Revised Version 1
May 2016

EDCTP

European & Developing Countries
Clinical Trials Partnership

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

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1 Preface

This document outlines the updated strategy for the second phase of the European & Developing Countries Clinical Trials Partnership (EDCTP2), covering the ten year period from November 2014 to December 2024. It summarises the scope, objectives, competitive advantage, implementation and evaluation of the multiannual EDCTP2 joint programme by the Participating States and its dedicated implementation structure, the EDCTP2 Association. It has been drafted by the Members of the EDCTP General Assembly (GA) and the Scientific Advisory Committee (SAC) with the support of the EDCTP Executive Secretariat (SEC).

The Strategic Business Plan describes the Participating States' common ambitions for further integration and alignment of their efforts in joint activities and investments in clinical research on poverty-related diseases in developing countries, in particular in sub-Saharan Africa, based on what has been set up and achieved in EDCTP1 since 2003, and launching of EDCTP2 in November 2014.

The previous version of the Strategic Business Plan was approved by the EDCTP General Assembly on the 29-30 May 2013 on behalf of the relevant national authority having the political responsibility for the country's participation in EDCTP. The previous version was part of the EDCTP programme proposal that was approved by the European Parliament on 15 April 2014 and the Council of the European Union in its meeting on Economic and Financial Affairs (ECOFIN) on 6 May 2014. The current version takes into account the post approval developments associated with the establishment of the EDCTP Association (as implementing structure of the EDCTP2 programme), input from the consultative stakeholders' meetings and alignment with the entrusted tasks in accordance with the Delegation Agreement between the European Union (represented by the European Commission) and EDCTP Association, including specific reporting requirements and indicators of programme success.

2 Executive Summary

The European & Developing Countries Clinical Trials Partnership (EDCTP) was established by the EU in 2003 in response to the global health crisis caused by the three major poverty-related diseases (PRDs), HIV, tuberculosis and malaria, as part of the EU's commitment to achieving the Millennium Development Goals (MDGs). EDCTP was the first initiative based on Article 185 of the Treaty on the Functioning of the EU (ex-Art. 169), which allows the EU's participation in research programmes undertaken by several EU and Associated Member States. The first EDCTP programme (EDCTP1) ran from 2003-2015, with a budget of €200 million from the EU matched by cash and in-kind funding contributions from 14 EU MSs (and two associated European countries).

EDCTP1's main aim was to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics in the treatment and prevention of HIV, tuberculosis and malaria through supporting clinical trials and associated activities in sub-Saharan Africa. Its unique funding approach, integrating clinical research and capacity building activities as 'Integrated Projects' conducted by large consortia of European and African partners, together with like-minded organisations, has facilitated alignment and coordination of European national research programmes and activities. Furthermore, this approach has fostered African leadership in clinical research and has strengthened the ethics and regulatory environment for conducting clinical trials in sub-Saharan Africa. The EDCTP programme thus brings together the individual strengths of participating European Partners States with those of sub-Saharan African Participating States.

EDCTP1 launched 65 calls for proposals and awarded 254 grants with a contract value of €207.99 million, comprising €149.318 million EU funding and €58.669 million co-funding from EDCTP Participating States and third parties. The majority of EDCTP1 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 pharma. The total amount of funding (EU plus co-funding) committed to these 254 projects was €377.688 million. EDCTP1 demonstrated that substantial funding can be leveraged through its programme to tackle PRDs in sub-Saharan Africa. Furthermore, the consortia funded by EDCTP1 have fostered sustainable collaborations (South-South, North-South and North-North) involving the participation of 30 countries in sub-Saharan Africa and 16 in Europe.

Through its strategic funding approach, the EDCTP1 programme managed a relatively balanced portfolio of projects per disease area. TB research received the largest share of the funding (€ 68.969M; 33.2%), followed by HIV (€ 61.412M; 29.5%) and malaria (€ 50.166M; 24.1%). Research on HIV/TB co-infections received € 7.131M (3.4%). EDCTP awarded 78 grants for ethics and regulatory activities (€ 4.99M; 2.4%), and a further 30 grants (€ 15.324M; 7.4%) were awarded for cross-cutting activities such as capacity building and networking, including grants to the EDCTP Networks of Excellence for Clinical Trials. Analysis of the portfolio according to type of intervention showed that there were 60 projects researching drugs for treatment and prevention (€ 91.079M; 43.8%), and 26 vaccine research projects (€ 61.738M; 29.7%). Diagnostics research was supported by 13 grants (€ 14.068M; 6.8%) and research into microbicides accounted for five projects (€ 9.386M; 4.5%) EDCTP supported 102 clinical trials and diagnostics studies through its grants. The trials, of which the majority were multi-site and multi-country, took place in 24 countries across sub-Saharan Africa: 34 on malaria, 30 on HIV, 29 on tuberculosis and 9 on HIV/TB co-infection. These trials tested new and improved drugs for treatment and prevention (60), vaccines (26), diagnostics (13), microbicides (3), and two trials used electronic devices to investigate methods to enhance retention rates in trials and adherence to treatment.

EDCTP's funding strategy has focused on research on key clinical challenges and policy-relevant questions in sub-Saharan Africa, whilst strengthening research capacity and the enabling environment for research in sub-Saharan Africa. The majority of clinical trials and studies have presented their results at national and international conferences, published in high profile journals and have produced results to inform national and international policy. There have been more than 600 publications from EDCTP-funded projects to date. A recent bibliometric analysis showed that the citation impact of EDCTP-funded papers (2003-2011) was high[1], particularly in the areas of HIV and HIV/TB co-infection, indicating EDCTP-funded projects deliver high quality research with major impact on the field.

EDCTP1 aimed to achieve sustainable capacity for conducting clinical trials by attracting, developing and retaining scientific leadership in Africa, improving and upgrading research infrastructure and strengthening the ethical, regulatory and legal framework for conducting trials. The programme supported the long-term training of 516 African researchers throughout their career from Bachelor's student to postdoctoral researcher. More than 400 PhD and Master's students have been supported, and 51 Senior Fellows, who almost without exception have remained in sub-Saharan Africa. The four Regional Networks of Excellence for Conducting Clinical Trials established under EDCTP1 have facilitated regional collaboration by uniting diverse institutions bringing their individual strengths in skills-based competencies and shared infrastructures in 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. EDCTP funding for the establishment of the Pan-African Clinical Trials Registry (PACTR), which has been officially recognised as a WHO Primary Clinical Trials Registry, has led to a rise in the registration of clinical trials taking place in Africa. Through the EDCTP1 ethics grants programme, funding has been awarded to 23 sub-Saharan African countries. Ethics committees have been established in countries that had no, or limited, support, such as Benin, Democratic Republic of Congo (DRC), Gabon, Guinea, Liberia, Mozambique, Rwanda and Togo. EDCTP1 grants supported infrastructure and office function support, setting up of websites, drafting of documents essential to the operation of the ethics review committee (including standard operating procedures (SOPs) and guidelines), improvements in administrative function through employment of staff and more efficient document handling and storage. EDCTP supported the production of a text book 'Research Ethics in Africa: A Resource for Research Ethics Committees', the first book to provide guidance tailored to African research ethics committees.

The second programme of EDCTP or EDCTP2 was launched on 2 December 2014 and will run over a ten-year period from 2014 to 2024. The European Union (EU) has decided to support the programme with a financial contribution of up to €683 million from the Horizon 2020 programme's societal challenge "Health, Demographic Change and Well-being" ("EDCTP2 basic act").

The EU's financial contribution is conditional upon the following: (a) the implementation by the EDCTP2 Implementation Structure ("the EDCTP Association") of the objectives and activities of the EDCTP2 programme as set out in annexes 1 and 2 of the EDCTP2 basic act, (b) the maintenance of an appropriate and efficient governance model for the EDCTP2 Programme as set out in annex 3 of the EDCTP2 basic act, (c) the compliance by the EDCTP2 Association with the reporting requirements set out in Article 60(5) of the EU's Financial Regulation (Regulation (EU, Euratom) No 966/2012) and (d) the fulfilment of the commitment by each Participating State to contribute to the financing of the EDCTP2 Programme commitments as referred to in Article 3.1 (point e)[1].

The EDCTP Association (hereafter "EDCTP") is legally established as an Association under Dutch law in the Netherlands. The Association currently counts 28 Participating States (PS) as full and equal members: 14 European countries (Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden and the United Kingdom) and 14 African countries (Burkina Faso, Cameroon, Congo, Gabon, The Gambia, Ghana, Mali, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda and Zambia).

The EDCTP Association is composed of the General Assembly as the governing body, the Secretariat as the executive body led by the EDCTP Executive Director, and the Board supervising the Secretariat.

Political context, challenges and choices

The international health landscape has changed considerably since the initiation of EDCTP. Research and aid budgets for international health development have increased substantially, although still inadequate to meet all needs, and are under new strain from the current financial crisis and increased population migration, especially into Europe. Many 'Global Health Initiatives' and Public Private Partnerships (PPPs) are active in, or related to, the field of the EDCTP scope.[2] In recent years, emerging economies such as China, Brazil, India and others are also claiming an important role in global health in terms of aid, research and trade.

The EU is one the major donors and arguably one of strongest players in international health aid and research, but due to fragmentation, its visibility is not proportionate and limits its influence and impact. Over the past years, a number of policy statements and collaborative agreements have laid the foundation for a stronger position of the EU. In 2010 the Commission Communication[2] and Council Conclusions[3] on the Role of Europe in Global Health (2010) established a conceptual framework, with emphasis on strengthening national health systems, maternal health and the continued fight against HIV, tuberculosis and malaria. The 2007 EU Programme for Action[4] 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. EDCTP is now one of the most visible global health initiatives emanating from Europe, a vital element of its research programme for PRDs, and one of its strongest instruments for fostering cooperation with Africa.[5]

Regarding aid policies, EDCTP is one of the few international research initiatives that explicitly pursues the principles of the Declaration of Paris on Aid Effectiveness (2005) and the Accra Agenda for Action (2008)[6], by fostering country ownership and integrating donor programmes. These Organisation for Economic Co-

[1] Delegation Agreement Number 1: The second European and Developing Countries Clinical Trials Partnership Programme (EDCTP2) (ref: Ares(2014)4213936 - 15/12/2014)

[2] WHO Special Programme for Research and Training in Tropical Diseases (TDR); African Network for Drug and Diagnostics innovation (ANDi); Bill and Melinda Gates Foundation (BMGF); Foundation for Innovative Diagnostics (FIND); Drugs for Neglected Diseases initiative (DNDi); Global Fund to fight AIDS, Malaria and Tuberculosis (GFAMT); Medicines for Malaria Venture (MMV); International Aids Vaccine Initiative (IAVI); Global Alliance for TB Drug Development (TB-Alliance); Global TB Vaccine Foundation (AERAS).

operation and Development (OECD) principles are at the very heart of EU's international partnerships, especially with Africa.

Several recent policy declarations, programmes and reports highlight the key role of EDCTP as an effective model for other programmes aiming at coordinated international collaboration. The Africa-EU Strategic Partnership, emanating from the 2007 Lisbon Declaration[3] and re-emphasised in the Europe 2020 Strategy[7], identifies EDCTP as an important actor in its first Action Plan for Implementation[8] , especially in the Eight Partnerships on Science, Information Society and Space. EDCTP is one of the flagship programmes contributing towards European effectiveness, visibility and coherence in international health research. In addition, its partnership model has been extended to broaden clinical and intervention research to all poverty-related infectious diseases. EDCTP can evolve to a common platform for conducting clinical trials contributing to a European Research Area, as envisaged for EU's international science and technology cooperation programmes[9].Further, in 2015 the G7 Ministers of Science in their Berlin meeting expressed their resolve to support the fight against neglected tropical and poverty-related infectious diseases, with EDCTP recognised as one of the mechanisms to be built upon.

With transition from the Millennium Development Goals (MDG) to Sustainable Development Goals (SDGs), science, technology and innovation are increasingly recognised as core contributors to sustainable development, and the basis for social economic development. SDG 3 "Ensure healthy lives and promote well-being for all at all ages" will only be achieved with a reduction of the disease burden, especially poverty-related and neglected disease (PRNDs) for sub-Saharan African countries. In line with sustainable development, the EDCTP programme promotes clinical development of new tools in the fight against PRNDs, research collaboration, interdisciplinary research and capacity development especially in sub-Saharan Africa where the majority of programme activities are implemented.

Apart from weak health delivery systems and inadequate prevention, a major challenge in the fight against HIV, tuberculosis and malaria remains the lack of affordable, efficacious and safe drugs. Not only new compounds, but also simpler formulations, such as single-dose and/or fixed combination therapies, are greatly needed to increase efficacy, lower the burden on health systems and avoid the emergence of drug-resistant strains. Significant progress has been made in the development of vaccines and microbicides, but preventive trials, especially Phase III, require enormous investments, capacity and tenacity. Improved case detection is crucial for the rational use of drugs; an extension of EDCTP to diagnostics would therefore be highly consistent with its mission and expertise.

In the past years, the international community has been alerted to the fact that functional health systems are key to the efficiency and sustainability of disease control. The social, economic and qualitative disciplines of health systems research are not within EDCTP's scope. However, within its product-oriented objectives and competencies, EDCTP2 extends its portfolio to operational and implementation research[10] on delivery and uptake of medical products, including post-marketing (phase IV) trials and collection of safety data that may be part of active pharmacovigilance and controlled community-based interventions.

This extension in EDCTP scope is envisaged to increase the direct relevance of EDCTP for health services and development agencies. African health services have to deal not only with HIV, tuberculosis and malaria, but with many other PRNDs for which no adequate diagnostics, drugs or vaccines are available. Co-morbidities and co-infections are the rule rather than the exception. The capacities needed for clinical interventions against NIDs are similar to those for HIV, tuberculosis and malaria.

[3] Lisbon Declaration EU-Africa Summit, December 2007.

3 Vision, Mission, Scope and Objectives

EDCTP2 will provide a push and pull mechanism for new or improved tools for PRNDs along the development pipeline from phase I to IV, thus facilitating their optimal development and deployment in developing countries. This is important since experience has shown that without such a purpose-driven and target-oriented mechanism, these products stagnate in the pipeline due to lack of commercial interest and motivation from the private sector. Furthermore, experience from EDCTP1 has shown that in medicinal product development generally, various special groups such as pregnant women, newborns, malnourished children, people living with HIV and other underlying diseases and marginalised populations affected by various social determinants of health are excluded from most, if not all, clinical trials. EDCTP has funded several clinical trials that included these groups, which have generated efficacy and safety information that will allow label expansion of medicinal products to include such groups. EDCTP2 will also continue to fund clinical trials that explore improvements and repurposing of tools and regimens in current use. This is important because quite often regimens in use are not optimised for efficacy, tolerability and ease of use in resource-limited settings. Further, there is a paucity of tailor-made products that proactively target specific population groups such as children, pregnant mothers, people living with HIV and those with co-infections and co-morbidities who are disproportionately represented in sub-Saharan Africa. This disparity and inequity in the availability of appropriate treatment can only be addressed by programmes such as EDCTP.

By coordinating the national programmes of the Participating States (PSs) through a common EDCTP scientific administration and funding, PSs will cooperatively work with their sub-Saharan counterparts in collaboration with like-minded organisations to launch over 200 projects during the lifespan of the EDCTP2. The programme will aim at supporting at least 150 clinical trials, of which 30 may be at phase I, 40 at phase II, 20 at phase III and 60 at phase IV. However, due to the constantly evolving health research landscape, EDCTP will need to be flexible in pursuing these indicative targets and recognises that achieving this optimistic challenge will involve collaboration with other partners in product development for PRNDs. During the ten-year period, over 400 African scientists will be trained in subject areas within the scope of EDCTP, including mentorship fellowships with attachments to pharmaceutical companies, career development fellows, senior fellows and post-doctoral scientists as well as Master and PhD students in various fields such as epidemiology, medical statistics, clinical pharmacology, parasitology, immunology, molecular biology, social sciences and related disciplines.

3.1 Vision

The vision of EDCTP2 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 PRNDs in partnership with sub-Saharan Africa.

This shall be achieved by accelerating the development of new clinical interventions to diagnose, manage and prevent HIV, tuberculosis, malaria and other PRNDs through cooperative research as well as by providing a critical mass of resources through a more efficient and effective use of European research capacities. This will be done 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.

EDCTP2 will strengthen capacity to undertake research in those countries most affected by these diseases. Strengthening local infrastructural and human resources will promote local ownership and leadership, as well defining the populations at risk and conducting high quality research in the affected countries. EDCTP will bring together stakeholders from Europe, other parts of the world and sub-Saharan Africa to identify the state of product development worldwide and to ensure the timely implementation of clinical trials of key products. The programme will require flexibility to respond to a constantly changing pipeline and landscape of potential interventions and to ensure that the activities contribute effectively to global efforts to control infectious diseases.

