Alignment at Trans-Regional Level: Case Study No.3

The European and Developing Countries Clinical Trials Partnership (EDCTP)

Alignment at Trans-Regional Level

Case Study No. 3 – The European and Developing Countries Clinical Trials Partnership (EDCTP)

Dissemination level: Wider public

Prepared by: Italian Ministry of Education, University and Research (MIUR)

Contributors: INRA, UNIMAN, AIT

ABSTRACT

The European and Developing Countries Clinical Trials Partnership (EDCTP) was established in September 2003 by 15 European countries with the aim to develop capacity building for clinical trials and new clinical interventions to address the needs of sub-Saharan Africa in the fields of HIV/AIDS, malaria and tuberculosis. Created as an Article 169 of the Treaty (since re-numbered as Article 185 of the Treaty on the Functioning of the European Union), the EDCTP aims at improving coordination and integration of research from different European Member States in the field of poverty related diseases.

The programme has facilitated alignment and coordination of European national research programmes and activities; has fostered African leadership in clinical research, and has strengthened the ethics and regulatory environment for conducting clinical trials in sub-Saharan Africa.

The study highlights the Article 185's many benefits. EDCTP has enabled participating countries to achieve an alignment at strategic and operational levels, thanks to:

(i) the coordination of European research and collaborations in Africa area;

(ii) the increase of research capacity in the Sub-Saharan Countries through the joint training and capacity building activities for participating researchers;

(iii) the harmonisation and standardisation of scientific techniques and methodologies;

(iv) the establishment of regional Networks of Excellence (NoEs) for conducting clinical trials and providing mentorship programmes in sub-Saharan Africa. These NoEs have allowed new partnerships to be established among sub-Saharan Countries;

(v) the harmonisation of the regulation, registration and ethics of clinical trials in Sub Saharan Countries;

(vi) The improvement and development of links with third parties, including: product development partnerships (PDPs), multinational pharmaceutical companies, philanthropic organisations, and like-minded organisations contributing to the development of new clinical tools against HIV/AIDS, tuberculosis, malaria and neglected infectious diseases.

Yet, the EDCTP programme has also been confronted with: (i) financial limitations (ii) low collaboration with other regional initiatives in sub-Saharan area and (iii) removal of the so-called "brokering approach".

The case study builds on the ERALEARN2020 Task 4.4 ("Alignment at Trans-Regional Level"), and relies on an analysis of existing and potential modalities for aligning national/regional activities.

ACKNOWLEDGEMENTS

The case study has been written by Luisa Garofalo from MIUR. The author is grateful to Dr. J. Gabrielle Breugelmans (EDCTP North-North Networking Manager), Dr. Ole F. Olsen (EDCTP Director of North-North Cooperation) and Dr Rafael De Andrés Medina, Instituto de Salud Carlos III (Spanish member in the EDCTP General Assembly), for their useful inputs. She would also like to thank the ERA-LEARN Consortium partners and Advisory Board for their useful suggestions on earlier drafts of this case study.

Table of contents

1. Introduction

This case study examines the key features and overall strengths and weaknesses of a specific alignment modality, namely the Article 185 Initiative - European and Developing Countries Clinicial Trials Partnership (EDCTP) - on common research priorities and health needs, particularly those relevant to Europe and sub-Saharan Africa.

According to the Typology of Alignment, the Article 185 instrument is used during the research implementation phase in view of establishing a strategic, long-term and integrated European research programme. The modality of this alignment is focused on financial, operational and strategic levels, and involves many actors in the research programming cycle (e.g., policymakers, government agencies in high-burden and donor countries, scientists, research funding agencies, individual researchers, multilateral organizations, nongovernmental organizations, academic institutions, and the private industry).

EDCTP has been instrumental in raising the European Union's (EU) visibility on the international agenda for global health and in one of its strongest instruments for fostering cooperation with Africa. The 2007 EU Programme for Action[1] and its 2009 Progress Report highlighted the key role of EDCTP in its own right and as a catalyst model for other programmes aiming at coordinated international collaboration.

The Africa-EU Strategic Partnership, emanating from the 2007 Lisbon Declaration[2] and re-emphasised in the Europe 2020 Strategy, identifies EDCTP as an important actor in its first Action Plan for Implementation, especially in the Eight Partnerships on Science, Information Society and Space. EDCTP is one of the EU's flagship programmes contributing towards European effectiveness, visibility and coherence in international health research.

2. Key features of ECDTP

2.1 Overview

In 2002, as part of the European Commission's Sixth Framework Programme (FP6) for research and Technological Development[3], the provision for participation in research and development programmes undertaken jointly by several Member States was announced, including the structures created for the execution of those programmes. At that time, Member States were already undertaking individual research and development programmes or activities in long term partnerships with Sub Saharan countries aimed at developing new clinical interventions to combat the global problem of HIV/AIDS, tuberculosis and malaria. However, these were "*not sufficiently coordinated and did not allow a coherent approach at European level for an effective research and technological development programme to combat the diseases in developing countries, or to find optimal treatments suited to the conditions in these areas*[4]*.*

The first EDCTP programme (EDCTP1) was established in 2003 as the European response to the global health crisis caused by the three main poverty-related disease HIV/AIDS, tuberculosis and malaria[5]. The EDCTP1 programme was jointly undertaken by 14 European Union countries and Norway and Switzerland in collaboration with countries in sub-Saharan Africa. By applying Article 185, each country participating in the EDCTP programme mobilises its publicly funded organisational and institutional activities to synchronise and pool resources into a joint programme.

In preparation for the continuation of the EDCTP programme, a dedicated FP7 Coordination and Support action, also known as EDCTP-Plus, was implemented in 2012. Under this CSA grant, an extensive mapping of national programmes, activities and stakeholders addressing clinical research on poverty-related diseases (PRDs) in

[1] Communication from the Commission to the Council and the European Parliament - A European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action (2007-2011).
[2] Lisbon Declaration EU-Africa Summit, December 2007.
[3] Decision No 1513/2002/EC.
[4] Decision No 1209/2003/EC.
[5] The diseases are characterised as poverty-related diseases not only because they are endemic in impoverished populations but also because they impede economic development and cause unnecessary death and suffering.

developing countries, particularly in sub-Saharan Africa, was conducted. The outcome of this mapping exercise provided the necessary insight on which the final EDCTP2 objectives were based. This involved internal and external consultations, stakeholder meetings and focussed surveillance of the targeted disease areas.

The EDCTP-Plus project aimed to prepare for EDCTP2, which would have an increased budget, a broader scope covering all phases of clinical trials from phase I to IV, as well as health services optimisation research, and an expanded disease remit with the inclusion of neglected infectious diseases (NIDs). Additionally, a comprehensive review and revision of the governance structure, as well as operational policies and procedures was required to ensure EDCTP2 compliance with the Horizon 2020 rules of participation. The EDCTP-Plus activities were completed in December 2014[6].

