to PANACEA II clinical trials.

Conclusions

Across the consortium, the most important lesson learned from this initiative was that for capacity development to be effective on all three levels (individual, institutional and societal), the process needs to be tailored to the needs of the sites, and must be owned and driven by the sites themselves. Empowerment of the local institutions is key to their own success. Ownership requires active involvement, including participation in decision-making on the required capacity, investing in the capacity development processes as well as utilization and retention of the developed capacity (44 MGONE). PanACEA incorporated this by providing training and especially by the 'learning by doing' approach of providing mentoring while actually performing clinical studies. By conducting a trial, staff could be trained in their roles and responsibilities whilst acquiring new core competencies. Clinical trials establish the evidence base for the prevention and treatment of disease (45 LANG). Trials are justified in the affected countries where the gain of improving health is attained from effective new interventions.

Whitworth et al. (46) state that the lack of career paths to attract and retain good researchers is the most serious barrier to health research in Africa. PanACEA is a collaboration which will continue

to allow people to have sustained employment and career development. This will reduce or prevent the need to move to more affluent countries, i.e. reduce brain drain, the migration of educated staff to more affluent countries in order to pursue a higher standard of living and quality of life, higher salaries, access to advanced technology and more stable political conditions.

The development of attractive career pathways is key to bringing research in sub-Saharan Africa to international standards of excellence. In order to pave the way for new career positions, an awareness of their need is necessary. The human and material resource capacity available to ensure a high standard of design, management, and operation of clinical trials in developing countries lags far behind that available in wealthier nations (46 WHITWORTH). Awareness, education and experience to design and perform clinical studies is necessary and was the underlying core of this initiative.

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