This is an ambitious undertaking, which cannot be delivered through a series of centrally managed research calls alone, but must build on the work that is already being carried out at national level. By joining EDCTP2, PSs are committing to its vision of aligning and coordinating their national programmes to better achieve the objectives of the partnership. To achieve this, EDCTP2 is established on the basis of Article 185 of the Treaty on the Functioning of the European Union (TFEU).

3.2 Mission

The aim of EDCTP2 is to enhance research capacity and accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics for the identification, treatment and prevention of HIV, tuberculosis and malaria as well as other PRNDs in sub-Saharan Africa, including emerging infectious diseases of particular relevance for Africa, through all phases of clinical trials with emphasis on phase II and III clinical trials.

3.3 Scope

The EDCTP2 disease scope includes HIV, malaria, tuberculosis and the following neglected infectious diseases(NIDs): dengue, rabies, human African trypanosomiasis (sleeping sickness), leishmaniases, cysticercosis/ taeniasis, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematodiases, lymphatic filariasis, onchocerciasis (river blindness), schistosomiasis, soil-transmitted helminthiases, Buruli ulcer, leprosy (Hansen disease), trachoma, yaws, diarrhoeal infections, lower respiratory infections and emerging infectious diseases of particular relevance for Africa, such as Ebola.

The programme supports clinical trials as a core function, product-focused post-registration operational and implementation studies (health services optimisation research) on PRNDs, as well as networking and capacity development for clinical trials and closely related research in sub-Saharan Africa. EDCTP2 supports all phases of clinical trials (phases I to IV) with emphasis on phase II and III clinical trials for new or improved medical interventions, as well as advanced testing and field validation of new diagnostic tools.

3.4 Objectives

The activities of the EDCTP2 programme will contribute towards achieving the following five specific objectives[4]:

1. Increase the number of new or improved medical interventions for poverty-related diseases (PRDs), including neglected ones[5],
2. Strengthen cooperation with sub-Saharan African countries, in particular in building their capacity for conducting innovative research for clinical interventions 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 and investments,
5. Increase impact due to effective cooperation with relevant EU initiatives, including its development assistance.

[4] The objectives of the EDCTP2 programme are in full detail described in Annex 1 of Decision No 556/2014/EU of the European Parliament and of the Council of 15 May 2014 and are presented here in an abridged version.

[5] In the EDCTP2 programme, "*poverty-related diseases (PRDs)*" include HIV/AIDS, malaria, tuberculosis and the following neglected infectious diseases (NIDs): dengue/severe dengue; rabies; human African trypanosomiasis (sleeping sickness); leishmaniases; cysticercosis/taeniasis; dracunculiasis (guinea-worm disease); echinococcosise; foodborne trematodiases; lymphatic filariasis; onchocerciasis (river blindness); schistosomiasis; soil-transmitted helminthiases; Buruli ulcer; leprosy (Hansen disease); trachoma; yaws; diarrhoeal infections; lower respiratory infections; as well as emerging infectious diseases of particular relevance for Africa, such as Ebola.

4 Current Context and Challenges Ahead

Before the first EDCTP programme was established, many EU PSs and their partners in the developing countries were already engaged in substantial collaborative research activities in the field of PRNDs. Unfortunately, these programmes were often fragmented and uncoordinated. Many of these programmes were also underfunded and lacked capacity in the field. New and specific requirements, such as the need for multicentre and multinational protocols, a demanding regulatory environment and universal ethical standards are additional reasons why a well-coordinated, intensified effort in a genuine and innovative partnership with the developing countries was required. The EDCTP programme has had a significant impact in this area by funding integrated clinical trials bringing together researchers and funding from a number of European and African countries, with as many as seven European PSs contributing funds to a single project. EDCTP2 will build on the successful work of EDCTP1 to further develop and expand this integration of European national research programmes and to complement the activities funded through EDCTP projects.

In the past two decades there has been a substantial increase in the funding of control programmes aimed at PRNDs. This has had a significant impact on sub-Saharan Africa, where many countries are heavily dependent on international development assistance for health services and faced with the huge burden that these diseases place on their communities. In parallel, the volume of global research & development (R&D) investments for PRNDs has shown a marked increase over the past decade, which is to be expected given the synergies between research and control programmes whereby both influence each other and cannot be considered as mutually exclusive.

In preparing for EDCTP2, under a dedicated FP7 Support action known as EDCTP-Plus, extensive mapping of national programmes, activities and actors, such as publicly-funded institutions, projects and researchers addressing clinical research on PRDs in 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.

Results from sub-Saharan Africa[11] indicated high relative coverage of HIV, in terms of research conducted and funding allocated, which is covered at a rate of more than double the next disease, which is malaria. Tuberculosis is third most covered, with NIDs trailing behind. In this respect the extended remit of EDCTP and new venture in the field of NIDs corresponds to the findings. As Carlos Moedas, the EU Research and Innovation Commissioner, spelled out on numerous occasions, there is urgency for research in sub-Saharan Africa "this continent alone accounts for 90% of the deaths from malaria and tuberculosis while three-quarters of HIV-related deaths and two-thirds of all people with HIV live in Sub-Saharan Africa"[12].

EDCTP recognises the regional differences in the volume of R&D in health research in sub-Saharan Africa. South Africa, Kenya, Uganda, Tanzania and Malawi make up the most observed geographical focal areas which correlates with the activities conducted under EDCTP1. Countries in East and Southern Africa also have the highest degree of centrality (the largest number of ties to other countries) amongst the sub-Saharan partners within the EDCTP network, although it is important to note that the number of connections does not necessarily imply higher funding allocations, for example the case of The Gambia.

Key outcomes of the mapping exercise for sub-Saharan Africa indicated the following gaps that could impede the further development of clinical research in the region:

- Lack of human resources, particularly a lack of trained technical and laboratory staff
- Poor research coordination in-country
- Lack of long-term collaboration between institutions
- A lack of clinical trial infrastructure, particularly in terms of information technology and laboratories with sophisticated diagnostic capacity

- Where infrastructure was in place, a lack of information regarding what was available or could be shared between different research groups
- Limited engagement of national policymakers in developing clinical trial capacity
- Lack of national and regional health information systems to measure impact
- Lack of reputable local peer-reviewed journals to increase publication opportunities.

Developing new drugs, vaccines, diagnostics or microbicides is costly with the major proportion of the costs associated with conducting clinical trials. Undertaking these clinical trials in a reasonable timeframe and for a reasonable budget is only possible with access to a sufficient number of patients, hence the need for these to be undertaken in disease-endemic regions. The only economical way to undertake such trials is by developing local capacity to perform them locally.

The EDCTP programme, strategy, tailor-made joint actions and tools addressing the commonalities of the different countries' research activities as well as funding mechanisms is expressed in the EDCTP2 annual work plans. The annual work plan approach is a true reflection of the concerted efforts of aligning national, regional and international research agendas in addressing the gaps in clinical research and capacity development for fostering African scientific leadership. These are linked to research networks that create an enabling environment for individuals with potential to access appropriate infrastructure and mentorship in sub-Saharan Africa and Europe.

In recognising the need to strengthen the European Research platform in matters of global health and as a means to consolidate the role of EDCTP, it was decided that all funding of clinical research in the field of PRNDs would be channelled via the EDCTP2 programme. In the current context EDCTP takes on the role of gatekeeper of funding in this area, given its unique position as a public-public partnership comprising 14 European countries and 14 sub-Saharan African countries.

EDCTP is now indeed one of the most visible global health research initiatives emanating from Europe: a vital element of its research programme for PRNDs and one of its strongest instruments for fostering cooperation with Africa.

4.1 The Global Health Case

Despite the considerable results and achievements of EDCTP1, PRNDs continue to represent a major obstacle to the sustainable development of developing countries due to their social and economic burden, especially in sub-Saharan Africa. Effective, safe and affordable medical treatments still do not exist for most PRNDs. Furthermore, investment in clinical research remains inadequate as conducting clinical trials is costly and the return on investment limited due to market failure. Further, European research activities and programmes are fragmented and thus either sub-critical in scale or overlapping, while research capacity and investment in developing countries are inadequate. Building on the progress made under EDCTP1, intensifying efforts on the current focus (including large-scale phase III trials) and extending the remit of the programme to include other NIDs with operational and implementation research on how best to deliver new interventions, presents the best opportunity to maximise returns on investment and impact on health and healthcare. The EDCTP2 programme retains its focus on sub-Saharan Africa and encourages the inclusion of new EU Member States in order to optimise impact.

The EDCTP2 programme has an extended mandate and duration, covering PRNDs over the period 2014-2024. A budget of up to €683 million will be allocated by the EU, to be matched by co-funding from the EDCTP Participating States. Furthermore, ambitious targets have been set to attract co-funding from third parties and the African Participating States in EDCTP2. In particular, EDCTP2 aims to:

- Support 150 or more clinical trials
- Generate more than 1000 peer-reviewed scientific articles from the research it funds

- Sustain or increase the number of sub-Saharan African countries supported by the EDCTP2 to at least 30
- Support more than 400 fellowships to sub-Saharan African researchers and MSc/PhD students with at least 90 % of these continuing their research career in sub-Sahara Africa for at least one year after their fellowship
- Increase its capacity-building activities to strengthen the ethics and regulatory infrastructure in sub-Saharan Africa
- Develop a common research agenda, criteria for priority setting and common evaluation
- To ensure that at least 50% of public investment by participating European States is integrated, aligned or coordinated through the EDCTP2 Programme.

In 2013, 11.8 million (11.3–12.3) deaths were caused by communicable, maternal, neonatal, and nutritional disorders: 2.7 million by lower respiratory infections, 1.3 million by HIV, 1.3 million by tuberculosis, 1.3 million by diarrhoeal diseases and 854,600 by malaria[13]. The vast majority of these deaths occur in developing countries, in particular sub-Saharan Africa where the burden of infectious disease is highest and exceeds that of non-communicable diseases. Furthermore, the most common infectious diseases, including HIV and tuberculosis, predominantly affect young and middle-aged adults in the prime of life while other big killers such as malaria, pneumonia and diarrhoeal diseases exact a high death toll among children. As a consequence, infectious diseases are a leading contributor to poverty in Africa.

The burden of PRNDs in Africa is exacerbated by weak health systems, with limited resources and infrastructure to deliver preventive and therapeutic interventions effectively. Furthermore, Africa has limited research capacity, although there are positive signs of increases in scientific research being conducted by African scientists. From 1996 to 2012, the number of research papers published in scientific journals with at least one African author more than quadrupled (from about 12,500 to over 52,000). During the same time, the share of the world's articles with African authors almost doubled from 1.2% to around 2.3%. An EDCTP-commissioned bibliometric analysis on research publications in PRDs[1] showed that EDCTP member countries accounted for ~33% of global research output in PRDs and sub-Saharan African countries for ~10% (2007–2011). In line with the trend seen for all scientific publications, the overall number of PRD papers from sub-Saharan Africa increased markedly (>47%) since 2003 particularly for HIV (102%) and tuberculosis (TB) (81%), mainly involving Southern and East Africa. In the period 2007–2011, European and sub-Saharan African research collaboration on PRDs was highly cited compared with the world average (normalised citation impact, NCI) corroborating the benefit of collaborative research on PRDs through programmes such as EDCTP.

Despite these positive trends, increased research activity in Africa is needed to provide the evidence-base on new cost-effective clinical interventions and health service strategy.

4.2 HIV

EDCTP's portfolio of HIV clinical trials includes studies to address the major clinical challenges and barriers to progress in ending the epidemic in sub-Saharan Africa. Significant progress has been made in the prevention of mother-to-child transmission (PMTCT). The results of the Kesho Bora study, financed by several funders including EDCTP, informed the 2010 revised WHO guidelines 'Antiretroviral drugs for treating pregnant women and preventing HIV infections in infants', and continues to produce papers that increase our understanding of foetal and early life exposure to HIV for child health. Intensive efforts at international level to implement PMTCT and eliminate mother-to-child transmission of HIV have resulted in a 40% decrease in the number of children newly infected with HIV in low- and middle-income countries to an estimated 240,000 in 2013. Despite these successes, it is estimated that more than 200,000 children per year become infected, mainly as a result of postnatal transmission through breastfeeding. The PROMISE-PEP trial, funded by EDCTP and several European Participating States, showed that postnatal transmission of HIV can be substantially reduced through provision of a prolonged prophylaxis (50 weeks) during the breastfeeding

period (peri-exposure-prophylaxis: PEP), resulting in very high survival rates in infants who remained uninfected. The trial findings have been presented to the WHO expert panel reviewing the PMTCT guidelines.

UNAIDS and WHO have highlighted expansion of diagnosis and provision of antiretroviral therapy (ART) for children as key challenges in the light of recent data indicating that, in 2013, less than one-quarter of HIV-infected children had been initiated on ART. EDCTP has been highly active in funding research to address this challenge. EDCTP supported the development of paediatric formulations of ART through the CHAPAS-1 trial, which led to the USA Food and Drug Authority (FDA) approval of the use of Triomune Baby/Junior for HIV-infected children. The CHAPAS-1 trial also provided data to support the WHO recommended weight-band dosing tables for ART. Subsequently, the CHAPAS-3 trial has provided important data on optimal first-line antiretroviral (ARV) regimens for treatment of HIV-infected children in Africa. The trial findings showed that the three regimens tested were well tolerated and that there was no difference in the primary toxicity end-point. These important results confirm that ART given as WHO-recommended fixed dose combinations is highly effective. The data on efavirenz have been shared with the US FDA for preregistration of the new, scored 600mg efavirenz tablet and the CHAPAS-3 trial results will be shared with the WHO for prequalification of these fixed-dose combination drugs.

ART is highly effective in preventing or reversing the decline in immune function in HIV-infected patients, however increasing HIV resistance to ART is making it necessary to switch therapy to a second-line or even third-line treatment. Following the massive roll-out of ART in Africa, large numbers of people are receiving first-line ART and increasing numbers are developing treatment failure and requiring second-line therapy. Given the high cost of second-line therapies, it is important that a strong evidence-base guides treatment policy and optimises drug use in sub-Saharan Africa. Two EDCTP-funded trials (2LADY and EARNEST) have investigated second-line treatment.

The 2LADY trial aimed to provide more evidence for the choice of nucleoside reverse transcriptase inhibitor (NRTIs) and boosted protease inhibitor (bPI) for second-line ART in resource-limited settings by comparing the safety and efficacy of three second-line regimens in Burkina Faso, Cameroon and Senegal. The trial results, published in AIDS 2015[14], showed that bPI-based regimens provide satisfactory results in bPI-naive patients even with NRTI-resistant viral strains. Good immune recovery and reassuring results of safety and tolerance for all three regimens, with very few interruptions or adverse events due to drug toxicity, were observed. Nevertheless, the worst toxic profile (especially neuropathy) and more complicated schedule of the combination with Abacavir/Didanosine (ABC/ddI) with no advantages in terms of efficacy argue for its elimination from the World Health Organisation (WHO) recommendations. The study observed that patients with high viral load at switch are at high risk of early failure and may require special management to avoid early second-line failure.

The EARNEST trial is the largest study so far of second-line treatment conducted in sub-Saharan Africa, with EDCTP funding. The trial, which reported its findings in the New England Journal of Medicine (NEJM) in 2014[15], showed that combining a boosted protease inhibitor with raltegravir, a heat-stable integrase inhibitor, to create a second-line regimen with two completely new drug classes was not superior to nucleoside reverse transcriptase inhibitors (NRTIs). The raltegravir-containing regimen is significantly more expensive and therefore not suitable as a standard second-line regimen for large-scale use in low income settings. Protease-inhibitor monotherapy was shown to be inferior in terms of suppressing viral load. This trial provided gold standard evidence to support the WHO-recommended regimen of a boosted protease-inhibitor (in this case, lopinavir). The trial results have been included in the 2014 revision of the International Antiviral Society-USA HIV treatment guidelines and have been made available to WHO.

Despite these achievements under EDCTP1 and the enormous progress made in the global fight against HIV, there are still major challenges and barriers ahead[75] Africa is the least populous continent and has by far the highest burden – in 2014 a staggering 25.8 million people were living with HIV-infection. The burden is highest in East and Southern Africa, where about 6 and 20% of adults respectively, are living with HIV-infection. In this region about 57% of all people living with HIV are women, and as a consequence the

majority of the more than 1.4 million babies born to HIV-infected mothers globally, are born in SSA. Previous reports noted that in several countries, including South Africa, Nigeria, Malawi, Zambia, and Swaziland, life expectancy had fallen below 50 years as a direct consequence of HIV, but this trend is now reversing with the widespread roll-out of antiretroviral treatment (ART)[16]. HIV predominately affects young and middle-aged adults in the prime of their working lives and the infection has had a devastating social and economic impact in Africa, driving countries into deeper poverty and deeper hardship.