The second EDCTP programme started in late 2014 and the current partnership consists of 13 European Union Member States[7], plus Norway (the EDCTP Participating States) and Switzerland as Aspirant member and 14 African countries[8], the European and African Participating States (PSs) of the EDCTP2 programme. The European Union and African regional organisations (i.e., African Union Commission for Social Affairs, Regional Economic Communities and WHO-AFRO) participate as observers on the EDCTP General Assembly.

The overall objective of EDCTP2 is to contribute to the reduction of the social and economic burden of PRDs in developing countries, in particular in sub-Saharan Africa, by accelerating the clinical development of effective, safe, accessible, suitable and affordable *medical interventions*[9] for PRDs in partnership with sub-Saharan Africa. The EDCTP2 programme will run over a ten-year period from 2014 to 2024, with an estimated budget of up to € 2 billion, of which a half (either as a cash or in-kind contribution) will come from the PSs working in collaboration with African Countries and third parties (e.g., private sector and like-minded organisations). The EU will financially support the programme with a cash-contribution of up to 683 million from the Horizon 2020 programme's societal challenge "Health, Demographic Change and Well-being" ("EDCTP2 basic act"[10]).

The EDCTP programme contributes to the European Commission flagship initiative 'Innovation Union' as the programme will enhance the effectiveness, visibility and coherence of global health research in Europe. It offers a shared approach to clinical research on PRDs and has the potential to contribute to a European Research Area, as envisaged for EU's international science and technology cooperation programmes. Further, at their Berlin meeting in 2015, the G7 Ministers of Science expressed their resolution to support the fight against "poverty-related infectious diseases and neglected tropical diseases", with EDCTP recognised as one of the mechanisms to be built upon[11].

2.2 Principal outputs to date

The EDCTP programme developed a unique funding approach, integrating clinical research and capacity building activities as 'Integrated Projects' conducted by collaborative consortia of European and African partners, together with like-minded organisations. This approach has facilitated a certain coordination and alignment of European national research programmes and activities. Furthermore, the approach has fostered African leadership in clinical research and has strengthened the ethics and regulatory environment for conducting clinical trials in sub-

[6] EDCTP Annual Report 2014, Starting EDCTP 2

[7] Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

[8] Burkina Faso, Cameroon, Congo, Gabon, The Gambia, Ghana, Mali, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda, and Zambia.

[9] In the EDCTP2 programme, "medical interventions" encompass measures whose purpose is to improve or sustain health or alter the course of a disease, in particular prevention and treatment based on medicinal products such as drugs, microbicides or vaccines, including their delivery modality, follow up of treatment and prevention in the affected population as well as medical diagnostics to detect and monitor disease/health evolution.

[10] EDCTP2 Basic Act: Decision No 556/2014/EU of the European Parliament and of the Council of 15 May 2014 on the participation of the Union in a second European and Developing Countries Clinical Trials Partnership Programme (EDCTP2) jointly undertaken by several Member States, Official Journal of the European Union, OJ L 169, 7.6. 2014, p.38.

[11] EDCTP Strategic business plan for 2014–2024.

Saharan Africa. The EDCTP programme thus brings together the individual strengths of participating European and African countries. The EDCTP outputs can be summarised as follows:

- EDCTP launched 65 calls for proposals and awarded 254 grants with a contract value[12] of €207.99 million;
- The majority of EDCTP grant funding (€154 million; 74.2%) has been awarded to African institutions and researchers;
- The grant funding from EDCTP has been supplemented with €169.695 million co-funding (cash and in-kind) from European Participating States, African countries and third-party organisations, such as product development partnerships (PDPs) and pharmaceutical companies;
- Increasing sustainable collaborations (South-South, North-South and North-North): researchers from 259 institutions in 30 sub-Saharan Africa and 16 European countries collaborated on EDCTP-funded projects
- 102 clinical trials supported;
- Several new clinical trial sites were established or expanded their capacity to conduct trials on new interventions or diseases (in Republic of Guinea, Guinea Bissau, Mozambique, Namibia, Senegal, Tanzania) through EDCTP funding;
- 8 projects led to improved medical treatments;
- EDCTP supported the long-term training of 516 scientists and clinicians in Africa from Bachelor's to postdoctoral researchers;
- Launch of four African networks of excellence that united 64 diverse institutions across 21 countries in sub-Saharan Africa to improve trials capacity;
- EDCTP provided start-up funding to the Pan-African Clinical Trials Registry (PACTR, www.pactr.org), which has advocated for and enabled an increase in prospective clinical trial registration in Africa. PACTR has since 2010 been officially recognised as a WHO Primary Registry;
- Launch of the African Vaccine Regulators Forum (AVAREF).

2.3 Mission and activities of EDCTP 2

The aim of EDCTP2 is to enhance research capacity and accelerate the development of new or improved drugs, vaccines, microbicides and diagnostic for the identification, treatment and prevention of HIV, tuberculosis and malaria and Neglected Infectious Diseases(NIDs) in sub-Saharan Africa, including emerging infectious diseases of relevance for Africa, through all phases of clinical trials with emphasis on phase II and III clinical trials.

EDCTP2 will provide a push mechanism through its grant funding system for new or improved tools for PRDs along the development pipeline from phase I to IV, thus facilitating their optimal development and deployment in developing countries.

The European PSs are committed to EDCTP's mission to align and coordinate their national programmes to better achieve the objectives of the partnership.

The activities of the EDCTP2 programme will contribute towards achieving the following five specific objectives:

1. Increase the number of new or improved medical interventions for PRDs, including neglected ones;
2. Strengthen cooperation with sub-Saharan African countries, in particular on building their capacity for conducting clinical trials in compliance with fundamental ethical principles and relevant national, EU and international legislation;
3. Better coordinate, align and, where appropriate, integrate relevant national programmes to increase the cost-effectiveness of European public investments;
4. Extend international cooperation with other public and private partners to ensure that the impact of all research is maximised and that synergies can be taken into consideration and to achieve leveraging of resources;
5. Increase impact due to effective cooperation with relevant EU initiatives, including its development assistance[13].

[12] Strategic Business Plan for the second phase of the European and Developing Countries Clinical Trials Partnership programme (EDCTP2, 2014-2024) undertaken by several Member States under Article 185 of the Treaty on the Functioning of the EU, May 2016.

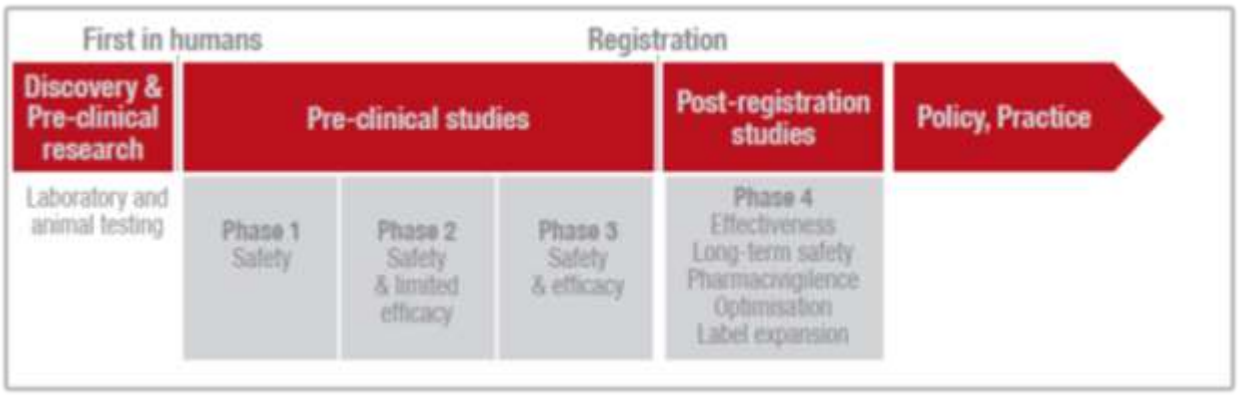
Activities shall be included in the work plan of the EDCTP2 Programme adopted annually by the EDCTP2-Association ('the EDCTP2 annual work plan'), following the positive outcome of their external evaluation by international peer review with regard to the objectives of the EDCTP2 Programme.