HIV incidence peaked about 1997 and since 2005 the estimated overall incidence for the region declined by 32%[42] in 2014, of the global 2 million new infections, 1.4 million people in sub-Saharan Africa were newly infected, of whom about 190,000 were children. Worldwide 1.2 million people died of HIV-related disease, of whom 790,000 in sub-Saharan Africa; new infections outstrip HIV-related mortality (partly due to the ART keeping infected people alive) and the number of people living with HIV thus continues to increase. A major impediment to the future success of antiretroviral programmes will be this year-on-year escalation in the number needing treatment, especially in light of the frequently updated WHO guidelines on ART eligibility, which in 2013 suggested that treatment should start when the CD4 count is below 500 cell/µl, which would apply to an estimated 75% of infected adults. In September 2015, these treatment guidelines were further expanded to recommend offering treatment to all HIV infected people immediately upon HIV diagnosis, irrespective of clinical or immunological disease progression.

In 2014, five out of seven people on ART lived in sub-Saharan Africa. There are currently around 11 million HIV-infected people on ART in Africa, representing 41% of people living with HIV in the region, with further increases in numbers since. Several studies have suggested a considerable increase in adult life expectancy with increasing ART coverage in areas of high HIV prevalence, and there are some suggestions that ART coverage in a population with high HIV prevalence may decrease HIV incidence in the surrounding population. Mathematical modelling suggests that with near universal ART coverage of all HIV infected adults it may be possible to reverse the HIV epidemic and drive it to extinction over the coming 15-20 years. It should be noted, however, that many assumptions in these models have been disputed and this includes practicability and unacceptable ethics.

However, it is unclear how African health services can sustain the delivery of chronic HIV care optimally to such large numbers and for decades to come, bearing in mind the prevailing constraints in infrastructure. With the ageing of the HIV infected population there will be an increase in age-related conditions, which means that HIV care needs to be extended to non-HIV conditions. Further, children are often not so well catered for with fewer drug options and failure to be identified as infected in a timely manner. The prevention of mother-to-child transmission programmes have shown considerable success, but have also identified many operational challenges which will hamper the aim of 'virtual' elimination of vertically-acquired HIV infection. Thus, research is needed in Africa on the efficacy of locally appropriate therapeutic interventions including better paediatric management of HIV, prevention of mother-to-child transmission, and management of co-morbidities, in particular hypertension, diabetes, tuberculosis and malaria and with other infectious diseases.

HIV has led to a huge rise in tuberculosis (people living with HIV have a 10% per year risk of developing tuberculosis compared to a 10% lifetime risk in those who are HIV negative). Although TB remains the leading cause of death among people living with HIV, tuberculosis-related deaths in HIV infected people have fallen by 42% since the peak in 2004. A link has also been shown between HIV and malaria. Thus, HIV has both a direct and indirect effect on families and populations and on health services.

Preventing HIV transmission thus remains a very high priority. Regular HIV testing and counselling is vital not only to ensure infected people have access to HIV care, but also to support HIV prevention in those who test negative. Acceptability of facility-based testing is still critically low and likely insufficient in reaching the 90-90-90 targets. However, consistent findings from cluster randomised trials in the sub-Saharan African region have revealed home-based and other community-based approach in counselling and testing to make a great difference in acceptance. This includes in reducing inequity in access (both geographical and socio-

economic), acceptance of couple counselling, in detecting infections earlier (several references), and in cost-effectiveness[17,18]. Furthermore, the home-based approach has been found protective against intimate partner violence, stigmatizing behaviour, having multiple sexual partners, and having casual sexual partners[19]. Aside from treatment, ART has also been used for prevention of transmission in discordant couples, as PrEP, and it has also been suggested to have an effect in high-risk populations. In addition, male circumcision and male condom use are important interventions used in controlling the infection, but their coverage remains relatively low and condom use inconsistent. In terms of PrEP, in addition to oral ART, results from a recent phase 3, randomized, double-blind, placebo-controlled trial of a monthly vaginal ring containing dapivirine, involving women between the ages of 18 and 45 years in Malawi, South Africa, Uganda, and Zimbabwe showed 27% efficacy for HIV-1 prevention in women[20]. Further research on sustainable HIV prevention at population level is urgently required although the ultimate aim remains the development and evaluation of a vaccine, which has proven to be elusive till now.

4.3 Malaria

EDCTP1 has supported 34 malaria trials, including 22 prevention and treatment trials. Many of these trials are Phase IV (post-registration), optimising use of antimalarials for possible label extensions to cover special populations such as HIV infected individuals, pregnant mothers and infants, evaluation of antimalarials in real life settings of low income countries, tackling issues of programmatic deployment of drugs, and gathering evidence on how to optimise real-life drug delivery, including against a background of co-infections such as HIV. The WANECAM consortium conducted a phase IIIb/IV clinical trial assessing the safety and efficacy of repeated administration of four ACTs (Pyramax® (artesunate plus pyrinaridine), Eurartesim™ (dihydro-artemisinin plus piperaquine), Coartem® or Coartem-D (artemether plus lumefantrine) and Coarsucam® (artesunate plus amodiaquine)) over a two-year period in children and adults with uncomplicated malaria. The trial data supported the European Medicines Agency's (EMA) positive opinion on Pyramax®, a once-daily, 3-day treatment for uncomplicated malaria. The new label allows it to be used for treating multiple episodes of malaria in the same person after registration in malaria-endemic countries. Further, the trial data provided evidence to support the child-friendly fixed-dose ACT Pyramax® granules, the first paediatric antimalarial to be approved by the EMA.

Finding new drugs to treat and/or prevent malaria infection in pregnancy has been a priority in EDCTP1. Five EDCTP-funded clinical trials conducted by members of the Malaria in Pregnancy consortium have together recruited more than 15,000 African women, following them through pregnancy and studying the outcomes of children born. The PREGACT trial tested the safety of ACTs when administered to pregnant women with *P. falciparum* infection during the second and the third trimester. It provides essential data to inform the WHO malaria treatment guidelines, particularly on the performance of dihydroartemisinin-piperaquine for which no recommendation has been made due to lack of data. Trials investigating malaria prophylaxis in pregnancy have shown that mefloquine is not a suitable drug, highlighting the need to find new preventive therapies in pregnancy.

EDCTP1 has also funded clinical trials of malaria treatment in children. The results of the 4ABC trial conducted in seven sub-Saharan African countries support the use of the ACTs, artemether plus lumefantrine (AL), artesunate plus amodiaquine (ASAQ), and dihydo-artemisinin plus piperaquine (DHAPQ), for the treatment of uncomplicated malaria in children. These findings support the WHO recommendation that DHAPQ should also be considered for the treatment for uncomplicated *P. falciparum* malaria. An EDCTP/DNDi-funded trial has provided data from Africa on the use of ASMQ, a fixed-dose combination which simplifies malaria treatment and is available in tablet form that can be crushed and taken by children. More child friendly formulations are needed. Other EDCTP trials have investigated treatment of malaria in HIV-infected individuals with a view to label extension of antimalarials for use in this group.

EDCTP has so far supported 6 malaria vaccine trials, including the GMZ2 vaccine which is the first blood-stage malaria vaccine to be evaluated in a large multi-centre, phase III trial. GMZ2 was well-tolerated and immunogenic. It reduced the incidence of malaria but further development is needed to increase its efficacy.

Accurate estimates of the current clinical and cost burden of malaria are difficult to make due to the variation in methods used to diagnose malaria and lack of adequate data. Many cases of malaria are defined based on fever, which lacks specificity, many do not present to health services and national reporting of deaths is variable and often incomplete, there are poor data on absenteeism and it is difficult to capture risk mitigation strategies that households may take. To address these issues, methodologies for identifying, estimating and tracking the malaria burden, as well as new strategies to measure transmission are indispensable. The WHO estimates that in the last 15 years malaria incidence has declined by 37% globally and death rates by 60%. However, serious bottlenecks remain in providing full access to malaria prevention, diagnostic testing and treatment. Moreover, about 214 million malaria cases (defined as fever probably due to malaria) are estimated to have occurred in 2015 leading to 430,000 deaths globally, though this number is probably an underestimate due to the difficulties in their correct calculation. More than 80% of malaria cases and 90% of deaths occur in SSA, the majority among children under 5 years of age and pregnant women[21].

In Africa, the cost to the health service due to malaria is large, despite many cases not seeking care. The African Leaders Malaria Alliance estimated that malaria costs the African continent approximately $12 billion a year. WHO estimates that malaria accounts for 25–35% of all outpatient visits, 20–45% of hospital admissions and 15–35% of hospital deaths in endemic African countries each year. The financial burden on households is enormous since, in malaria endemic countries, many households have multiple episodes of malaria each year.

Nearly 30 million pregnancies are exposed to malaria in Africa annually and it has been estimated that 10,000 of these women and 200,000 of their infants die as a result of malaria infection during pregnancy every year[22]. Although current preventive strategies for malaria in pregnancy are highly cost-effective, their coverage is unacceptably low. Innovative solutions to overcome this problem are urgently needed. In addition, it is estimated that at least 1 million pregnancies occur in HIV infected women who are exposed to *P. falciparum* infection in the African region. The interaction between HIV and malaria is particularly deleterious in pregnant women, leading to increase risk and severity of both infections. Moreover, HIV reduces the efficacy of malaria control interventions and complicates the use of antimalarials due to potential drug interactions, leading to the paradox that the most vulnerable women are the less protected. Thus, there is an urgent need to find new drugs for malaria prevention that are not contraindicated with the concomitant administration of antiretroviral drugs[23].

In the era of malaria elimination, radical cure of asymptomatic infections of both *P. falciparum* and *P. vivax* in the entire population may be the goal. This will include vulnerable groups of the population such as infants, pregnant women, HIV infected individuals, and/or individuals with genetic haemoglobinopathies, for whom well evaluated highly efficacious antimalarials with adequate safety profiles will be needed. Although a number of antimalarials have been developed under the umbrella of the EDCTP1 over the last 10 years, the mentioned challenges and the potential development of resistance require a continuous research effort in the quest of finding the most adequate drug. The rise in insecticide resistance is an added challenge to the success of malaria control and elimination.

Additionally, there are hopes that the partially effective Mosquirix ^{TM} candidate vaccine (RTS,S) will be licenced as a first generation malaria vaccine, while the malaria genome mapping has raised hopes that new types of effective vaccines will be forthcoming. But it may be many years before highly effective products are available assuming that there will be resources to distribute them amongst the most at risk populations. Although important progress has been made in the last years in the field of malaria vaccines, research is still much needed into finding efficacious candidates. The EDCTP1 has supported five candidate malaria vaccines and has enhanced capacity to conduct such trials. There is a need to build on these investments and efforts and participate in the evaluation of the currently most promising ones, such as sporozoite and second generation combination vaccines.

4.4 Tuberculosis

The EDCTP1 portfolio included 27 clinical trials on TB and 9 on HIV/TB.

EDCTP has made considerable investment in research into TB diagnostics, through a diverse portfolio of research studies from early stage testing of biomarkers, evaluation of new and improved diagnostics through to implementation of diagnostics in a real life setting.

One of the fellowship projects provided supporting data leading to the WHO endorsement of GeneXpert. The TB-NEAT consortium has measured the clinical impact of GeneXpert in a clinical trial which showed that whilst GeneXpert can be administered accurately by a nurse in primary-care clinics, resulting in more patients starting same-day treatment, more culture-positive patients starting therapy, and a shorter time to treatment, the benefits did not translate into lower tuberculosis-related morbidity.

The TB-CHILD consortium has explored the performance of several diagnostic tests in children, including a promising sputum-independent test, TAM-TB, which is the first immunodiagnostic tool which can detect active tuberculosis disease in children with sensitivity similar to culture and with excellent specificity in a tuberculosis-endemic setting. Patents have been filed by the EDCTP-funded AE-TBC consortium for host cytokine signatures as diagnostic biomarkers for active TB.

Control of drug-susceptible TB is reliant on a standard six-month treatment that has been in place for more than 30 years. EDCTP has supported several clinical trials aiming to shorten and simplify TB treatment as this could improve patient adherence, reduce toxicity and decrease treatment costs such as REMoxTB, a phase III global clinical trial of new tuberculosis drug regimens, co-funded by the TB Alliance. EDCTP funded the trial sites in sub-Saharan Africa which contributed approximately 70% of the 2000 patients enrolled in the trial. The RIFAQUIN trial reported in the NEJM that a six-month TB treatment regimen that included weekly administration of high-dose rifapentine and moxifloxacin was as effective as the control regimen. Both trials failed to demonstrate the non-inferiority of a four-month treatment regimen. EDCTP has supported innovative approaches to testing new TB treatments, such as the multi-arm, multi-stage (MAMS) trial design carried out for the first time in tuberculosis. This approach allows early triage of the most promising regimens for selection for phase III trials.

The Global TB report estimated that 13% of the 9 million people who developed TB in 2013 were HIV-positive. The African region accounts for about four out of every five HIV-positive TB cases and TB deaths among people who were HIV-positive. EDCTP has supported clinical trials aiming to reduce high mortality and morbidity in HIV-TB co-infected patients and more needs to be done. Optimising the drug combinations and dosage in these co-infected patients is particularly challenging, due to drug-drug interactions. Furthermore, there is often limited pharmacological data from the African region to guide treatment, while treatment guidelines that are based on European patients may not be applicable. The EDCTP-funded Pharmagene trial demonstrated that there were no significant differences in the long-term plasma efavirenz pharmacokinetics, virologic and immunologic success between patients receiving 600mg efavirenz-based HAART with or without rifampicin based anti-TB therapy. Thus there is no need to increase efavirenz dose during concomitant rifampicin-based anti-TB therapy in TB-HIV co-infected patients, thereby reducing the risk of drug-induced liver injury in these patients.

Tuberculosis (TB) remains a leading cause of death from an infectious disease globally. In 2013, the World Health Organization estimated that of 9 million people who developed TB, an estimated 1.1 million (13%) were HIV-positive. Of the 9 million incident cases, an estimated 550 000 were children and 3.3 million were women. The African Region accounts for about four out of every five HIV-positive TB cases. Sub-Saharan Africa also had the highest TB rates of cases and deaths relative to population. The 2014 annual WHO Report shows reversal in previous downward trends of estimated global TB case load with half a million more cases of TB globally in 2013 than previously estimated. Three million people with TB are still being 'missed' by health systems each year and an increasing number (1.5 million) of people are dying from TB.

Multi-drug and extensively-drug resistant TB (MDR-/XDR-TB) continue to spread relentlessly in Eastern Europe, Asia and Africa, with an estimated 480,000 new MDR-TB cases and 210,000 deaths in 2013. In 2013, about 3.5% of new TB cases were MDR-TB and about 20.5% of previously tested cases had MDR-TB. One hundred countries have reported extensively drug resistance TB (XDR-TB) (9% of all MDR-TB), where resistance occurs in second-line drugs and which can take two or more years to treat, with a particularly high case-fatality rate. The incidence of XDR-TB is thought to be a staggering 25,000 cases a year. In Africa more than 90% of XDR-TB cases are fatal. Furthermore, only 71% of the MDR-TB cases notified in 2013 were started on MDR-TB treatment and the cure rates for MDR-TB globally remain very low (below 50%).

TB is a leading cause of death among people living with HIV. HIV has a major detrimental impact on TB management and control. Despite this known association a substantial number of TB-infected patients are not screened for HIV-infection in Africa and less than 50% of HIV-infected subjects are tested for TB. Thus, in 2013, only 48% of notified TB patients had a documented HIV test result globally (in Africa 76%). Progress in increasing coverage of HIV testing among TB patients slowed between 2012 and 2013. In 2013, only 21% of countries globally and 14 of the 41 high TB/HIV burden countries in Africa reported provision of Isoniazid Preventive Therapy (IPT) to people living with HIV, which aims to reduce the likelihood of developing TB. Key interventions for reducing the burden of HIV-associated TB is HIV testing for TB patients, commencing ART in those with low CD4+ T cell counts, and IPT.