The EDCTP2 Programme shall include the following activities:

a) promoting networking, coordination, alignment, collaboration and integration of national research programmes and activities on poverty-related diseases, including neglected ones, at scientific, management and financial level;
b) supporting clinical trial research and related activities on poverty-related diseases, in particular HIV/AIDS, malaria, tuberculosis and other poverty-related diseases, including neglected ones;
c) fostering capacity development for clinical trials and related research in developing countries, in particular in Sub- Saharan Africa, through grants for: career development of junior and senior fellows, promoting mobility, staff exchange grants, research training networks, strengthening ethics and regulatory bodies, mentoring and partnerships at individual or institutional or regional level;
d) establishing cooperation and launching joint actions with other public and private funders;
e) assuring awareness, endorsement and acknowledgment of the EDCTP2 Programme and its activities through advocacy and communication, not only at Union level and in developing countries, but also at global level[14].

The scope of EDCTP2 was extended, covering neglected infectious diseases, diarrhoeal diseases, lower respiratory tract infections and emerging infections affecting sub-Saharan Africa (such as Ebola and yellow fever) in addition to HIV, TB and malaria.

Figure 1:Scope of EDCTP



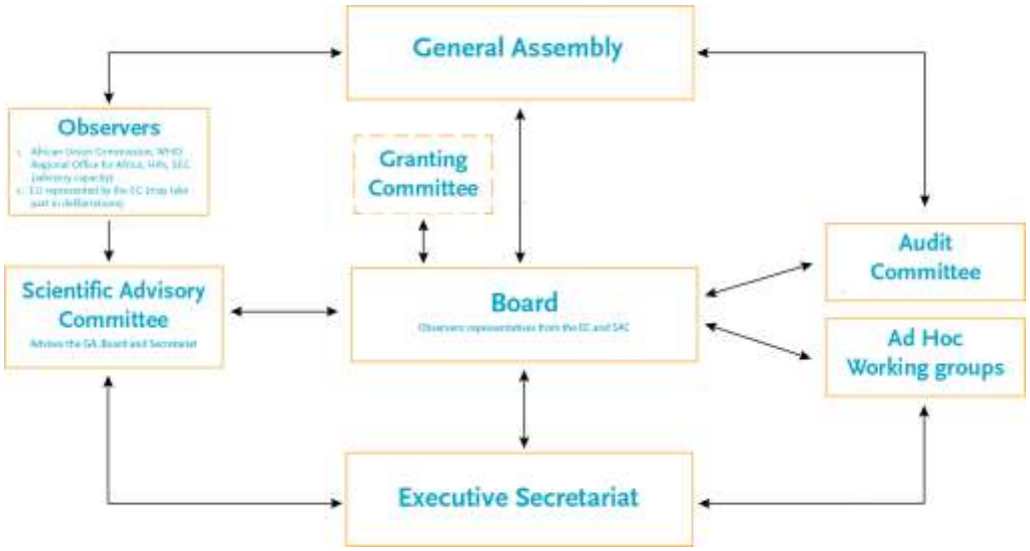
Source: EDCTP2 in a nutshell

2.4 Governance structure

Moving toward EDCTP2 the legal structure of the partnership changed from an European Economic Interest Group(EEIG) to an Association under Dutch law. The EDCTP Association [15] is governed by the Participating States through its General Assembly. Representatives of the European Commission, the African Union and the World Health Organisation are observers on the General Assembly. This new legal structure enables both European and African countries to become members of the EDCTP governing body. One of the main requirements to become a member of the EDCTP partnership is to commit to an annual cash or in-kind contribution of €200.000 to activities that fall in the scope of the EDCTP2 programme.

[13] EDCTP Workplan 2016.
[14] Annex 2 "activities and implementation of the EDCTP2 programme": Decision No 556/2014/EU of the European Parliament and of the Council of 15 May 2014 on the participation of the Union in a second European and Developing Countries Clinical Trials Partnership Programme (EDCTP2) jointly undertaken by several Member States, Official Journal of the European Union.
[15] The EDCTP Association was registered in April 2014.

Figure 2: Governance: legal setup of the EDCTP Association



Source: EDCTP website

3. Overall strengths and key achievements of programme

3.1 Networking of European and African Programmes

The vision of EDCTP is to:

> *"Contribute to the reduction of the social and economic burden of poverty-related diseases in developing countries, in particular in sub-Saharan Africa, by accelerating the clinical development of effective, safe, accessible, suitable and affordable medical interventions for PRDs in partnership with sub-Saharan Africa*."

This will be realized through networking and integration of European national programmes and investments and by maintaining and reinforcing the partnership with sub-Saharan Africa and like-minded organisations.

The mission of networking is to build relationship and brokering sustainable partnerships in order to leverage funds and align global and local health research agendas to facilitate EDCTP's overall mission.

Networking is one of the main pillars of EDCTP's programme and is conducted through activities that strengthen the coordination and integration of European national programmes; build strong north-south partnerships; support the transfer of technology, and ensure the sustainability of the partnership. Experience from EDCTP1 has shown that improved coordination of European research and collaborations in Africa is of great benefit to all partners, reinforcing the impact of the European contribution.

European (north-north) networking: coordination of national funding

The objectives for national programme networking and coordination at the European level are:

- coordination of national research objectives, strategies and activities in the European PSs to promote efficiency, complementarities and avoid duplication;
- integration of national research agendas and programmes for PRDs;
- creation of synergies and added value between national funded activities;
- collaboration and brokering between national programmes;
- collaboration with industry and like-minded organisations.

North-south networking: strengthening project and institutional collaboration

The Participating States recognize that the objectives of their National Programmes (NPs) or activities on Poverty-related diseases (PRDs) and therefore the Joint Programme as implemented through EDCTP cannot be achieved without the full participation of the Developing Countries. The reasons for this are as follows:

- the targeted diseases are predominantly prevalent in DCs;
- the DCs own the sites and expertise necessary for clinical trials, but need strengthening;
- EDCTP supported interventions should be ethically and socially acceptable at a reasonable cost that helps ensuring their distribution.

Therefore, the major objectives of the Joint Programme, under this heading will be to:

- institutional level: forging alliances between European institutes and their African partners to promote joint strategies in training, research and capacity strengthening within the scope of EDCTP and
- ensure that the EDCTP programme has full political support by governments and decision makers in the DCs;
- scientific level: identify and secure the support of the scientific and clinical communities in the DCs.

These interactions and collaborations tend to be determined by a joint history, institutional affiliations, and personal relations, or are based on national research agendas and national development aid and foreign policies. Moreover, the programme has been one of the few international initiatives to have developed a partnership with African scientists by building ownership and leadership by those working on the ground in disease-endemic countries. Through its projects and collaborative approach, EDCTP is supporting African researchers to establish their own networks.

African (south-south) networking

South-South collaboration, which includes regional Networks of Excellence, supports sharing of local expertise and enables local capacity in multicentre international studies. Specifically, south-south networking objectives and activities are:

- improve and promote interaction between scientists, institutions, national disease control programmes and health policy makers;
- leverage support for the already established regional networks to encourage growth and sustainability
- Increase contributions from developing countries to at least €30 million compared to €14 million in ECDTP1;
- work very closely with regional bodies and national health research focal persons to create a database of national health research expenditures;
- secure the support of scientific, clinical and political authorities in the African countries and regional organisations, and in general the co-ownership by Africa of the EDCTP programme;
- analyse gaps, overlaps and potential synergies (opportunities) in health research in Africa;
- organise media training for scientists and training for scientific journalists in Africa;
- improve the capacity of African reviewers and journal editors;
- improve capacity for Institutional Review Boards (IRBs), National Ethics Committees (NECs), regulatory and legal agencies dealing with clinical trials;
- assess, monitor and evaluate clinical trial sites, reference laboratories and training institutes within the regional Networks of Excellence.

EDCTP1 improved the impact of networking in the clinical trials in Africa and it was relatively new. The activity brought together people who did not work together before. EDCTP was the key success factor behind these south-south networks.

Networking with external stakeholders: strengthening collaboration with partners

This networking ensures that the impact of all research is maximised and that synergies can be taken into account and can achieve leverage of resources and investments. Hence, strengthening the collaboration with partners in the private sector is actively sought.

During the initial phase of EDCTP2 (2015-2016) the EDCTP Secretariat primarily focused on informing partners in the private sector of the new opportunities in EDCTP2 through frequent and targeted contacts to individual pharmaceutical companies as well as EFPIA (European Federation of Pharmaceutical Industries and Associations). Other international funders of health research are natural allies, and the Secretariat sought active collaboration on best practices and organised joint activities, such as the EDCTP–TDR Clinical Research and Development Fellowship scheme run in partnership with the WHO's Special Programme for Research and Training in Tropical Diseases (TDR). Furthermore, EDCTP offers a comprehensive approach and funding for non-profit and for-profit organisations and product development partnerships to evaluate innovative new medicinal products in high-quality clinical trials.

Possibilities to leverage resources and contribute to global health improvements could be either through:

1. co-funding of strategic research opportunities that are resource-intensive and/or high risk, requiring financial investments that a single funder cannot bear, or
2. jointly launching Calls for Proposals to address global issues in the scope of EDCTP2 and of strategic relevance and importance to both parties. Concrete collaborations and opportunities for co-funding or joint or coordinated calls will be explored with partners in the private sector. This will be done through leveraging established relationships and building on new opportunities.

3.3 Alignment at operational level: Regional Networks of Excellence (NoEs)

Sub-Saharan Africa has limited adequate research infrastructure and also in the capacity to initiate and maintain competitive research outputs due to the isolation of the work.

There is a need to combine south-south collaboration and sharing of facilities and expertise in resource-limited settings in order to enhance synergy.

In 2007, to promote collaborative research EDCTP launched a call for proposals for the establishment of regional Networks of Excellence (NoEs) for conducting clinical trials and provide mentorship programmes in sub-Saharan Africa. The NoEs, which comprises at least three institutions from at least three different African countries.

Each regional network was up to the individual institutions in each network to come up and implement the networks' own procedures and work plan activities. The EDCTP networks have been established and set up as regional hubs for clinical science and yet they will require more time and support to achieve their intended goals

Initially all networks conducted a needs assessment and then drafted a workplan to address the regional gaps.

The Networks have been instrumental to develop local capacity but to date none of the Networks actually have conducted a clinical trial.

The four Regional Networks of Excellence for Conducting Clinical Trials [16]established under EDCTP1[17] have facilitated regional collaboration by uniting diverse institutions bringing their individual strengths in skills-based

[16] These networks are organised on sub-regional basis, namely: (i)WANETAM (West Africa) with a total funding €3.5 million; (ii)CANTAM (Central Africa) total funding €2.8 million; (iii)EACCR (East Africa) total funding €3.46 million; (iv)TESA (Southern Africa) total funding €2.3 million. This allows institutions to work together in accordance with African regional economic communities or sub-regions. Similarly, all the regional networks are encouraged to foster local ownership and sustainability by involvement of host countries, and to network at a Pan-African level.

[17] Under EDCTP2 a new call has been launched in November 2015 and the composition of the 4 networks is slightly different as under EDCTP1. The Four Regional Networks have been selected but the grants have not been signed yet.

competencies and shared infrastructures in various areas such as Good Clinical Practice (GCP), Good Clinical Laboratory Practice (GCLP), data management, laboratory techniques and epidemiology, to conduct clinical trials across sub-Saharan Africa.

Indeed, the EDCTP has continued to support the institutions in sub-Saharan Africa to strengthen regional networks to conduct the following:

- organise mentorship programmes and training of staff members working at African institutions where clinical trials will be conducted;
- conduct systematic epidemiological and demographic studies that facilitate the planning of future trials;
- support less established institutions by providing additional expertise to enable them to participate in multi-centre clinical trials. Such expertise shall include design of trials, data management, financial management, administration, quality assurance and required laboratory techniques.

Figure 3: Regional Networks of Excellence (NoEs)

Source: Annual Report EDCTP 2015

The 4 NoEs with 64 institutions from 21 African countries are African-led, multi-disciplinary, and multi-disease-oriented. They are comparable to the subsequent Wellcome Trust initiative comprising 7 consortia which interlink 52 institutions from 18 African countries In contrast, the Malaria Capacity Development Consortium, Multilateral Initiative on Malaria and the ALPHA network have a single-disease orientation.

Currently, the strategic role of the EDCTP regional networks should be clearly defined and a plan to operationalize responsibilities and deliverables should be developed. The plan should include a focus on the networks' capacity building activities, with emphasis across the spectrum of scientist career development, and their support of weaker institutions and regions.