The current status quo of the lengthy treatment duration and poor treatment outcomes associated with MDR-TB, and those with co-morbidity of TB with HIV and non-communicable diseases (NCDs), in sub-Saharan Africa is unacceptable. New innovations for more pro-active screening and early diagnosis of active TB, shortening duration of therapy, improving treatment outcomes for both drug-sensitive and drug-resistant TB, preventing relapse, reducing drug resistance, preventing long term lung damage, and preventing latent TB infection progressing to active TB are urgently required. Crucial to achieving TB control will be availability of affordable, short, effective and well-tolerated treatments for all forms of TB (latent TB infection, drug-susceptible and drug-resistant TB disease), a point-of-care diagnostic test with capacity to identify resistance to anti-TB drugs and an effective vaccine. Efforts to develop new TB diagnostics, drugs, and vaccines have intensified during the past decade.

There are major gaps in the TB diagnostic pipeline and there remains a great need for more rapid and accurate diagnostic tests for all clinical forms of active TB, latent TB infection and co-infection with HIV in adults and children at all points of healthcare with alignment of TB/HIV services. The most common method for diagnosing TB worldwide is the age-old sputum smear microscopy. Following recent breakthroughs in TB diagnostics, the use of rapid molecular tests to diagnose TB and drug-resistant TB is increasing although their usefulness in improving management outcomes under operational conditions remains uncertain[24]

In countries with more developed laboratory capacity, cases of TB are also diagnosed via culture methods (the current reference standard). Also, in addition to the GeneXpert MTB/RIF Assay which has been extensively evaluated[25,26], approved by WHO and is being widely rolled-out in African countries, new rapid point of care diagnostic technologies are now available on the market[24] and will require evaluation for accuracy, usefulness in both HIV and non-HIV-infected patients, in children and for extra pulmonary TB, cost-effectiveness, and ability to be implemented into health services.

To shorten duration of TB therapy remains an important priority. Trials of four-month treatment regimen for drug-susceptible TB showed that they were not non-inferior to the six-month standard of care regimen currently recommended by WHO. There are several new or repurposed anti-TB drugs currently in the late phases of clinical development which will soon enter the new TB drug portfolio [24, 27] requiring evaluation. In the last two years, two new drugs have been approved for the treatment of MDR-TB under specific conditions: bedaquiline and delamanid. A series of new combination regimens are required for treatment of both drug- susceptible and drug-resistant TB. While for the first time in four decades, new TB drugs are

starting to emerge from the new TB drug pipeline, and combination regimens that include new compounds are being tested in clinical trials, the new TB drug pipeline remains very thin.[27,28]

The sparse new TB drug pipeline and widespread emergence of MDR-TB signal an urgent need for additional therapeutic interventions to improve treatment outcomes[23]. A wide range of host factors are responsible for increased susceptibility to developing active TB disease, the poor treatment response and for increased mortality of MDR-TB [28, 29]. These include immune-dysregulation from any cause (such as stress, poor living conditions, socio-economic factors, micronutrient deficiencies, HIV), malnutrition, aberrant or excess host inflammatory response to infection, alcohol and substance abuse, co-morbidities with non-communicable diseases such as diabetes, smoking and chronic obstructive airways disease, pneumoconiosis; all of these factors are also important drivers of the global TB pandemic. A range of host-directed therapies (HDTs) have now been identified[29, 30], which can modulate anti-mycobacterial protective innate and adaptive immunity, reduce excess inflammation, repair or prevent tissue damage or enhance the effectiveness of TB drug therapy by modulating host factors. Those suggested include: 'repurposing' commonly used drugs for diabetes, epilepsy, peptic ulcers, hypercholesterolemia, asthma, cancer and arthritis which have shown promise *in-vitro* and in animal models; other immunomodulators (micronutrients, probiotics, anti-microbial peptide inducers and therapeutic vaccines) use of Vitamin D and phenyl butyrate, doxycycline, etc. However, there is no safety and efficacy data from well-designed studies proving their utility in humans.

4.5 Neglected Infectious Diseases (NIDs)

NIDs (also known as Tropical Neglected Diseases or Neglected Infections of Poverty) have normally received low priority in national and international health agendas. Together they are responsible for a significant, although hidden and often silent, suffering, with an estimated 1.2 billion people affected and 500,000 deaths occurring each year. However, the greatest impact of NIDs is the severe physical disability that is inflicted, resulting in 57 million disability adjusted life years.

WHO presently focuses on 17 NIDs including onchocerciasis and trachoma which are major causes of blindness, leprosy and lymphatic filariasis causing deformities that hinder economic productivity and prevent normal social life, Buruli ulcer which may lead to amputations, human African trypanosomiasis (sleeping sickness) which severely debilitates and almost invariably leads to death when untreated, rabies which is always fatal, leishmaniasis which causes skin disfigurement or, in its most severe form, infects visceral organs and is rapidly fatal if untreated, schistosomiasis which has a high level of morbidity and contributes to poor school attendance, malnutrition and impaired cognitive development of children, guinea-worm disease causing debilitating pain sometimes for extended periods and often coinciding with the peak agricultural season and dengue, a leading cause of hospital admissions in several countries. This is far from being an exhaustive list of NIDs, but it includes some of the most common diseases that contribute to their heavy burden, especially in sub-Saharan Africa. In addition, the EDCTP2 programme will cautiously include lower respiratory infections and diarrhoeal infections in its remit, in recognition of the high mortality resulting from these infections, particularly in children.

4.6 Emerging infectious diseases of particular relevance to Africa[6]

Emerging novel and re-emerging infectious diseases with epidemic potential are a persistent threat to global health security.

The past two decades have witnessed several rapidly spreading outbreaks of novel and re-emerging infectious diseases (such as the recent 2014/2015 Ebola Virus disease in west Africa; Marburg Haemorrhagic fever, verotoxin producing *Escherichia coli* 0157, cholera, HIV, tuberculosis, dengue, chikungunya), which have threatened global health security and were declared global health emergencies.

[6] See Annex 2 for References

Whilst Ebola Virus Disease (EVD) arose from within Africa, infectious diseases threats with epidemic potential can arise from other continents, such as severe acute respiratory syndrome (SARS), swine-origin influenza A H1N1, bird flu H7N9 and Middle East respiratory syndrome (MERS) coronavirus. The acute and rapid presentation of these diseases, and associated high morbidity and mortality rates, focus media and international attention.

There are other equally important emerging, re-emerging or novel infectious diseases which pose a grave threat to global health security but do not generate media attention The emergence and spread of antimicrobial-resistant bacterial, viral, protozoal and fungal pathogens for which diminishing treatment options are available is also of major global concern, but has received less media publicity.

Globally, the substantial rise in the numbers of patients with respiratory tract infections caused by pan-antibiotic-resistant Gram-positive and Gram-negative bacteria, multi-/extensively-drug resistant *Mycobacterium tuberculosis*, drug resistant *P. falciparum* malaria and multiazole-resistant fungi. Successful identification, treatment, prevention and containment of any new or re-emerging infectious disease threat will necessitate rapid, precise diagnosis, more effective pathogen-specific therapies, vaccines and prevention and surveillance measures.

There are several weaknesses and lessons that have been learnt from the EVD outbreak in West Africa:

1. Weaknesses in surveillance, emergency risk management response systems for infectious disease outbreaks
2. Lack of real-time active surveillance response systems, research priorities and innovative mechanisms for outbreaks including lack of the development of tools targeting early active diagnosis especially at the onset and during the low level of transmission; tracking and mapping; monitoring human and host population migration; forecasting outbreaks based on risk factors; prevention programmes and response packages tailored to local settings
3. Several countries in Africa, as well as governmental and research institutions, are inadequately equipped in diagnostics, tracking, active reporting, prompt healthcare delivery, and accessible and affordable treatment to combat the Ebola infection and other emerging infectious diseases
4. Inadequate national and regional leadership
5. Limitations of health systems and absence of effective infrastructure, and weaknesses in operational and human technical capacity for prevention and control responses
6. Lack of active early warning alert and surveillance response systems for infectious diseases outbreaks and response systems for tackling emerging infectious diseases
7. Inadequate education and knowledge among HCWs and community triggering panic, isolation, community stigmatization and ostracism
8. North-South collaborations can rapidly enhance diagnostic capabilities and their optimal use in remote settings
9. Lack of local capacity to effectively utilize new technologies and perform research on evaluation of new diagnostics, drugs, new treatment options and vaccines.

Priority Issues

In order to tackle the priority issues the following will be potential ways forward:

1. To promote, establish, build and strengthen national, regional and pan-African capacities and monitoring systems that can determine disease burden. To predict and identify infectious disease threats capacities through early warning and pro-active surveillance, enabling rapid response to emerging infectious diseases threats arising from within Africa or imported from overseas. These national and regional inter-sectorial and trans-disciplinary surveillance response systems should

include early warnings, and critical human resources development, which can be quickly adopted by allied ministries and organisations in African countries in epidemic and pandemic responses and linked to global networks for real-time bio-surveillance. These should also promote the establishment of networked information-sharing platforms and bioinformatics systems; and networks that link to regional disease detection hubs. This should lead to development of emergency operations centres; trained, functioning, multisectoral rapid response teams, with access to a real-time information system; and capacity to attribute the source of an outbreak.

2. To ensure that all stakeholders commit to putting in place surveillance systems for rapid and early identification of infectious diseases with epidemic potential. Develop additional means to deliver laboratory and public health information informing health professionals about emerging infections and antimicrobial drug resistance
3. To develop and deploy novel diagnostics and strengthen laboratory systems: Strengthen country and regional capacity at the point-of-care and point-of-need to enable accurate, timely collection and analysis of information, and laboratory systems capable of safely and accurately detecting all major dangerous pathogens with minimal bio risk. Training and deploying an effective bio-surveillance workforce with trained hands-on disease epidemiologists and laboratory scientists.
4. To get commitment for sustained funding to allow for increased collaboration, ownership empowerment, communication and networking (including community participation).
5. To ensure patient independence and dignity, as well as ensuring human rights for all ages in order develop a productive and sustainable system.
6. To promote the 'one health' approach and establish meaningful and trusting co-operation between animal, human and environmental health sectors to allow earlier interventions to be in place.
7. To develop the capacity to conduct locally led high quality clinical trials research, translational basic science research and operational research on evaluating effective diagnostic, therapeutic and preventive interventions.
8. To discuss ways in which a 'Global' EIDTs response group can be established and to encourage politicians to build health systems which can engage in surveillance, information sharing, research and development activities, and to learn from experiences from organisers with most experience of organising health services during mass gatherings events such as the annual religious pilgrims and global sports events
9. To effectively engage communities in research, end user involvement, and build trust through effective communication to facilitate rapid testing and introduction of high quality research interventions in emergency situations.
10. To define current status quo of African countries preparedness and surveillance mechanisms for emerging global infectious diseases threats outside Africa which can potentially be imported such as African country pilgrims attending the annual Hajj.
11. To review of existing capacity and critical gaps to be bridged and to define needs for laboratory and training support required to support evaluation of EIDTs in multi-country clinical randomized clinical trials.

4.7 Lower Respiratory Tract Infections

The EDCTP1 remit did not include research into diarrhoeal diseases and respiratory tract infections, apart from TB. These diseases are in a stepwise manner gradually being included in the remit of EDCTP2. Respiratory tract infections (RTIs) rank among the top five causes of adult and paediatric morbidity and mortality worldwide and cause nearly 5 million deaths each year. Pneumonia is the leading cause of death in children under the age of 5, with Sub-Saharan Africa accounting for 43% of pneumonia-related deaths despite representing less than 20% of this age category worldwide[31,32].

RTIs are caused by a wide range of bacteria (including mycobacteria), viruses, fungi and parasites. Autopsy studies of adults and children from all regions of sub-Saharan Africa reveal a huge undiagnosed burden of treatable respiratory tract infections, and co-infections (bacterial, viral and mycobacteria) which were missed ante-mortem by the attending physician or healthcare worker. Antibiotic resistance is becoming a major

problem in sub-Saharan Africa and reports of pan-antibiotic resistant bacteria from hospitals are of concern. RTIs due to viruses and bacteria transmit rapidly in communities and cause regional spread which can develop into epidemics. The actual burden of RTIs in sub-Saharan Africa may be higher than estimated due to inadequate microbiological services and poor public health surveillance systems. In this area EDCTP will limit its scope on lower respiratory tract infections in children and immune compromised individuals (children and adults).

Patients with RTIs display a contextual variety of clinical presentations at various points of healthcare: RTIs acquired in the community are called Community Acquired Pneumonia (CAP) and those acquired in hospitals are called Hospital Acquired Pneumonia (HAP), which include Ventilator Associated Pneumonia (VAP). Opportunistic RTIs (ORTIs) are also major causes of pneumonia in HIV infected patients, in the elderly, diabetics, and those with cancer or those who are immunocompromised due to other conditions. Currently, all ill patients presenting at point of care in developing countries with any form of RTIs (bacterial, viral or TB) are treated empirically without an accurate diagnosis of the causative microorganism and their antibiotic sensitivity patterns. Correctly identifying the exact microorganism causing RTIs and treating RTIs with appropriate antibiotics they are susceptible to is essential, since morbidity and mortality rates are high. RTIs remain difficult to diagnose accurately since a broad range of pathogens and opportunistic microorganism are involved in their aetiology. Patient management mainly relies on clinical evaluation where there is limited access to x-ray facilities and expertise to optimally interpret of x-ray findings. Inappropriate antibiotic therapy contributes greatly to increased morbidity and mortality rates, and inappropriate antibiotic overuse generates antibiotic resistance, which is a major public health concern. In addition, it often leads to repeated visits to the general physician or extended stay in hospital and increases the risk of complications of sepsis and laboratory and treatment costs. It is necessary to establish a microbiological diagnosis for epidemiological surveillance of common pathogens, in order to define general and local diagnostic algorithms; local microbial antibiotic resistance patterns, and for infection control purposes.

Other important challenges to the improvement of management outcomes of respiratory tract infections are development of tests for prediction and monitoring of treatment response, rapid identification of drug resistant pathogens, more widespread surveillance of infections, locally and internationally and those viruses with pandemic potential that require a global response. Effectively using therapies for treating requires timely and accurate diagnostics for identifying pathogen specific aetiology and ascertaining their antibiotic resistances or sensitivities. Additionally, improved management of hypoxemia in children with severe pneumonia is important to reduce the case fatality rate of low RTI. Simplified methods of continuous positive airway pressure are needed[33].

Currently only the GeneXpert MTB/RIF assay is available in some settings for screening of TB operationally within 24 hours of consultation although many patients who are acutely ill with RTIs do not have TB or those chronically ill have multiple lung co-morbidities of TB and other bacterial infections as shown by autopsy studies. Correctly identifying the exact microorganism causing RTIs and treating RTIs with appropriate antibiotics they are susceptible to is essential, since morbidity and mortality rates are high. Autopsy studies from sub-Saharan Africa, reveal that a substantial proportion of patients autopsied were on inappropriate antibiotic therapy. Microbiological culture remains the gold standard for the diagnosis of RTIs, the limitations of which include long analysis times (>30 hrs) and labour intensiveness. The use of these methods remained challenged by the difficulty to collect adequate respiratory specimens, especially in children and by the difficulty to distinguish infection from colonisation of the respiratory tract. Thus, there is a great need for rapid, accurate diagnostics tests for the detection of RTIs, capable of identifying a large panel of causative microorganism/s that could be combined to simple specimen collection methods to enable appropriate microorganism-specific therapy to be rapidly initiated for improved treatment outcomes.
Thus, there is a great need for rapid, accurate diagnostics tests for the detection of RTIs, capable of identifying a large panel of causative microorganism/s that could be combined to simple specimen collection methods to enable appropriate microorganism-specific therapy to be rapidly initiated for improved treatment outcomes.

The actual burden specific microbial aetiology of RTIs, their antibiotic resistance patterns, regional spread and epidemiological patterns in sub-Saharan Africa remains undefined due to lack of resources and laboratory infrastructures to perform microbiological analyses of RTI samples. Accurate documentation of the microbial aetiology and antibiotic resistance patterns of causative pathogens is important in achieving the optimal clinical management, public health surveillance, and control outcomes. Furthermore it is necessary to establish a microbiological diagnosis of RTIs for epidemiological surveillance of common pathogens and to assess the impact of the vaccination against *Streptococcus pneumonias* and *Haemophilus influenza* on the microbial diagnosis of RTIs, in order to adapt general and local diagnostic algorithms. Other challenges in improving management outcomes for RTIs are more accurate and widespread surveillance, locally and international for RTIs with pandemic potential and rapid identification of RTIs and drug resistant pathogens (including MDR-TB).

Current antibiotic guidelines for RTIs are non-existent in some countries in sub-Saharan Africa and many general practitioners or health clinics empirically use antibiotics for which there is widespread antibiotic resistance or do not adequately cover for all these pathogens. Definition of common microbial aetiology of RTIs and evaluation of new antibiotics including those with single dose administration, and other treatment regimens require evaluation. With pan-antibiotic resistant bacteria now becoming important in hospitals in sub-Saharan Africa, and the scant new antibiotic pipeline, newer approaches to treatment are required. More optimal use of existing antibiotics and use of adjunct therapies provide alternative options. A range of HDTs are becoming available, including micronutrients and commonly used drugs with good safety profiles, which could be repurposed, however there is lack of substantive safety and efficacy data in humans for these indications. Additionally, vaccine development for Streptococcus pneumoniae has advanced and requires evaluation.

EDCTP2 will invest on the greatest clinical need for management of LRTIs and improving treatment outcome in children and immune compromised individuals. This will focus on evaluating existing and new diagnostic platforms for diagnosing the microbial aetiology of LRTIs, defining antibiotic resistance patterns of bacterial pathogens causing LRTIs; new antibiotic treatment and dosing regimens and pneumococcal vaccines, including those which might be effective in populations with a high burden of HIV and; improvement of existing or alternative imaging methods. For seriously ill patients with LRTIs, among other options, 'Host Directed Therapies' and simplified methods to control hypoxemia will be evaluated.
Research on new diagnostics, new antibiotic regimens and evaluation of new therapeutic regimens and vaccines will be essential to optimise the impact of the products and prevent drug resistance and other complications. EDCTP2 will support the evaluation of different strategies for evaluation, delivering and scaling-up of diagnostics, vaccines and treatments for RTIs as well as research to maximise the synergies with TB/HIV control since TB/HIV co-infected patients can present with acute or chronic RTIs and have co-infections with other bacteria and viruses.

4.8 Diarrhoeal Diseases

Although global mortality from diarrhoea has declined in recent years, from approximately 4.6 million deaths during the mid-1980s to the current estimate of 1.6–2.1 million, largely due to implementation of oral rehydration therapy and mothers education, most of these deaths occur in children in developing countries under the age of five years, particularly in sub-Saharan Africa. However, the incidence of diarrhoeal episodes has not changed (3.2 episodes per child per year). The peak of incidence is between 6 months (weaning) and three years. Global disease burden is estimated to be approximately 62 million disability-adjusted life-years (DALYs), also taking 30-60% of mothers' time. Severe infantile diarrhoea accounts for 15-34% of all deaths in children under 5 years of age.

The expanding use of the newly available rotavirus vaccine is likely to improve the current situation if one extrapolates to sub-Saharan Africa the encouraging 60% reduction in mortality observed in Mexico in children under the age of five years[34]. Similarly encouraging results were reported from South Africa and Malawi, particularly in infants[35]. One has therefore clearly entered a period where a combination of

interventions, including the use of dedicated vaccines may achieve a major reduction in disease burden, if not the control and elimination of diarrhoeal diseases.

Two major issues remain:

1. With the exception of oral rotavirus and cholera vaccines that eventually made it to the market, none of the vaccine candidates against the other major classical aetiological agents of paediatric diarrhoea such as *Shigella* and Enterotoxigenic *Escherichia coli* (ETEC) have made it beyond phase II studies with the exception of one orally-administered ETEC vaccine that unfortunately proved inefficient in a large efficacy study in Egypt[36]

   A large multicentre case controlled study (GEMS) carried out in four African and three Asian countries has shown that in children below five years of age, most cases of moderate-to-severe diarrhoea were due to four etiological agents: Rotavirus, Cryptosporidium, entero-toxigenic *E. coli* producing heat-stable toxin, with or without co-expression of heat-labile enterotoxin), and *Shigella*. This three-year study, even if limited to a few sites, encompassed a considerable number of children with diarrhoea and an equivalent number of matched controls, giving this study value to set priorities for vaccine development that remains an essential goal. However, more recently, the MAL-ED study has revealed that in rather similar settings, the dominant diarrhoeal pathogens in children in their first year of life were somewhat different and were by decreasing order: Campylobacter, norovirus, rotavirus, astrovirus and *Shigella*[37]

   On pathogen-specific burdens of community diarrhoea in developing countries, results from a multisite birth cohort study (MAL-ED)[7] show that the epidemiological landscape of diarrhoeal diseases is rather unstable and reveal a few noteworthy observations:

- Viruses are predominant and as rotavirus is increasingly controlled, but unlikely to be eradicated, other viruses may appear on the radar screen, thus justifying steady surveillance and good research on these viruses is needed. There is also need to develop vaccine candidates against these viruses.
- Similarly, other bacterial genera may emerge, such as Campylobacter and these need to be controlled
- Shigella is a common cause of infection in children under five years of age and ETEC requires more attention since it also concerns adults (i.e. the main cause of traveller's diarrhoea). There is need to develop a vaccine that will benefit especially children in endemic areas.

Significant progress has been achieved with rotavirus provided the current vaccines do not fail in some areas, due to different genotypes or progressive loss of efficacy due to emergence of new escape variants. The situation is different for the three other pathogens highlighted by the GEMS study. As of now, there is no candidate vaccine available for *Cryptosporidium* whose complex biology and pathogenesis, as well as late recognition, have delayed both basic and applied vaccine research. Better understanding of the biology of *Cryptosporidium*, with subsequent identification of protective antigens and vaccine development needs to be prioritised[36].

Additionally, the situation is different for ETEC and *Shigella* for which an array of vaccine candidates is available, although very few have so far made it beyond phase II trials[39]. An EU FP7-funded program (STOPENTERICS, 2010-2016) aimed at developing novel approaches in vaccination, from orally-administered to parenterally-administered candidates; two of them are currently undergoing phase 1 testing in Europe. It is timely to move these vaccine candidates to testing in endemic areas for extended phase II and beyond trials if the results are encouraging. This programme also encompassed a global vaccinology component which will improve delivery conditions and immune-monitoring of the trials to hopefully optimize

[7] Platts-Mills JA1, Babji S2, Bodhidatta L3, Gratz J4, Haque R5, Havt A6, McCormick BJ7, McGrath M7, Olortegui MP8, Samie A9, Shakoor S10, Mondal D5, Lima IF6, Hariraju D2, Rayamajhi BB3, Qureshi S10, Kabir F10, Yori PP8, Mufamadi B9, Amour C11, Carreon JD7, Richard SA7, Lang D12, Bessong P9, Mduma E11, Ahmed T5, Lima AA6, Mason CJ3, Zaidi AK10, Bhutta ZA10, Kosek M13, Guerrant RL1, Gottlieb M12, Miller M7, Kang G2, Houpt ER14; MAL-ED Network Investigators

immunogenicity and its proper evaluation including immune memory. The ultimate aim may be to combine the *Shigella* and ETEC vaccine in a single product to facilitate introduction of this vaccine into the already busy routine immunisation schedule of infants in the most impoverished regions that justify antidiarrhoeal vaccination. Other vaccine candidates are in the pipeline, particularly in the USA, some of them under sponsorship of PATH and constant communication is maintained in order to harmonize future developments[40]. This situation offers opportunities for co-funding.

2. The incidence of diarrhoea-related mortality is decreasing while morbidity remains rather stable, this effect increases the effect of recurrent enteric infections and intractable diarrhoea on child nutrition. This is the vicious circle of diarrhoeal diseases and malnutrition that belongs to the broader syndrome of paediatric environmental enteropathy (PEE), a condition that starts early in infancy and affects both physical and psychomotor development, as well as the quality of the children's response to vaccines, particularly those administered orally like the polio and rotavirus vaccines[41]. Clinical and experimental research is essential to decipher PEE's pathophysiology and accordingly propose relevant prophylactic and therapeutic interventions. Availability of efficient vaccines against the most deleterious enteric pathogens may efficiently participate to the disruption of the diarrhoea-malnutrition vicious circle.

5 Capacity Building

The general objective of EDCTP2 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. The area of focus for capacity development mainly lies in the following specific objectives of EDCTP2: **Strengthening cooperation with sub-Saharan African countries, in particular on building their capacity for conducting innovative research that will support clinical trials and implementation research activities in compliance with fundamental ethical principles and relevant European Union and international regulatory standards as well as good practices.** In order to achieve this objective EDCTP will:

- Increase the number of fellowships at MSc and PhD level from 400 in EDCTP1 and encourage the retention of trained scientists in sub-Saharan Africa
- Increase number of capacity building activities for the conduct of innovative research that will support clinical trials and surveillance activities in sub-Saharan Africa from 74 in EDCTP1

The relevant programmatic activities will include:

- Fostering capacity development through training and mobility grants through a comprehensive fellowship programme tailored towards identified capacity needs and gaps. Currently the following fellowships will be implemented: Preparatory Fellowships, Career Development Fellowships, Industry Placement Fellowships and Senior Fellowships
- Fostering staff exchanges, mentoring partnerships at individual or institutional or regional levels and research training networks through grants to regional Networks of Excellence (NoE)
- Foster collaboration between trainees through a recognizable alumni platform
- Strengthening ethics and regulatory human and infrastructure capacity at national and regional levels
- Strengthening country mechanisms for efficient utilization of new or improved tools and interventions
- Strengthening health systems to become resilient to emerging epidemics and conduct relevant clinical research.

Training Fellowships and Mentorship Programmes

As scientific capacity can be limited by the lack of suitably qualified researchers, EDCTP's strategy is to support researchers at different stages of their careers. Fellowship calls will identify and support researchers capable of building and leading research groups at sub-Saharan African institutions that will be internationally competitive and capable of winning grants from international funding bodies. The objectives of the fellowship programme are to:

- Develop capacity for research in sub-Saharan African institutions
- Promote the career development of sub-Saharan African researchers by encouraging them to upgrade their profile and/or return or continue to work in Africa
- Strengthen the capacity to undertake clinical trials of interventions on any of the EDCTP1 infectious diseases in Africa conducted using best practices
- Senior or established researchers to provide mentorship for young and upcoming scientists through Masters and PhD training that involve learning by doing through on- going research in Africa and through sandwich training programmes.

Ethics and Regulatory Support

EDCTP wishes to strike a balance between the public health interest, the interests of the innovative pharmaceutical industry, those of the generic pharmaceutical industry, and ethical values. Despite increasing investment in this area, many African countries have weak and inefficient ethical review mechanisms and some still lack or have nascent national regulatory bodies.

In order to strengthen local capacity in both ethical review and the national regulatory framework in Africa, EDCTP2 will provide support in the following areas:

- Establishment and strengthening of national ethics committees
- Ethics training in Africa through courses and seminars
- Promoting regional cooperation for activities in clinical trials and related research ethics
- Strengthening of the national regulatory frame work in Africa and the relevant regional disease programme review groups through collaboration with the WHO and NEPAD.

Networks of Excellence
EDCTP will continue to support 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.

Currently these networks are organised on sub-regional basis namely Eastern, Western, Southern and Central regions of sub-Saharan Africa. 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.

6 Networking

The mission of the networking teams is to build relationship and brokering sustainable partnerships to leverage funds and align global and local health research agendas in order to facilitate EDCTP's overall mission. To achieve this, the objectives for networking and coordination at the European and African level are to:

- Promote efficiency and avoid duplication by bringing together and aligning European and African public funders and authorities with common objectives to increase the cost-effectiveness of investments
- Create synergies and broker new partnerships between and among European and African researchers, research institutes and centres
- Facilitate creation of, and support to, consortia where appropriate
- Design common funding strategies
- Attract and leverage additional financial investments from other public and private funders, including development cooperation partners, product development partnerships (PDPs), philanthropic and charitable organisations, pharmaceutical companies, small and medium-sized companies (SMEs), non-governmental organisations and non-European Union (EU) countries.

Specific South-South networking objectives are:

- Leverage support for already established regional research networks to encourage growth and sustainability
- Increase contributions from developing countries to at least EUR 30M compared to EUR 14M in EDCTP1
- Respond to African needs and cooperating with national authorities in Africa:
  - Work closely with regional bodies and national health research focal persons to create a database of national health research expenditures
  - Analyse gaps, overlaps and potential synergies (opportunities) in health research in Africa.
- 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 regional Networks of Excellence.

To achieve these objectives, EDCTP networking activities will include:

1. Coordination of national funding

As a means of accelerating the development of new products, EDCTP promotes and facilitates the coordination and pooling of resources at the level of national ministries and funding agencies by encouraging European and African PSs to develop calls for proposals together and with other third parties through the framework of EDCTP2. This could be achieved either through 1) developing joint Participating States Initiated Activities (PSIAs) that are funded and managed by the countries themselves; 2) through inviting PSs to joint Call for Proposals that are developed, managed and financed by the SEC; and 3) to develop together with the SEC joint calls for proposals that are of strategic importance to both EDCTP and the PSs.

To facilitate these activities the EDCTP Secretariat works closely with PSs, primarily through the country representatives on the GA, to identify and follow up on national research activities and priorities in the scope of EDCTP2 and to identify and develop opportunities for collaborations between PSs and their researchers.

PSs are requested to annually submit their PSIAs to the EDCTP Secretariat as a means of demonstrating how much they support activities in the scope of EDCTP2. PSIAs are identified upfront and form an integral part of the EDCTP2 annual work plans, provided that they are co-labelled as part of the EDCTP2 programme. Once include in the EDCTP annual work plan the EDCTP Secretariat will look at the PSIAs in more detail to capture where there is and may/should be alignment or overlap in order to take this discussion forward with the PSs.

EDCTP funding for European networking will aim at achieving a benefit to existing national or European mechanisms and promote greater coordination as a means of accelerating product development. Related to this, one of EDCTP's networking objectives is to increase participation of new EU Member States, to expand opportunities for their participation in European research programmes on PRDs, and ensure significant participation of all European countries.

2. Strengthening project and institutional collaboration

Currently European and African scientists and institutions interact in many ways. However, these collaborations have often been motivated by shared history, foreign policy priorities or institutional affiliations. In some cases, scientists from different European countries work closely with the same groups of African scientists or institutions with little or no interaction. EDCTP aims to ensure coordination and increase synergy between institutions and research groups in order to coordinate and accelerate development of new products in the fight against PRDs.

EDCTP provides funding through open calls which are highly competitive for European and African research teams. This benefits the research partnerships and projects funded (from bilateral to multi-lateral teams and projects), strengthens the development of European capacities and competences, and increases the outcomes and impacts of public investments. This also enables including researchers from countries with both well-established and newer research activities in the field of PRDs and researchers from countries without established national research programmes to collaborate in leading research.

Experience from the first EDCTP programme has shown that coordination of European research and collaborations in Africa is of great benefit to all partners, and strengthens the visibility and the impact of the European contribution. EDCTP will continue to stimulate and encourage multi-site activities, ensuring closer collaboration between national research programmes in the north and the establishment of new North-South collaborations where appropriate. A biennial EDCTP forum will provide a platform for scientists from Europe and Africa to share information and views, and to create and strengthen collaborative links. The EDCTP-funded regional networks will also encourage collaborative research and training activities involving partners from Europe.

3. Strengthening collaboration with national and international development cooperation agencies

To date, there have been varying levels of collaboration between EDCTP and development cooperation agencies, both at the European Union and national level. While some development cooperation agencies have supported EDCTP directly and through contributions to the 'common pot', there have also been collaborations through projects. EDCTP has also benefited indirectly from funding given by national development agencies to Product Development Partnerships that then collaborate in EDCTP projects. However, there are varying levels of engagement with development cooperation agencies.

The Secretariat, with the assistance of the GA representatives, will engage with the development cooperation agencies of the EDCTP Participating States bilaterally to identify potential areas of mutual interest with a view to potentially include joint Calls for Proposals in the future EDCTP2 work plans.

4. Strengthening collaboration with partners in the private sector

To ensure that the impact of all research is maximised and that synergies can be taken into account and achieve leverage of resources and investments, strengthening the collaboration with partners in the private

sector is actively sought. During the initial phase of EDCTP2 (2015-2016) the SEC will primarily focus on informing partners in the private sector of the new opportunities in EDCTP2 through frequent and targeted contacts to individual companies as well as EFPIA (European Federation of Pharmaceutical Industries and Associations). 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 Open 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.

5. SAC involvement to address networking objectives

As part of their role of EDCTP, SAC members are requested to:

- Work closely with regional bodies, national health research focal points (such as Horizon 2020) and networks of excellence to advocate for participation in EDCTP activities and provide strategic planning advice
- Advise the SEC on the organisation of regional meetings where regional bodies, national health research focal points and representatives of networks will be requested to provide relevant information. Such information will be provided to the GA members for their use at that level. This strategy will also be used to analyse the gaps and existing synergies
- Advise the SEC on supporting Networks of Excellence in activities such as meetings, workshops, exchange visits and mentorship programmes, dedicated websites, resource sharing and the biennial EDCTP forums
- Encourage SAC to advocate for the EDCTP2 programme in international meetings.