3.4 Alignment at operational level: research implementation, coordination, harmonisation and standardisation of scientific techniques and methodologies - PanACEA

In the first programme, EDCTP funded its activities through three different approaches. In addition to the more common and most frequently used open calls for proposals, it defined two alternative funding approaches: brokered approach and single source approach. The latter is discussed in 3.5.
On 31 May 2007, in Dublin, Ireland, the European and Developing Countries Clinical Trials Partnership (EDCTP) held a stakeholder meeting to address the state of TB drugs. With the goal of shortening and simplifying treatment of drug-sensitive TB, EDCTP recommended a brokered approach to conducting clinical trials for new drugs. An important outcome of this meeting was a Call for Expression of Interest issued on 1 August 2007.
Subsequently, EDCTP invited five applicants, each representing a consortium of institutions, to participate in a brokering meeting held in The Hague on 4 December 2007. One outcome of this meeting was the formation of a consortium of consortia to develop a proposal to EDCTP focused on (1) collaboration across the consortia in the conduct of regulatory-standard Phase IIa, IIb, and Phase III clinical trials for 4 TB drugs, and (2) collaboration across the consortia to develop increased capacity in sub-Saharan Africa for the conduct of ICH-GCP and GCLP compliant clinical trials for TB drugs.
This TB consortium of consortia, known as *the Pan African Consortium for Evaluation of Antituberculosis Antibiotics* (PanACEA)has been established by EDCTP as a different approach towards funding clinical trials than through normal calls for proposals. It was concluded that the amount of funds for clinical trials and number of funding options were limited. For this reason, a so-called brokered approach has been chosen as most efficient in setting up a pan-African consortium for developing innovative tuberculosis treatments with the aim to closely align with the overall objectives of EDCTP and to aims to shorten and simplify tuberculosis treatment.

PanACEA, which is funded by EDCTP (including sub-Saharan African countries and the EC), Bill and Melinda Gates Foundation, Sequella (a pharmaceutical company) and TB Global Alliance (a PDP), comprises three networks involving 22 institutions; 11 in Africa, 10 in Europe and 1 in USA.
Therefore, EDCTP, as well as providing added European value in channelling common efforts to tackle the societal challenges of PRDs, also provides a cost-effective mechanism where member countries may work with other stakeholders to share risks and benefits. The value of this mechanism is clearly pronounced with regards to the resource intensive pivotal phase III clinical trials.

Finally, in terms of operational challenges, a number of factors can result in delays in clinical trials. This is particularly pronounced in developing countries where multiple factors such as lack of capacity among the clinical trial personnel, inadequate infrastructure including for ethical and regulatory review, and logistic challenges in the shipment of investigational products and samples may come into play[18].

The brokered approach was used for overcoming the lack of amount of funds for clinical trials and it was an efficient tool in setting up a pan-African consortium for developing innovative tuberculosis treatments with the aim to closely align with the overall objectives of EDCTP. The objectives have been defined specifically oriented towards tuberculosis to:

- shorten and simplify treatment of uncomplicated pulmonary tuberculosis;
- increase the tuberculosis clinical trial capacity in Africa;
- develop sustainable tuberculosis clinical trials network in Africa.

The network has also brought together co-funding from other partners, including the Global TB Alliance, Bill and Melinda Gates Foundations, Sequella and the South African Medical Research Council.

3.5 Alignment at operational level: common regulatory framework- The Pan African Clinical Trials Registry (PACTR)

The single-source approach[19] has been applied in two phases during the first years of EDCTP1.

[18] Strategic Business Plan, 2013.
[19] The single approach is used only when a product or service is available from one source and for particular reasons, it must be purchased from a specific vendor".

A grant was awarded to the World Health Organization (WHO)in 2004 to facilitate the assessment of the national regulatory environment of various African countries and to support the development of a common regulatory framework where possible at a regional level. The total of the first grant awarded was €360,000 comprising €200,000 from EDCTP and €160,000 from the Netherlands–African Partnership for Capacity Development and Clinical Interventions against Poverty-Related Diseases (NACCAP). The second grant of a total value of €530,532 was awarded to WHO in 2008. The purpose of the grant was to further strengthen regulatory systems in African countries with focus on clinical trial application and inspection of clinical trials.

The two grants led amongst others to the following achievements:

- the funding contributed to the formation of the African Vaccine Regulators Forum(AVAREF);
- regulators and members of national ethics committees from various African countries have been trained;
- training has been provided on Good Clinical Practices (GCP) and site inspection for regulators;
- the constitution of the HIV/AIDS, Tuberculosis (TB), and Malaria (ATM) Clinical Trials Registry became the Pan African Clinical Trials Registry (PACTR) in June 2008[20].

PACTR is operated by the Cochrane South Africa (CSA), an intra-mural research unit of the South African Medical Research Council (MRC). PACTR is currently funded by the South African Medical Research Council and managed by Cochrane South Africa (CSA). Its aim was to increase the prospective registration of clinical trials for HIV/AIDS, TB and malaria in Africa, to include all randomised and controlled clinical trials conducted in Africa regardless of disease. In 2009 PACTR expanded its remit to include all diseases for all regions of Africa.
PACTR became the first and is presently the only African member of the World Health Organization's Network of Primary Registers[21]**.**
PACTR is an African initiative to support regional clinical trial registration. The aim of the registry is to:

- provide a repository for prospective registration of clinical trials conducted in Africa;
- promote prospective clinical trial registration in the African region;
- ensure the WHO-stipulated minimum dataset for registered trials is publicly and freely available to all users of the registry;
- provide a searchable database of all clinical trials conducted in Africa.

More broadly, EDCTP activities have contributed to the development of capacity and infrastructure that have enabled clinical trials to be conducted in sub-Saharan African countries in accordance with internationally recognised standards and in partnership with both European individual researchers and institutions. In addition to contributing to product registration and new treatment guidelines, these trials have also contributed through the generation of information and publications to inform future research and healthcare. That notwithstanding, PRDs continue to weaken health systems and affect societies across sub-Saharan Africa, and European research policies and activities remain weakened by fragmentation and inefficiencies.

PACTR is considered beneficial for a large variety of different stakeholders:

- policymakers can have a full overview of clinical trials that are being conducted in their countries;
- health professionals may advise patients about appropriate trials to participate in; funders of clinical trials and development agencies can learn what research is being conducted where and by whom;
- researchers are provided with a way to identify gaps in the research landscape and better focus their research activities[22].

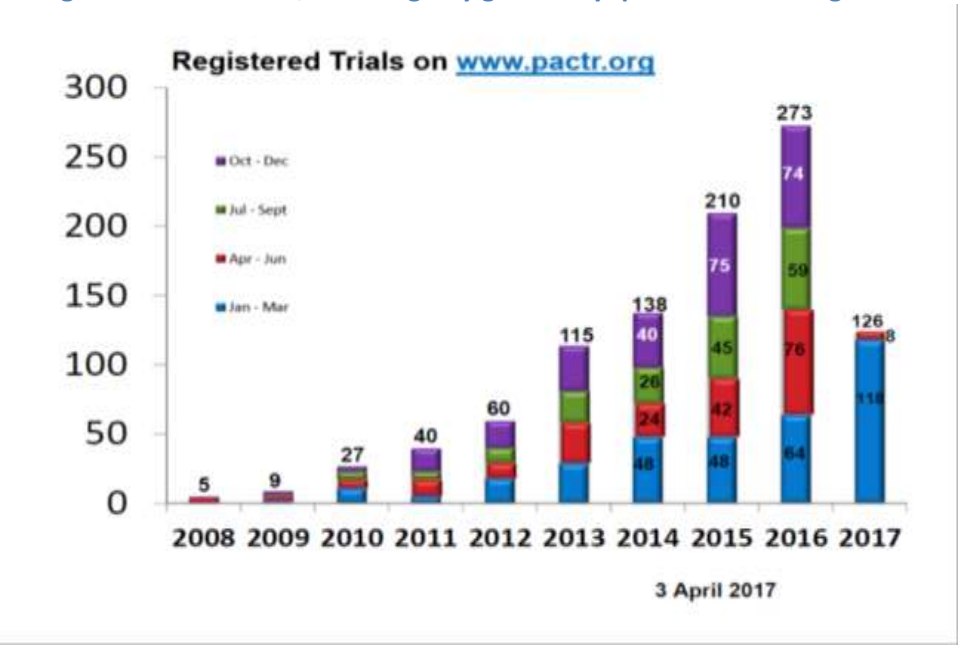
The registry itself is growing at a rapid rate, as are activities relating to the goals of the registry. The Child Strategy, which aims to increase awareness of the need to conduct research in children, is a sub-project within