The EDCTP office in The Hague, The Netherlands will serve as the focal point for any networking occurring in Europe while the Africa Office will serve as the focal point for African networking and provide support to the SAC in this effort.

6. High Representatives involvement to address networking objectives

The two High Representatives will act as goodwill ambassadors for EDCTP in increasing visibility of the EDCTP2 programme and promotion of partnerships with other stakeholders in the fight against PRDs in Africa, Europe and globally.

The main duties and responsibilities for High Representative in the South will include:

- Raising the visibility of EDCTP and promoting programme awareness globally with emphasis in Africa
- Promoting cooperation among the African Participating States with the aim of aligning their national research programmes within the scope of EDCTP
- Promoting EDCTP interaction with national policy makers and regional organisations
- Mobilising the African Participating State inter-sectorial and national-wide support for funding and participation in the programme
- Promoting partnerships with private sector, international development partners and other like-minded organisations
- Representing EDCTP at meetings, conferences and other forums as appropriate
- Promoting active participation and commitment among the African Participating States as the drivers and co-owners of the EDCTP2 programme
- Advocating and gaining political support for the EDCTP, particularly in Africa
- Contributing to the EDCTP fund raising activities
- Developing annual plans and activity reports for submission to the General Assembly
- With the assistance of the EDCTP Secretariat, liaising with the High Representative in the North to ensure harmonisation of efforts and consistency of messaging.

The main duties and responsibilities for High Representative in the North will include:

- Raising the visibility of EDCTP and promote programme awareness globally with emphasis in European and other industrialised countries
- Promoting cooperation among the European Participating States with the aim of coordinating and where possible integrating their national research programmes within the scope of EDCTP
- Mobilising European Participating State inter-sectorial and national-wide support for funding and participation in the EDCTP2 programme
- Promoting partnerships with private sector, international development partners and other like-minded organisations, particularly in Europe
- Representing EDCTP at meetings, conferences and other forums as appropriate
- Advocate and gain political support for the EDCTP, particularly in Europe
- Contributing to the EDCTP fund raising activities
- Developing annual plans and activity reports for submission to the General Assembly
- With the assistance of the EDCTP Secretariat, liaising with the High Representative in the South to ensure harmonisation of efforts and consistency of messaging.

7. Advocacy / Outreach / Fundraising Activities

EDCTP will engage in strategic initiatives that foster collaboration with like-minded funders, raise awareness regarding the EDCTP2 programme and increase its visibility. EDCTP will use such opportunities to showcase its activities and also organise meetings or symposia with the objective of collecting information necessary for future updating of its strategic business plan especially in priority areas where larger stakeholders meetings are not feasible. In addition to the EDCTP biennial Forum, EDCTP will aim to have a strong presence in a selection of international conferences where maximum impact is foreseen. The following approaches are explored for increased programme visibility and fundraising:

- Track sessions/symposia at identified and prioritised meetings highlighting outputs of EDCTP-funded research
- Pilot new ways on generating alternative funding streams e.g. Crowd funding, donation programme
- Sponsorship opportunities for the EDCTP Forum
- The Africa Office will continue to be the link of collaboration with other initiatives and networks in Africa, such as ANDi, INDEPTH, ASLM, NEPAD, African Academy of Sciences (AAS), Alliance for Accelerating Excellence in Science in Africa (AESA), and Regional Economic Communities (ECSA, OCEAC , SADC, EAC) and their health and research arms as well as with African regional bodies (WHO-AFRO, WAHO)
- The implementation of advocacy activities will be further elaborated in the EDCTP communications strategy.

7 Programme Management and Strategy

7.1 Governance and Management Structures

Currently **EDCTP-Association** (registered in the Netherlands under Dutch law and established in April 2014) is the legal governing, executive and representative body of the EDCTP programme (refer to figure 1). This new legal structure enables countries from Europe as well as from sub-Saharan Africa to become members of the EDCTP governing body. The EDCTP Association reflects EDCTP's commitment to equal partnership built on joint ownership and leadership. Presently, 14 European countries (Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden and the United Kingdom) and 14 African countries (Cameroon, Burkina Faso, Congo, Gabon, The Gambia, Ghana, Mali, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda and Zambia) have joined the Association as full members participating in EDCTP2. The principle of one vote for each EDCTP full member applies. Unlike EDCTP1 it is not be possible to join as an associate member. However, countries eligible to join, who have not yet made a decision to join, may be invited to attend meetings of the General Assembly as Aspirant members to inform the decision-making process and to familiarise themselves with the activities of EDCTP. EDCTP2 has a streamlined governance structure. It is made up of a General Assembly, the Board and the Executive Secretariat. The EDCTP Advisory Body on scientific and strategy matters is the Scientific Advisory Committee (SAC).

The supreme body of EDCTP is the **General Assembly**, in which all members are represented. It is the ultimate and exclusive decision-making body of the EDCTP-Association. Its principal responsibility is to ensure that all necessary activities are undertaken to achieve the statutory objectives of the programme, and that its resources are properly and efficiently managed. The GA takes responsibility for the provision of Participating States' matching financial contribution to EDCTP. GA members must have a mandate from the State which they represent to enable them to facilitate a direct decision-making process leading to the allocation of funding from the national budgets for the EDCTP programme. European Participating States on the General Assembly will have legal liability for the management of the programme. The General Assembly will be supported by the Secretariat.

The **Board of EDCTP-Association** consists of such number of Board Members as the GA shall determine, but no less than five. Nomination for Board membership is only for an individual who is already an appointed GA representative or deputy/alternate representative. The Board is entrusted with the management of the Association and supervises the Secretariat in preparing the Association's annual work plan and multi-annual strategic work plan.

The **Secretariat** is the executive body that implements the EDCTP programme, assures the day-to-day management of EDCTP and provides support to the other EDCTP bodies. The Secretariat is fully responsible for the execution of the EDCTP2 programme and is accountable to the General Assembly. The key executive position on the Secretariat is the Executive Director (ED) assisted by the Director of Finance and Administration (DFA), Director of North-North Cooperation (DNNC) and Director of South-South Cooperation (DSSC) (see Annex I). The Secretariat has two offices, one in Europe and the other in Africa. Notwithstanding its dual location, the Secretariat is one, with the Executive Director charged with managing both offices and the DSSC acting also as Head of the Africa Office. The **Europe Office** serves as the main administrative, legal and financial centre serving EDCTP as a whole and act as a focal point for EDCTP2 in Europe, with a key role in promoting Participating State coordination and integration. The **Africa Office** serves as a focal point for EDCTP in Africa, with a key role in promoting South-South networking activities, and for the coordination of capacity building activities. The Secretariat shall be staffed sufficiently to deliver the programme over ten years, including evaluating the impact of trials that are completed. To support its advocacy role the Secretariat shall include two High Representatives, one based in Europe and one based in Africa, capable of representing the programme at the highest diplomatic levels.

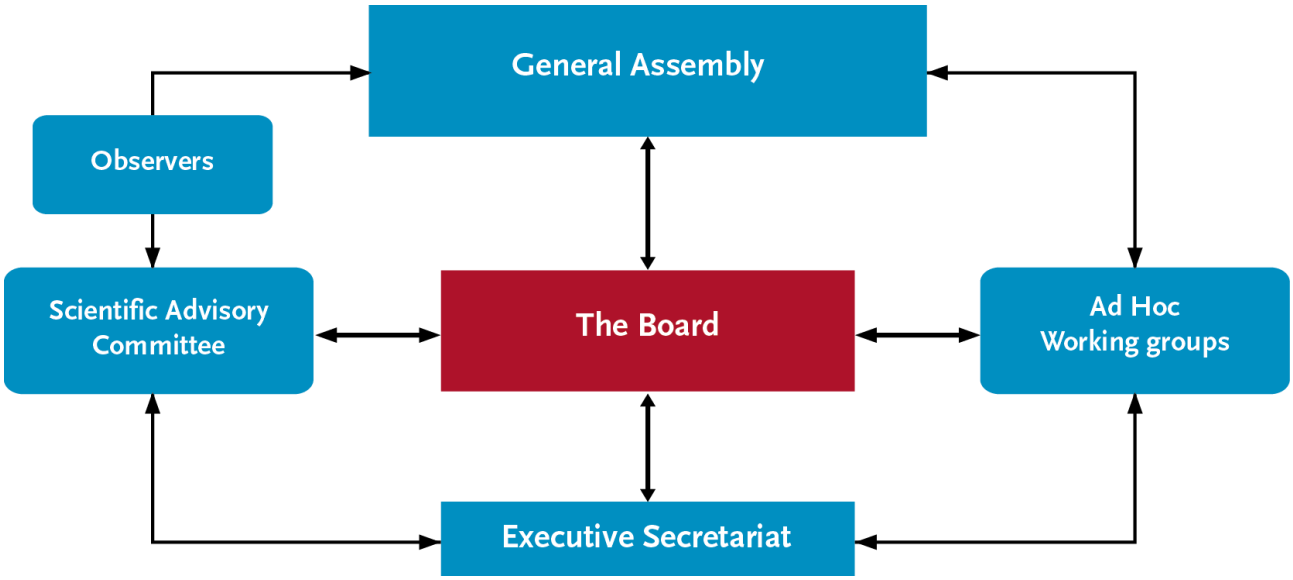
The strategic direction of EDCTP2 is supported by scientific and strategic advice from an expert **Scientific Advisory Committee (SAC)**. The SAC has representation from North and South, particularly European and

African scientists, across the relevant disease areas, including NIDs and health systems research, health economics and planning as required to deliver the strategic research agenda. New terms of reference for the SAC have been prepared (dated November 2012) and these permit specialist working groups to be established under the auspices of the SAC with additional experts co-opted for specific projects. A key role of the SAC is to assess the state of global product development pathways and the critical paths for future product development. The SAC works with the Secretariat to identify opportunities to coordinate calls in specific fields as products become available or to hold initiatives. On an annual basis, the SAC prepares a Strategic Research Agenda (SRA) which forms the basis for the Secretariat to propose the annual work programme of the following year to the General Assembly for approval. The SAC may form sub-committees on different diseases and interventions and to assess African needs and priorities.

The EDCTP programme as such takes place in, and belongs indeed to the African partner countries. Apart from the considerable input from sub-Saharan African institutions, communities and ministries, the ultimate authority over the activities befall to the governments representing the populations which take part in the research and who should benefit from its results. In line with the Paris-Accra principles and the EU's Strategic European Framework for International Science and Technology Cooperation, EDCTP2 has developed a governance and management structure that respects the African co-ownership as well as the European partnership and input.

While research may, in some circumstances, be performed in other developing countries outside sub-Saharan Africa, there will be no representation from other geographical regions on the General Assembly during EDCTP2.

Figure 1: Legal structure of the EDCTP Implementing Structure



7.2 Strategic Roadmap 2014-2024 (milestones)

EDCTP2 will pursue its objectives in a step-wise approach over a period of ten years, consisting of the programme implementation phase (2014 to 2020) plus the phasing out and conclusion of the grant management processes (2020-2024). EDCTP2 will be divided into terms of three to four years. The strategic vision will be translated into a logical framework that will guide actions, monitoring and evaluation. The Agreement between the EU and EDCTP will be concluded for 2014 to 2024. The time frame and milestones include:

2014 15 April, European Parliament approval decision of EDCTP2 programme 556/2014/EU
6 May 2014, the Council of the European Union approval decision of EDCTP2 programme in its

meeting on Economic and Financial Affairs (ECOFIN)
2 December 2014, launch of EDCTP2 (first term) with extension to include NIDs, diagnostics and phase I-IV.

2017 Not later than 1 February 2017, the EDCTP Association to provide the Commission with a report (covering years 2014-2016) providing input to the first interim evaluation of the EDCTP2 programme

First quarter of 2017, EDCTP2 programme first interim evaluation

2023 Not later than 1 March 2023, the EDCTP Association to provide the Commission with a report (covering years 2014-2022) providing input to the second interim evaluation of the EDCTP2 programme.
First quarter of 2023, EDCTP2 programme second interim evaluation

2026 Not later 31 March 2026, the EDCTP Association to provide the Commission with a report (covering years 2014-2026) providing input to the final evaluation of the EDCTP2 programme
First/second quarter of 2026, EDCTP2 programme final evaluation.

7.3 Cofunding arrangements for EDCTP2

Apart from the EU funding, the resources of EDCTP consist mainly of:

1) Resources of national programme activities linked to EDCTP, managed by the European Participating States
2) Unrestricted cash contributions of European Participating States to the EDCTP common pot
3) Cash contribution of European Participating States that is restricted or directly managed by the Participating States and therefore not in the common pot
4) In-kind and cash contributions of African Participating States to EDCTP
5) Contributions from third parties.

Resource types 1-3 were, and remain, the most important in political and legal terms, as they constitute the Participating States' co-funding conditional to the EU co-funding. EDCTP2 will establish a transparent and predictable co-funding system. **For accounting purposes** only the funds that are channelled to the Secretariat to be centrally used without any restriction will be counted as cash contribution and the rest as in-kind contribution. This is summarised in the chart below:

MANAGED BY EDCTP SECRETARIAT		**MANAGED BY MEMBER STATES**	
COMMON POT	**IN KIND**	**IN KIND**	**IN KIND**
1. EU cash contribution 2. Participating states *unrestricted* cash contribution	Participating States *restricted* cash contribution	Participating States restricted cash contribution	Participating States in-kind contribution

In addition, development aid agencies at national and community level could contribute to capacity strengthening and operational research, while science agencies should mainly cover the research *per se*. Furthermore, EDCTP will proactively seek to generate resources from African and external partners (type 4 and 5) and ensure that such resources are made more visible.

Whereas many trials funded by Participating States are now co-funded by EDCTP, the more ambitious aim of EDCTP2 will be the integration of national programmes and projects into one strategically coherent "Joint Programme." During EDCTP1 this objective remained challenging not least because of different understandings of the principles of integration and the various constraints on national funding. However, the

majority of members are committed and able to accelerate integration of existing national programmes in EDCTP2 and to increase their contributions, including unrestricted or restricted cash contributions.

In-kind contributions that are under national administration are eligible as co-funding only if the national activity they relate to is explicitly framed within the EDCTP joint programme.

Contributions from Participating States and third parties will be possible as either cash contributions or in-kind contributions. All such contributions may themselves attract matched funding from the EU and contribute to co-funded activities. For the purpose of EDCTP2 co-funding will be defined as the contribution in cash or in-kind that is raised by parties other than the European Union to support the EDCTP programme. Co-funding may come from the European Participating States, African partner countries or third parties. Third-parties include all other funders, private sector, like-minded organisations, Product Development Partnerships or any other organisation that may participate in EDCTP programme. In EDCTP2 matched contributions will be assessed over the whole of the programme and not on a project by project basis. There will thus not be a need to apportion co-funding to each individual project.

For accounting purposes, in-kind contributions will be defined as contributions, other than unrestricted cash, that directly make it possible for a clinical trial, networking or capacity development activity, or other activities that are within the scope of EDCTP to be performed when undertaken with cash funding from the European Commission. It may include provision of goods or services that are required to undertake or enhance the EDCTP programme.

Cash contributions may be allocated to the EDCTP Secretariat to administer centrally or directly to a project. Cash administered centrally may be referred to as a common pot. Individual cash contributions may have restrictions on use (e.g. limited to specific calls). It must however, be emphasised that although a common pot approach is desirable, the complex, multifaceted nature of the EDCTP programme does not make this a necessity or a prerequisite.

8 Programme Implementation and Activities

8.1 Actions for achieving the objectives including:

The EDCTP programme goals will be realised through Participating State joint programmes with a common research administration and funding. This will include a common peer-review, co-financing, projects oversight, and monitoring and evaluation. The action will be implemented through calls launched by the Secretariat in consultation with the European Commission and Participating States. Participating States will jointly fund clinical trials through cash contributions to EDCTP or to projects, as well as provide in-kind contributions thereby making available to the projects the research laboratories, clinical trial sites and training programmes that they fund through their national programmes.

Participating States will also launch their own-initiated activities. These will be described in the annual work plans agreed by the General Assembly and will support the objectives of EDCTP for the integration of National Programmes.

The programme will achieve its objectives by supporting clinical trials of the appropriate products. This will require strengthening of the capacities and enabling environment in sub-Saharan Africa to enable the conduct of clinical trials using best practice. This will include:

- Funding of clinical trials through open calls
- Supporting of ethical review and regulatory framework
- Training of personnel (short- and long-term courses)
- Infrastructure upgrades (laboratory, clinical trials sites, trial recruitment facilities, etc.)
- Networking including continuing support to the Regional Networks of Excellence
- Career Development and Senior Fellowships as well as other post-doctoral training activities addressing specific skills and expertise capacity gaps.

Based on this strategic business plan the SAC will prepare a Strategic Research Agenda to assist in the preparation of three year work plans that will include annual activities and estimated budgets. The Participating States will be asked to give upfront annual, or where possible multi-annual, contributions to cover for the running of the activities. The contributions may be in-kind or cash. Annual work plans and budgets will be drawn by the Secretariat in consultation with the SAC for the approval of the General Assembly six months in advance of each calendar year. This will take account of the state of art, prevailing status of the landscape of diseases of poverty and product development pipeline as well as other requirements such as capacity needs based on consultation with all partners and stakeholders through stakeholders' meetings. Experience from EDCTP1 has shown that stakeholders' meeting involving all potential players including partner Participating States from north and south, funders, scientists, SMEs, pharmaceutical industry and like-minded organisations are very useful for deciding on research areas for funding, fostering joint ownership of projects and stimulating working in partnership. This will also take into account the need to be flexible as new issues emerge and the landscape changes. This may include teaming up with other partners to facilitate registration of promising candidate products through phase III clinical trials.

8.1.1 Key Principles

- Flexibility to allow EDCTP to react and adapt to the changing landscape in terms of needs resulting from new threatening challenges or promising opportunities
- Improved integration of national activities through existing or novel innovative funding schemes and funding mechanisms at individual, project, institution and programme level
- Ensuring leadership and ownership of EDCTP-funded clinical research and related capacity building activities by sub-Saharan African countries
- Increased third-party funding and industry participation

- Assured availability, accessibility and delivery of medical products that have been proven to be efficacious through strategic partnerships and coordination with relevant partners
- Alignment and integration of scientific activities and resources
- Sound operational funding strategy that includes thematic and upfront financial commitment of partners on an annual basis
- Transparency, planning security, accountability and visibility of the programme.

8.1.2 Type of grants

The EDCTP programme supports three distinct types of actions, namely: Research and Innovation Actions (RIA), Coordination and Support Actions (CSA), and Training and Mobility Actions (TMA).

Research and Innovation Actions (RIAs)
Actions primarily consisting of clinical research activities and clinical trials in partnership with African countries aiming at increasing the number of new or improved medical interventions for HIV, tuberculosis, malaria and other poverty-related diseases, including neglected ones, in particular in sub-Saharan Africa.

Actions may normally include one or more clinical trials (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 for secondary study endpoints and 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 (CSAs)
Actions primarily consisting of accompanying measures, 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 researchers and among African researchers, clinical research institutions and sites, and 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).

Further, 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 Actions (TMAs)
Actions primarily consisting of activities fostering career development of individual junior and senior fellows from sub-Saharan Africa, supporting training and mentorship of researchers, and promoting mobility of individual researchers and research staff.

8.1.3 Participating States Initiated Activities (PSIA)

PSIAs are national or transnational clinical research and capacity development activities that are implemented or funded by a single Participating State (PS) or by several PSs (independently or jointly), and fall within the scope of EDCTP2. PSIAs are included in the EDCTP2 annual work plan to facilitate and promote networking, cooperation and, where appropriate, integration of national programmes and activities. This will enable PSs to foster research collaborations with other European and sub-Saharan African countries in the area of clinical research and capacity development in the scope of EDCTP2. PSIAs in the EDCTP2 annual work plan will be implemented in compliance with agreed common principles (between EC and PSs) that are aligned with the rules for participation in Horizon 2020. PSIAs included in the EDCTP workplan are based on national priorities but should where possible be strategically aligned with the EDCTP2 programme. Any communication or publication related to a PSIA shall be labelled or co-labelled as "[name of the activity/ grant code] is part of the EDCTP2 programme supported by the European Union". Whenever relevant and feasible, the EDCTP logo should also be included.

8.1.4 Other Activities & Prizes

EDCTP will implement activities supporting programme operations such as: Independent experts assisting in proposal evaluations and project reviews; the hosting an EDCTP Alumni Platform; EDCTP Forums, stakeholder meetings; financial and project management training; open source pilot for clinical trials; contribution to the development of a web-based financial management assessment tool (FMAT) among others.

Additionally, EDCTP shall provide different Awards with an aim of driving innovation through the recognition of achievements and the promotion of role models. EDCTP will award four prestigious international prizes dedicated to the promotion of scientific research, improved health and Africa-European collaboration. These awards are to be presented to outstanding individuals and research teams especially from Africa and Europe. The Awards will be announced every two years at the biennial EDCTP forum.

The four awards are:

- **Scientific Leadership Award**: Awarded to excellent world-class scientists in Africa up to up to 50 years of age
- **Outstanding Female Scientist**: Awarded to excellent world-class female scientists working and residing in sub-Saharan Africa in the remit of EDCTP2.
- **Outstanding Research Teams**: Awarded to outstanding research teams in Africa and Europe working on HIV, tuberculosis, malaria and neglected infectious diseases (NIDS) in the scope of the EDCTP2 programme.
- **Dr Pascoal Mocumbi Award**: This is an award set up in recognition of the work of Dr Pascoal Mocumbi towards the mission of EDCTP. It is to be awarded scientists, policy makers or advocates for health and research from anywhere in the world and has no age restriction.

9 Criteria for prioritisation of Actions

Experience from EDCTP1 has shown that calls for proposal that are narrow and target specific subject areas may be restrictive and limit wider participation. It is therefore proposed that in EDCTP2 calls should cover a broader scope to attract a wider and high quality of research applications. This change in approach will require review after the first three years to ensure the right catchment of applications and spread across diseases is received. The importance of partnering with other funders to support large trials, especially taking into account the need to support more phase II and III clinical trials is emphasised. Prioritisation of Actions in EDCTP2 will take into account the following:

1. *Progressive review of product development landscape based on disease categories*
   This will focus on treatment, prevention, diagnostics and implementation research to optimise impact of interventions
2. *Disease burden and need for appropriate interventions*
   As an example, in HIV the scaling up of treatment has expanded very rapidly and on an immense scale to an extent that it has now created a growing and urgent need for optimisation of HIV care. In contrast, HIV prevention interventions have received less attention compared to the scale up in treatment and hence the need for prioritisation
3. *Emerging opportunities for EDCTP value-addition within expanded remit of the second programme*
   EDCTP will take advantage of product development opportunities in respect to the expanded remit that will include NIDs and post registration programmes including effectiveness studies and pharmacovigilance
4. *Balance between immediate and long-term priorities and in clinical trial phase*
   This is important not only to ensure that the development pipeline remains robust, but also to allow a steady flow of products.

9.1 HIV

Sub-Saharan Africa remains home to the largest number of individuals infected and affected by HIV globally[42]. Reduction of new HIV infections and its attendant co-morbidities is a public health priority. EDCTP2 will continue to support research and clinical trials of HIV prevention, treatment (testing new treatment options), implementation research of proven strategies, point of care diagnostics, and studies on linkage and retention in care. Building on the success of HIV programme in EDCTP1, the EDCTP2 HIV strategy will build on the current successes and challenges to address the epidemic in the future.

EDCTP2 plans to support several trials in both HIV prevention and treatment in various population groups, such as men who have sex with men (MSM), HIV-discordant couples and heterosexual men and women and other key affected populations. We now have numerous tools for HIV prevention including medical male circumcision, HIV counselling and testing, safer sex education, pre- (PrEP) and post- exposure prophylaxis (PEP) with ARVs, PMTCT and treatment of infected people (TasP). The public health priority is now to demonstrate their success as HIV prevention from efficacy trials to effectiveness trials and implementation research. This will require health systems strengthening and optimisation of treatment and care programmes, with effective linkage to, and retention in, care. EDCTP will support research to identify models of delivery, which increase coverage of interventions safely, effectively and equitably. This research may extend to studies evaluating strategies for detecting and managing co-infection, getting people into care and retaining them in care. In addition, EDCTP will continue to support trials of new biomedical technologies including HIV vaccines, antiretroviral drugs with different formulations to address the challenge of adherence, and research on effective use of combination prevention (using effective products) strategies for more targeted interventions in high-risk groups. Given the global commitment to the 90-90-90 target (90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, 90% of all people receiving antiretroviral therapy will have viral

suppression[43]), it is imperative that EDCTP aims to support this global agenda. As more prevention options become available, the efficacy trials are likely to be much larger and will require multiple donors to support such trials to achieve an "HIV-free" generation. Partnerships with donors and other like-minded initiatives will be critical to the success of these programmes.

EDCTP1 has supported a number of trials on the use of antiretroviral therapy in Africa. EDCTP2 will aim to build on this research portfolio and support future trials on the improvement of treatments, as well as address other clinical questions, which might become pertinent with the use of newer regimens in Africa. EDCTP1 successfully conducted policy-relevant research on the prevention of mother-to-child HIV transmission and ARV treatment optimisation. This will be improved upon with the use of newer combination antiretroviral therapy and with support for pregnant and breastfeeding women as well as HIV-infected infants and children to adhere to lifelong therapy. Opportunities will be sought to support research on the evolution and impact of resistance to antiretrovirals in different population groups.

Following improved access to ART, HIV-associated mortality has declined, and survival has increased globally. HIV has now become a manageable chronic disease that requires life-long therapy. The use of ART has escalated in sub-Saharan Africa as part of implementations of the expanding WHO HIV management guidelines. Efavirenz (EFV) + Tenofovir (TDF) with emtricitabine or lamivudine is the current first-line regimen for the treatment of HIV and the prevention of mother-to-child transmission of HIV. ARV use in pregnancy has significantly reduced the rate of mother-to-child transmission of HIV globally[44]. Further clinical research is required to ensure the short and long-term impact of ART on maternal toxicity and infant safety. ARV-associated adverse events such as EFV-induced CNS and liver toxicities as well as TDF-associated bone and renal toxicities may cause adherence problem and treatment failure. The high mortality and ART failure rate in HIV-infected infants and children in resource-limited countries[45,46] indicates the need for optimal ARV treatment guideline tailored for paediatric population that might be lifesaving, reducing mortality and disease progression. Although EFV is licensed to treat HIV-infected infants who are at least three months old weighing 3.5 kg and children[47] further evaluation of its pharmacokinetics and appropriate dosing in young children is required[48,49]. Viral resistance partly due to inadequate dosing may result in the loss of EFV, which is a backbone of current first-line ART in sub-Saharan Africa. Furthermore, second line ART option for younger children is limited. Therefore establishing EFV-based first-line therapy for infants/children will also preserve protease inhibitors for a second line treatment regimen. EDCTP2 will continue supporting research to identify simpler ARV formulations with appropriate dosing for children and also monitor for other emerging priorities, such as the use of treatment for prevention in selected populations should feasibility studies provide positive findings.

Co-treatment of TB-HIV or HIV-malaria is challenging because of possible drug-drug interactions and overlapping toxicities. Rifampicin, a potent drug metabolizing enzyme inducer, lowers plasma EFV concentration particularly in the white population[50]. Accordingly the US-FDA, International Antiviral Society-USA panel and the British HIV Association guidelines recommend body weight based EFV dose adjustment during rifampicin co-treatment[51,52]. However, EDCTP1 funded studies in black African population report the insignificant effect of rifampicin, supporting the current WHO HIV treatment guideline that recommends no EFV dosage adjustment during concomitant RIF-based anti-TB therapy[53]. Thus, population-specific clinical research in SSA is imperative where the burden of TB-HIV is highest.

Likewise, HIV and malaria co-infection is common in sub-Saharan Africa and optimization of HIV-malaria co-infection needs prioritization due to potential interactions between ARV and anti-malarial drugs[54]. Recent studies from Africa indicated EFV-based ART co-treatment significantly reduces lumefantrine plasma exposure[55] and high rates of malaria treatment failure in HIV patients being treated with EFV-based cART[56,57]. Sub-therapeutic malaria drug levels may provide a selection pressure for resistant parasites and survival. EDCTP2 will continue supporting studies that provide evidence-based recommendation for policy makers to develop effective TB–HIV and HIV-malaria co-treatment guidelines, particularly in resource-limited settings.

Delivery of HIV treatment services is particularly challenging because HIV requires continuous care. Similarly, adherence to antiretroviral drugs and other prophylaxis measures is sub-optimal because these interventions need regular application. To optimise the scale-up and effectiveness of interventions against HIV in real-life, EDCTP will support research to identify models of delivery which increase coverage of interventions safely, effectively and equitably. This research may extend to studies evaluating strategies for detecting co-infection, getting people into care and retaining them in care.

9.1.1 Prioritisation of Calls for proposals for HIV

1. **Treatment**

   Optimization of ART to increase both the safety and efficacy is vital for the achievement of the global 90-90-90 targets. As part of this global commitment, EDCTP2 will support clinical trials and research focused on improving ART treatment outcomes using new and existing drugs.

   A Call for Proposals on treatment will be launched during the first period of EDCTP2, but further calls may feature later on. Treatment priority includes:

- The current treatment gap between adult and children[58] need to be addressed. Lack of palatable fixed dose combinations, which does not need refrigeration for paediatric use, is one of the gaps and EDCTP2 will support clinical research focused on bridging the gap. Evaluation of new simple and tolerable paediatric ARV formulations as well as dose optimization studies in infants and children.
- Novel therapeutics and novel use of existing therapeutics (e.g. to prevent the evolution and impact of resistance);
- HIV treatment is lifelong. The burdens of long-term ART-associated complications such as lipodystrophy, neuropathy, and cognitive impairment, ageing populations and associated co-morbidities involving cardiovascular diseases and diabetes remain a concern. EDCTP2 will support studies that investigate reducing the short and long-term ART-associated complications and its impact on adherence and ARV resistance.
- Optimization of ART using existing drugs for the general adult population and targeted populations, such as pregnant and breastfeeding women, infants/children, and MSM. E.g., to improve treatment outcome, reduce ART-associated adverse events and improve PMTCT.
- HIV co-infection with tuberculosis or malaria requires co-treatment of both diseases. However, co-treatment is complicated by drug toxicity and drug interactions and this may influence treatment outcome. Studies on the issue of drug interactions between ARVs and antimalarial or anti-tuberculosis drugs and dose optimization studies to improve HIV-TB and HIV-malaria co- treatment will be prioritized.
- The same ARV regimen is used to treat HIV infected pregnant and non-pregnant women. Physiological and hormonal changes in pregnancy can affect the pharmacokinetics of antiretroviral drugs[59], and this may influence the safety and efficacy of ART. Optimizing ARV use for treatment and PMTCT in pregnant women is important to lower HIV-associated maternal and infant/child mortality. Clinical research evaluating the safety and efficacy of ARV use and potential drug interactions with other medications during pregnancy and breastfeeding will be supported.
- Better formulations and dose optimization for special population in clinical trials, e.g. pregnant women, women of child-bearing age and the increasing population of elderly HIV-positive individuals

2. **Diagnostics**

   The diagnosis of HIV in young infants born to HIV-infected mothers remains challenging, with rapid HIV antibody detection not sufficiently specific. The diagnosis in young infants thus depends on the detection of virus, for which point of care approaches are urgently required.

   Point-of-care diagnosis of HIV drug resistance also urgently required to ward off an emerging problem of widespread HIV drug resistance.

3. **Operational and implementation research to optimise impact of interventions**
   This will include research to identify delivery models for sustainable, equitable and full-scale access to diagnostics, prevention and treatment interventions. Community-oriented and integrated approaches will be prioritised.

Examples:

- A core barrier to HIV prevention and linkages to care is acceptability of HIV counselling and testing hence the need for models of delivery that can increase acceptability in an equitable, sustainable and ethical way. Linkage to care remains a major hurdle and support for people identified as HIV-infected should be explored and evaluated in programmatic settings.
- Optimising the integration of HIV/PMTCT and TB services and HIV/sexual and reproductive health/family planning programmes should also be a priority area, as it may improve linkage to, and retention in, care.
- Optimisation of PMTCT programmes in identifying HIV infected women in late pregnancy or while breastfeeding, and in long-term adherence to lifelong ART for the mothers, diagnosis of infection in infants and children.