[20] EDCTP funding came to an end at the end of 2014.
[21] Strategic Business Plan for the second phase of the European and Developing Countries Clinical Trials Partnership programme (EDCTP2, 2014-2024) undertaken by several Member States under Article 185 of the Treaty on the Functioning of the EU, May 2006.
[22] Technopolis group, Assessment of the performance and impact of the first programme of the European & Developing Countries Clinical Trials Partnership (EDCTP), 18 September 2014.

the registry, and is also steadily picking up momentum. It has focused on increasing awareness of the role of the registry, and the success of these efforts can be seen in the growth of the registry. PACTR is a key resource for researchers, clinicians and policy makers on the continent[23].

PACTR is considered one of the highlights of the capacity building approach of EDCTP, created with African leadership. Furthermore, WHO endorsed the registry as it complies with the standards required to be a Primary Registry. A couple of benefits have been mentioned: (1) the practical advantage of having a system in place to see what is happening in the area of clinical trials in Africa (“*if we cannot enumerate the clinical trials in Africa we cannot do anything”*), (2) it is instrumental in identifying potential collaboration partners, but (3) also for a mind-set, to build a mechanism to report on the results from a trial (both positive and negative) which influences the way we think about clinical trials.[24]

Figure 4: PACTR 2016/2017 Registry growth by quarters actual registrations



Source: PACTR website

3.6 Alignment at operational level: Strategies to strengthen human capacity-building and ethics and regulatory capacities

More than 75% of all projects funded by EDCTP (161 projects out of 254) have focused on building human capacity, strengthening research networking and establishing a conducive environment for conducting clinical trials in sub-Saharan Africa in line with European standards. Indeed, one of the core elements of the capacity strengthening approach of EDCTP2 is the training of people through the projects grants that have been supported.

EDCTP2 supports various fellowship schemes including, to date: Senior Fellowships, Career Development Fellowships and Clinical Research and Development Fellowships in joint collaboration with WHO-TDR25. Under EDCTP1 521 people have been trained on EDCTP funded projects, including 51 senior fellows, 400 PHD and 242 master’s students.

The second gap of research capacity in Africa is lack of critical mass of well-networked researchers.

[23] Amber L Abrams, One of a Kind-The Pan African Clinical Trials Registry, a regional registry for Africa, 23 August 2013.

[24] Technopolis group, Assessment of the performance and impact of the first programme of the European & Developing Countries Clinical Trials Partnership (EDCTP), 18 September 2014.

[25] TDR, the Special Programme for Research and Training in Tropical Diseases, is a global programme of scientific collaboration that helps facilitate, support and influence efforts to combat diseases of poverty. It is hosted at the World Health Organization (WHO), and is sponsored by the United Nations Children’s Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and WHO.

EDCTP's capacity building activities in sub-Saharan Africa are essential to the development of clinical research capacities in Africa. Namely the career development schemes and training opportunities offered to junior and senior African scientists through the various fellowships, MSc and PhD programmes that contribute to a strengthening of local research and clinical trial capacity for PRDs in line with international standards.

Furthermore, the establishment of novel sub-regional centres of excellence networks in Africa, the support for infrastructural development (e.g. lab equipment) and the strengthening of ethical and regulatory frameworks (funded by the CSA call "Ethics and regulatory capacities) are seen as important contributions to build up sustainable research conditions on the African continent.

The research capacities in universities and research organisations have been improved considerably by EDCTP. Nevertheless, many countries in sub-Saharan Africa are still lacking the basic know-how and infrastructure to conduct clinical trials that meet international standards in terms of scientific research quality and ethical conduct. EDCTP has certainly built capacities for individual researchers that have benefited from EDCTP funds and training but some of the stakeholders stated that institutional capacity has not been strengthened sufficiently through a proper regulatory environment. The sustainability of the research capacities built through EDCTP investments depends on the institutions' capacities to retain and attract trainees and research fellows in Africa and to make sure that they continue their careers in research through clinical trials[26]. A large portion of the PhDs and Senior Fellows that have been funded on EDCTP projects continue their scientific career in Africa and transfer their knowledge within their institutions. Some of them have even managed to set up their own laboratory facilities or research groups. In general, a situation in which incentives are put in place to retain people at least for a couple of years after the EDCTP projects has finished would be preferable to be able to transfer the knowledge they have gained through the project to others.

The impact of the EDCTP programme on the capacity to conduct clinical trials in sub-Saharan Africa through the development of laboratories and training of researchers and other staff is considered to be tangible in many countries. It can be observed through EDCTP's contribution to develop concrete clinical trial sites that can operate more or less autonomously now. Increasingly, African researchers can lead their own research projects and raise funding for new projects[27]. Overall, more than 70% of the projects were led by the people working in African institutions (meaning that the grant contract was signed with an African legal entity in the role of coordinator). The percentage of African coordinators varied according to grant type as one might expect given the various remits and eligibility criteria for the EDCTP1 funding schemes. For example, 88% of ethics and regulatory grants have an African coordinator whereas 41% of EDCTP grants that support clinical trials and clinical research (Integrated Projects and SPGs) have an African coordinator. Possible reasons why coordination from Africa is less common for clinical trials projects include:

- the clinical sponsor of the trial tends to be in Europe and it is common for the coordinator and sponsor to be the same organisation
- co-funding arrangements tended to be at the project level, which may have inhibited African coordinators from initiating proposals and finding the required two European partners and co-funding
- high administrative burden of managing a multi-country project, with restrictions in Africa on transferring funds out of the country that may inhibit African coordinators.

[26] Technopolis group, Assessment of the performance and impact of the first programme of the European & Developing Countries Clinical Trials Partnership (EDCTP), 18 September 2014.

[27] .Good examples are the Centre National de Recherche et de Formation sur le Paludisme (CNRFP) in Burkina Faso, this centre has established two public centres and created one private clinical trials centre (offering services similar to a CRO) the Uganda Virus Research Institute (UVRI) is currently collaborating with the International AIDS Vaccine Initiative (IAVI and the Kilimanjaro Clinical Research Institute (KCRI) in Tanzania. These centres initially have received small grants to develop a basic infrastructure then followed by larger grants from EDCTP and other funding organisations to extend these facilities (such as the Bill & Melinda Gates Foundation, National Institutes of Health and the Wellcome Trust).

4. Overall limitations and difficulties encountered during implementation

4.1 Low alignment at financial level

Prior to the inception of EDCTP, each of the European PSs in the programme had their own approach and guidelines in relation to PRDs and collaboration with sub-Saharan African countries. Many of the African countries also did not have national programmes and had limited activities, particularly regarding clinical trials on these diseases. Moreover, where such programmes or activities were present there were limited mechanisms for cross-border funding within Europe and as such each country undertook these activities as a bilateral agreement rather than in partnerships with other European Member States[28].

In the light of those issues, EDCTP promotes and facilitates the coordination and pooling of resources at the level of national ministries and funding agencies encouraging European and African PSs to develop calls for proposals together and with other third parties through the framework of EDCTP2.

The application of Article 185 implies a national (European) commitment by each European PS to mobilise their publicly funded organisations active in the field of the EDCTP to maintain the levels of support to this field at minimally equal levels throughout the programme and to provide an annual up-front minimum funding commitment over its lifetime. This will enable EDCTP to facilitate coordination of the European PSs' national programmes and activities on PRDs to carry out essential research and competence building programmes, and to gain from the diverse and complementary aspects covered by the programmes. This will include Research and Innovation Actions, Coordination and Support Actions, Training and Mobility Action Activities and Participating States Initiated Activities (PSIA).

Participating States Initiated Activities (PSIA): PSIAs are national or transnational research and capacity development activities that are independently funded or implemented by a single Participating State or by several Participating States (independently or jointly). These activities are counted as in-kind contribution and are included in the EDCTP annual work plans[29] with the agreement of the EU. The PSIAs are based on national priorities but should where possible be strategically aligned with EDCTP2 programme. The role of EDCTP is to work as a platform of integration.

However, the alignment at financial level is too low compared to the mechanism foreseen in the EDCTP2 proposal. Indeed, few members of the EDCTP Association provide cash funding directly to EDCTP under EDCTP. Most of the EDCTP contribution comes through the in-kind contribution via the PSIAs but since these are national activities they are not strategic in reference to the goals of the EDCTP2 programme.

Indeed, during the preparation of EDCTP2 the following funding schemes had been foreseen:

1. Integrated activities: are selected, administered and funded by the EDCTP from unrestricted cash contributions of the PSs to the EDCTP common pot. Through these activities, EDCTP mainly supports clinical trials and is equally open to collaborative clinical activities from public and private sectors, profit and not-for-profit organisations. Also, third parties contribute to those activities through cash contributions.

[28] Strategic Business Plan for the second phase of the European & Developing Countries Clinical Trials Partnership programme (EDCTP2, 2014-2023) undertaken by several Member States under Article 185 of the Treaty on the Functioning of the European Union (EU), 18 October 2013.

[29] EDCTP's work plan sets a common strategic research agenda for all Participating States. It identifies activities to be implemented: including call for proposals to be launched by EDCTP. The work plan is firstly drafted by the Executive Secretariat in consultation with the research community. EDCTP's Strategic Advisory Committee ensures in particular that activities included in the work plan are in compliance with the strategic scope and objective of EDCTP. The annual work plan is then reviewed by an independent review panel. This independent review panel is made of experts in the field of public health and project implementation. These experts are selected within the Horizon 2020 expert database. Finally, the European Commission approves the work plan before it is formally endorsed by EDCTP's General Assembly.

2. Joint activities: are activities between one or more third parties, EDCTP and Participating States. These mainly joint activities are reserved and useful for complex research opportunities of strategic importance in the scope of EDCTP2 that require a coordination response from the field to maximise their impact. This scheme will be desirable in the case of an expensive undertaking, such as are phase II clinical trials.

This mechanism has been removed as it is not allowed by Horizon 2020 rules. Since EDCTP is a part of Horizon 2020 is bound to the same Call types as H2020 (RIA, CSA and TMA). The joint activities were rearranged as strategic RIAs under EDCTP1. Integrated activities are now called RIAs.

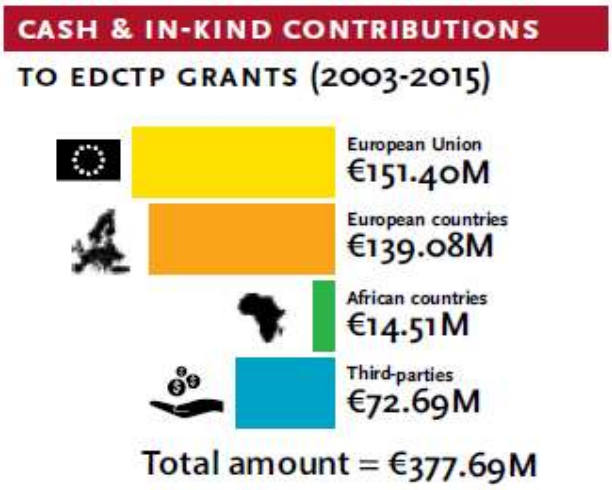
4.2 Low financial contribution

It is as yet hard to judge the 'value for money' of the EDCTP programme as it will take years before the benefits can be reaped from the 102 clinical trials that were funded under EDCTP1, in terms of new products and long-term improvements in health outcomes, although some of the clinical trials have already contributed to registration of new products (Triommune for paediatric HIV and Pyramax for repeated treatment of malaria) and changes of treatment guidelines.
It is only possible to judge the real financial contribution of EDCTP in this field.
Indeed, the EDCTP's financial contribution remains small compared to that of private institutions such as the Wellcome Trust, the Bill & Melinda Gates Foundation and Global Fund.

The Bill & Melinda Gates Foundation will donate another $5 billion during the next five years to help sustain economic progress, including against diseases like AIDS, Zika and malaria. The Bill and Melinda Gates Foundation have already donated $9 billion to Africa since 2001 with a major focus on public health, which Bill Gates calls a necessary bedrock for economic prosperity.

The EDCTP2 programme has foreseen a budget of up to € 2 billion but in reality the amount is approximately 1.5 billion of which a half should come from the PSs through in-kind and cash contributions, but the vast majority of PS contributions are in-kind so far. This limits severely the capacity of EDCTP to integrate European efforts in the area of clinical trials for PRDs. It reduces also the implementation of the programme, which requires a significant increase to make a real impact and to position EDCTP as world leader.

Figure 5- Cash & Kind Contributions



Source: EDCTP2 in a nutshell

4.3 Elimination of brokering approach

In EDCTP 1 the possibility was foreseen to fund EDCTP activities through three different approaches.
The brokering approach enhanced the partnership with different stakeholders and made it easy to increase partnerships. Nowadays, in the EDCTP 2 the only way to increase the partnerships is through call for proposals.

Due to legal restrictions as set by the European Commission we are not able to do a brokering approach in EDCTP2.

5. Conclusions: Suitability and key factors for success

The combination of support for clinical trials with capacity building and networking (the 'holistic approach') is considered unique and a best practice in funding clinical research activities in Africa.

Key factors of success:

1) At strategic level:

- build and reinforce networking: north-north, north-south and south-south. A long history of collaboration among key research partners is crucial in enabling the transition towards a massive alignment initiative such as an Article 185 research programme.

2) At operational level:

- the establishment of a common regulatory framework that provides a database of all clinical trials conducted in Africa for the improvement of the clinical trials;

- development of dedicated instruments for capacity building and ethical training of researchers focusing on (i) involving the wider scientific community in order to benefit from their expertise and equipment; (ii) facilitating staff exchange grants (iii) implementing training and networking activities and promoting mobility. The aim is to develop a critical mass of well-networked researchers;

- creation of a consortium targeted at treatments for the tuberculosis (PanACEA consortium) with the involvement of different stakeholders and it provides a cost-effective mechanism where member countries may work with other stakeholders to share risks and benefits;

- the establishment of Regional Networks of Excellence (NoEs) to aim at facilitation of regional collaboration by sharing of facilities, competencies and expertise.

REFERENCES

Literature

Strategic Business Plan for the second phase of the European and Developing Countries Clinical Trials Partnership programme (EDCTP2, 2014-2024) undertaken by several Member States under Article 185 of the Treaty on the Functioning of the EU, May 2016

Available at:
http://www.edctp.org/web/app/uploads/2016/06/EDCTP2_Strategic_Business_Plan.pdf

EDCTP Workplan 2016

Available at:
http://www.edctp.org/web/app/uploads/2016/07/EDCTP2-Workplan-2016.pdf

Decision No 556/2014/EU of the European Parliament and of the Council on the participation of the Union in a second European and Developing Countries Clinical Trials Partnership Programme (EDCTP2) jointly undertaken by several Member States, Official Journal of the European Union, 15 May 2014

Available at:
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014D0556

EDCTP Annual Report 2014, Starting EDCTP 2

Available at:
http://www.edctp.org/news/edctp-annual-report-2014-available-online/

EDCTP Strategic business plan for 2014–2024

Available at:
http://www.edctp.org/web/app/uploads/2016/12/EDCTP-Strategic-Business-Plan-2014-2024.pdf

Technopolis group, Assessment of the performance and impact of the first programme of the European & Developing Countries Clinical Trials Partnership (EDCTP), 18 September 2014

Available at:
http://www.technopolis-group.com

Communication from the Commission to the Council and the European Parliament - A European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action (2007-2011)

Available at:
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Ar12537

Strategic Business Plan for the second phase of the European & Developing Countries Clinical Trials Partnership programme (EDCTP2, 2014-2023) undertaken by several Member States under Article 185 of the Treaty on the Functioning of the European Union (EU), 18 October 2013

Available at:
http://cp-opportunities.co.uk/edctp/assets/downloads/EDCTP_Strategic_Business_Plan_EDCTP2.pdf

EDCTP 2 in a nutshell

Available at:
https://www.dsw.org/uploads/tx_aedswpublication/1406_EDCTP-English_A4_web.pdf

Analysis of the impact of a new EDCTP Report of the Independent Expert Panel contributing to the Impact Assessment report on the new EDCTP, Brussels, August 28, 2010

Available at:
http://cordis.europa.eu/fp7/art185/docs/impact-assessment-edctp-final_en.pdf

Decision No 1209/2003/EC of the European Parliament and of the Council on Community participation in a research and development programme aimed at developing new clinical interventions to combat HIV/AIDS, malaria and tuberculosis through a long-term partnership between Europe and developing countries, undertaken by several Member States, 16 June 2003

Available at:

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003D1209&from=EN

Decision No 1513/2002/EC of the European Parliament and of the Council of 27 June 2002 concerning the sixth framework programme of the European Community for research, technological development and demonstration activities, contributing to the creation of the European Research Area and to innovation (2002 to 2006)

Available at:

http://publications.europa.eu/en/publication-detail/-/publication/5a016937-b81d-41ca-aac5-1b5bedd26f46/language-en

Amber L Abrams, One of a Kind-The Pan African Clinical Trials Registry, a regional registry for Africa, 23 August 2011

Available at:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3215564/

Consulted websites

http://www.edctp.org
http://technopolis-group.com
http://publications.europa.eu/en/home
http://www.ecsahc.org/
http://www.oceac.org/

Interviews:

Dr Rafael De Andrés Medina, Instituto de Salud Carlos III (Spanish member in EDCTP General Assembly)
Dr Ole F. Olsen (EDCTP Director of North-North Cooperation)
Dr Gabrielle Breugelmans (EDCTP North-North Networking Manager)

ANNEX 1. Overview of the different EDCTP funding schemes by grants scheme category

Research and Innovation Actions (RIA)

In the EDCTP2 programme these are actions primarily consisting of clinical research activities and clinical trials in partnership with sub-Saharan Africa aiming at increasing the number of new or improved medical interventions for HIV/AIDS, tuberculosis, malaria and other poverty-related diseases, including neglected ones, in particular in sub-Saharan Africa. Actions should normally include one or more clinical trial (phase I to IV) conducted in sub-Saharan Africa, in particular phase II and/or III trials. Actions involving the conduct of phase II and III trials of drugs and vaccines shall normally include a regulatory strategy. Whilst clinical trial(s) represent the main.
activity, the action may involve additional relevant research studies such as nested sub-studies or epidemiological studies. These actions may also involve supporting activities fostering networking (within Africa and within Europe, as well as between Africa and Europe) or capacity development of researchers, institutions and sites in sub-Saharan Africa to conduct clinical trials and related research, including observational studies.

Coordination and Support Actions (CSA)

CSAs address activities such as: i) activities to develop, strengthen and extend clinical research capacities in sub-Saharan Africa, ii) activities to promote networking and collaboration both between European and African and among African researchers, clinical research institutions and sites, as well as iii) activities to foster coordination and cooperation between public and private funders. Actions may involve activities of standardisation, dissemination, awareness-raising and communication, conduct of preparatory and accompanying studies, networking, coordination or support services, policy dialogues and mutual learning exercises and studies. Actions may also include complementary activities of strategic planning, networking and coordination between regional and national programmes. Actions may also involve targeted measures to maximise the public health impact of research results stemming from EDCTP-funded activities in sub-Saharan Africa by promoting their translation and supporting their uptake in policy-making, health systems and clinical practice at local, national and/or international level. In particular, CSAs will support sub-Saharan African countries in developing a robust ethical and regulatory framework for conducting clinical trials, targeting both national ethics committees (NECs) and national regulatory authorities (NRAs). Furthermore, CSAs will support regional clinical research networks in sub-Saharan Africa ("EDCTP regional networks") in order to build and strengthen regional, national, institutional and individual capacities to conduct clinical trials according to ICH-GCP standards

Training and Mobility Awards (TMA)

These are actions primarily consisting of developing clinical research capacities and skills of researchers and clinical research staff from sub-Saharan Africa, and/or promoting mobility of researchers and research staff.