4. **Prevention**
   Although we have had enormous success with treatment and partly prevention with ARVs, it remains critical to reduce the number of new infections. Behavioural, structural and clinical risks for HIV acquisition have been identified[60]. These include multiple sexual partners, unprotected sex, early age of sexual debut, access to HIV prevention care such as distance to health services, gender-based violence, migration[61], clinical risks such as presence of sexually transmitted infections (STIs), and inflammation. As part of the long-term undertaking planned to start in the second period of EDCTP2, the aim will be to reduce incident HIV infections by building on the current success achieved globally as well as through the EDCTP1 program. EDCTP2 will aim to address this challenge in the following priorities:

- Women-initiated HIV prevention: Over 50% of new HIV infections in sub-Saharan Africa occur in women. In order to address this, trials of long acting ARVs formulated as injectable and vaginal rings would be of EDCTP2 interest. Both these products aim to alleviate the current adherence challenges[62] in reduction of HIV transmission and acquisition.
- Prevention of HIV and pregnancy – Pregnancy although highly desirable in some women, is not so for large numbers of women who face the challenge of unplanned pregnancy. Biomedical research focused on multipurpose technologies to prevent both pregnancy and HIV is in early stage of development with early phase trials in humans set to advance soon[63]. EDCTP2 would aim to support early and late stage trials of these multipurpose technologies such as vaginal rings containing ARVS and contraception in women in Africa.
- HIV vaccine remains the ultimate goal to address the HIV epidemic. In partnerships with Pharma such as GSK, Merck and other donors, EDCTP will aim to support trials of HIV preventative vaccines of products found to show suitable level of immunogenicity in early phase trials.
- Not everyone is at equal risk of HIV acquisition. It is therefore critical to provide targeted interventions to individuals at highest risk of infections. Given that current biotechnologies are not 100% efficacious, there is a need to test tailored combination prevention methods in population at risk of HIV infections. Combination prevention strategy will likely include behavioural, structural and clinical interventions to prevent incident HIV infections. EDCTP will support implementation science research to address a decline in population level incidence through combination prevention trials.
- It is noted that ARVs for prevention and treatment are not a priority for further clinical trials on proof of principle of efficacy in reducing HIV incidence, as several trials are ongoing and in light of the most recent WHO treatment guidelines, which now recommend treatment for all HIV-infected people. Treatment as prevention, or universal Test and Treat has now become more of an implementation research area.

5. **Key short- and medium-term priorities**

- The first call will be general and planned to cover novel use or optimisation of existing therapies and diagnostics to improve treatment and/or prevention of HIV. Partners and opportunities will be sought for calls involving new products. This will, however, unlikely be in the first call since the product pipeline is currently unclear.
- HIV treatment priorities are highlighted above, and relate mostly to pregnant women and children, adherence support to address the issue of drug resistance, and co-infections.
- Prevention in HIV Prevention include testing combination prevention of efficacious strategies to reduce incidence of HIV; Testing novel formulations with minimal adherence challenges for HIV prevention in women and Implementation science for Test and treat and PrEP strategies for population impact on HIV.
- Optimisation of treatment and care programmes involving Implementation sciences will be focused on ensuring full coverage of HIV treatment and care for all, including PMTCT and integration with other care services, such as TB, Malaria, antenatal and chronic care.

9.2 Malaria

Malaria prevention in the most vulnerable groups, pregnant women and children, relies on the use of long-acting antimalarial drugs; the cornerstone of malaria elimination it is also based on this type of drugs. The evaluation of new long-acting antimalarial drugs for these objectives will be prioritised in EDCTP2. A large array of anti-malarials is also going to enter the development pipeline[64]. Building on EDCTP1, EDCTP plans to lead the evaluation of new drugs or drug combinations (including combinations of new and existing drugs) with a particular focus on children and pregnant women and on tackling uncomplicated malaria, which has a massive burden. Treatments for severe malaria, which can act rapidly and against resistant strains, will also be evaluated. Tracking antimalarial drug resistance is an important activity in the context of malaria control, but it becomes less important as elimination is approached, since there are fewer cases that all must receive curative treatment. New assays of molecular markers for resistance, especially for arteminisins, need to be developed. Simple, field PCR-based tests would be useful, both for resistance testing and to differentiate recrudescence from new infections[65]. This question will be explored in EDCTP2 within the drug clinical trials for malaria prevention and treatment.

In the next ten years, a number of new malaria vaccines are likely to emerge from the discovery pipeline and be ready for evaluation. Our aim will be to test new vaccines. Vaccines for evaluation will include those which might protect young children and pregnant women and which will be delivered through existing mechanisms such as the Expanded Programme on Immunisation (EPI), the antenatal care clinic (ANC) or through other novel schemes. Trials of such vaccines are likely to be large, complex, and expensive so that these undertakings will need to be done in partnership.

It is essential to optimise the effectiveness of products in the real world after efficacy has been demonstrated in controlled trials. Thus, EDCTP2 will support the evaluation of different strategies for delivering and scaling up access to drugs, vaccines and diagnostics, including evaluation of different delivery schemes of drugs and vaccines that might be more optimal in the African setting.

Africa has the highest prevalence and incidence of HIV infection globally, and many HIV infected individuals in the region live in malaria endemic areas[66,67]. New national and international policies expanding HIV treatment to all infected people to reduce the burden of HIV, will increase the number of HIV infected individuals on ARTs[68]. In addition of being more likely to receive antimalarial drugs for case management, because of increased risk for severe malaria infections[69], HIV infected individuals will be exposed to antimalarials during mass drug administration as part of malaria elimination campaigns. It is critical to know the safety, efficacy and drug interactions between antimalarials and ARTs[23] . In addition, finding optimal malaria preventive and therapeutic schemes for this vulnerable group of the population, for whom malaria control strategies are poorly defined or not evidence-based, is a clear priority.

Malaria has declined in some settings across sub-Saharan Africa, raising exciting questions of malaria elimination/eradication. Whether and how elimination might be feasible will require research that EDCTP2 plans to support. This will include testing of potential malaria elimination strategies, for example evaluating the impact of drugs in combination with various vector control strategies and surveillance strategies. However, malaria surveillance is currently weakest in countries with the highest malaria burden. Improved surveillance will be key in this new phase of malaria elimination, with development of robust and continuous malaria monitoring and surveillance systems critical. Novel methods that provide accurate real time epidemiological information on the burden of infection are needed, new methodologies for identifying, estimating and tracking the malaria burden, and new strategies to measure transmission are indispensable. In this regard pregnant women, who are relatively easy-to-access through antenatal care, represent a potential sentinel group to monitor malaria trends in the general population, as well as monitoring the impact of malaria control and elimination interventions[70].

There have been recent advances in malaria diagnostics[43]. EDCTP2 will support the evaluation of new diagnostic tools, which are more accurate, rapid, easy to use and less invasive than those available currently, and could be use as "point of care".

The proposed research agenda will tackle the different forms of human malaria prevalent in Africa, but with a particular focus on *P. falciparum*. However, *P vivax* detection and management will become increasingly important as control measures reduce *P falciparum* transmission. Because *P. vivax* can remain latent in the liver but produces relapse, its effective management normally requires the use of 8-aminoquinolones to clear hypnozoites from the liver. No current diagnostic tool can detect hypnozoites and it has become a research priority for the success of malaria elimination in areas of vivax malaria endemicity including those in the African region. In addition, research to find newer non-8-aminoquinolone drugs for *P. vivax* radical cure that do not induce haemolysis in G6PD-deficient individuals is much needed[41].

9.2.1 Prioritisation of Call for Proposals for Malaria

1. **Treatment**
   This will be given immediate priority, planned to take place in the first period of the programme. This will be looking at safety and efficacy of new drugs and optimization of existing ones including drug-drug interactions between antimalarials and other drugs such ARVs and anti-TB drugs. A call on Malaria-HIV co-infection to asses and optimize new antimalarials for treatment and prevention among HIV infected individuals including children and pregnant women will be considered.

2. **Prevention**
   This will be given immediate priority, planned to take place in the first period of the program. Evaluation of novel drugs and vaccines targeting different populations such as infants and pregnant women will be done in partnership with other funders. Taking into account the changing diseases landscape and the declining in the incidence of malaria, elimination feasibility studies will be given priority.

3. **Diagnostics**
   This will be planned to take place in the second period. This will include both the evaluation of novel tools (priority given to point of care tests) including those for detection of *P. vivax* hypnozoites, and innovative use of existing technologies for malaria control and elimination efforts.

4. **Operational and implementation research (health services and systems optimization research)**
   This will be given immediate priority. It will include the evaluation of novel delivery channels and mechanisms of new and existing interventions. The monitoring and evaluation of scale-up of access to drugs, vaccines and diagnostics. Defining indicators for surveillance would be prioritised changing from measuring morbidity and mortality to detecting infections and measuring transmission.

Evaluation of the feasibility, efficiency and cost-effectiveness of new information systems will be undertaken.

9.3 Tuberculosis[71]

EDCTP1 made a significant investment in new TB drug, vaccine and diagnostics evaluation research. A steady stream of new TB interventions are emerging from the current and developmental pipeline of new diagnostics, TB drugs, combination drug regimens, host-directed therapies, and vaccines. EDCTP2 will build on progress made in EDCTP1, preferably in partnership with others as determined at the stakeholder meetings.

EDCTP2 will support evaluation of new TB treatment regimens for: improving treatment outcomes of both drug-sensitive and drug-resistant TB, reducing the duration of therapy, and preventing long-term pulmonary complications and functional disability. Apart from evaluation of new drugs with conventional anti-TB drugs, new therapeutic regimens will include systematic testing of adjunct 'Host Directed Therapies' with 'repurposed' commonly used drugs, cellular therapy and other immunomodulators.

EDCTP2 will evaluate novel TB vaccines, including those which might be effective in populations with a high burden of HIV, in whom TB risk is very high, and vaccines which might be effective in latently infected individuals (post-exposure vaccination). Opportunities will be sought from these vaccine and treatment trials to identify surrogate markers of treatment response, relapse and those predicting cure.

The EDCTP2 programme will also support evaluation of existing and novel TB diagnostics for increasing earlier detection of active TB and latent TB in HIV-negative and HIV-positive adults and children at all points of healthcare.

Research on the requirements or conditions for the effective and efficient operational use of new interventions (diagnostics, treatment regimens and vaccines) after they have been evaluated successfully will be essential to enable rapid uptake and optimise the impact of the new interventions for implementation into policy and practice.

EDCTP2 will support epidemiological and operational research to optimize delivery and scaling-up of new diagnostics, new treatments and vaccines for tuberculosis as well as research to maximise the sustainable synergies in management of HIV/TB co-morbidity including strategies for integrated delivery of TB/HIV care.

9.3.1 Prioritisation of Call for Proposals for Tuberculosis

1. **Treatment**
   This will include immediate, medium and long-term plans during the entire period of EDCTP2. Calls for Proposals will be on clinical trials evaluating novel interventions using new TB drugs or formulations with new combination regimens; treatment regimens using a range of adjunct 'host-directed therapies' to shorten duration of therapy, improve treatment outcomes, and prevent long term pulmonary and extra pulmonary complications and other co-morbidity in adults and children with drug-sensitive and drug- resistant TB.
2. **Prevention**
   This will include medium and long term plans for evaluation of new vaccines and chemoprophylactic TB drug regimens. TB vaccine research and development will span the entire EDCTP2 programme.
3. **Diagnostics**
   Work on evaluation of TB diagnostics will be included in the immediate, mid- to long-term plans and will include evaluation of new diagnostic products, particularly those that are sensitive, specific, cheap, easy to use, yield a rapid result, and are applicable for use at all points of healthcare point-of-care for the diagnosis of both drug-sensitive and drug resistant TB. This will include existing and new diagnostics in HIV-negative and HIV-positive adults and children. Evaluation of diagnostic and prognostic pathogen and host biomarkers will also be considered.

4. **Epidemiology**
   This is of immediate importance in the context of drug resistant TB in both HIV-infected and HIV-uninfected adults and children, but such studies should be done when there is a product/regimen in mind that will subsequently be evaluated.
5. **Operational and implementation research (health services and systems optimization research)**
   Activities on implementation research will be planned throughout the entire period of the EDCTP2 programme starting from the mid-period. Priority will be on delivery methods and research on the use of diagnostics and drugs after they have been tested successfully and in a cost-effective manner. This will also include the scale up and integration of HIV/TB prevention, treatments and services, innovative use of existing and new strategies to prevent, diagnose and manage TB, MDR-TB and TB/HIV co-infections.

Key short- and medium-term priorities: Support the evaluation of products e.g. new TB drugs, host-directed therapies, vaccines, diagnostics and chemoprophylactics in partnership with other stakeholders linked to relevant operational, implementation and cost-effectiveness studies.

9.4 NIDs

Since the launch of EDCTP2, NIDs have been propelled to the top of the global health agenda for PRDs through a series of high profile events including but not limited to: a) the publication of the Bill and Melinda Gates Foundation's seventh annual letter promoting efforts for elimination of NIDs[72], b) the G7 nations call to action on NIDs[73] and c) the Nobel Prize for Medicine and Physiology awarded for the discovery of ivermectin – a novel therapy against several NIDs[74]. This growing visibility of NIDs in the political, academic and global health arenas ensured a specific mention of neglected tropical diseases (Goal 3.3) in the Sustainable Development Goals (SDGs)[75]. Furthermore the burden of NIDs has been closely associated with the Human Development Index[76] underscoring their growing importance among PRDs. In the light of these events and the limited resources currently allocated to clinical trials on NIDs in Africa[77], EDCTP considers this group of diseases as high priority in its enlarged disease portfolio in EDCTP2. Some of the NIDs are tools-ready diseases and will only require clinical trials to investigate the impact of combination treatments of available drugs[78, 79], whilst others, where tools are poor or absent, will require support from Phase 1 clinical trials onwards[80, 81]. This can be achieved effectively through implementation research and the clinical development of novel treatments, both which should be given the highest priority.

9.4.1 Prioritisation of Call for Proposals for NIDs

1. **Operational and implementation research**
   Studies will be on evaluation of new drug combinations, the optimisation and integration of the management of co-endemic NIDs (e.g. co-endemicity of lymphatic filariasis and onchocerciasis with loiasis), evaluation of the different disease burden (regional versus localised), effect of mass drug administration (MDA) including drug delivery, uptake, compliance and adherence and strategies for accessing treatment especially during the endgame phase for PRDs targeted for elimination. These activities will be given the highest priority to start in the first period.

2. **Treatment**
   The evaluation of novel drugs, drug combinations and formulations will, in partnership with relevant stakeholders, be given priority (eg for human African trypanosomiasis, the leishmaniases , the filariasis, schistosomiasis, Buruli ulcer) to start in the first period.

3. **Diagnostics**
   Evaluation of diagnostic products, including response products, will be planned to start during the second period.

4. **Prevention**

Candidate vaccines will be evaluated as they become available. This will be prioritised to start from the second period, through the entire EDCTP2 programme. It should take place in collaboration with other partners and stakeholders.

9.5 Diarrhoeal Diseases

Recent epidemiological studies in children below age five years encompassing sub-Saharan African sites, the GEMS study funded by BMGF[82] and MAL-ED funded by BMGF and NIH[83], have confirmed the high prevalence of Rotavirus, *Shigella* and ETEC, although *Campylobacter* and *Cryptosporidium* also unexpectedly appeared in this category and *Vibrio cholerae* remained prevalent in certain areas. Another striking feature is a constant decrease in the mortality rate attributed to diarrhoeal diseases, in spite of a relative stability of the morbidity rate.

The epidemiological spectrum is therefore drifting from severe, possibly deadly, diarrhoeal episodes towards recurrent diarrhoeal episodes contributing to the development of a chronic enteropathy, a vicious circle of diarrhoea-malnutrition leading to stunting and delayed psychomotor development. This evolving pattern of diarrhoeal diseases calls for a certain degree of prioritisation regarding possible EDCTP input: large epidemiological studies are no longer warranted, although sustained surveillance is required in sites identified for future vaccine trials. The strong impact on incidence of severe diarrhoea observed in resource-limited countries that have implemented global rotavirus vaccination[84], and several ongoing studies in sub-Saharan Africa, provides a strong incentive to tackle the second block of aetiological agents and implement vaccines against *Shigella* and ETEC[85].

In the longer term, upstream work is needed to better understand the biology of *Campylobacter* and *Cryptosporidium* to inform development of vaccine candidates and innovative drugs against *Cryptosporidium* that tends to cause severe chronic conditions[38]. In parallel, work is needed to decipher the mechanisms of paediatric environmental enteropathy[41] to design control measures and counteract its negative effect on child's development and efficiency of orally-administered vaccines (i.e. rotavirus and polio vaccines).

9.5.1 Prioritisation of Call for Proposals for Diarrhoeal diseases

1. **Treatment** [86]

Cryptosporidiosis: due to severity of acute cases and devastating effect of chronic forms on nutritional status, there is urgent need to test candidate molecules, including drug repurposing, as cases occurring in non-immunocompromised patients are on the average refractory to current treatment.

2. **Prevention** [87]

The existing rotavirus vaccines are increasingly used, but their protective effect may be altered by the high prevalence of paediatric environmental enteropathy. Studies are urgently needed to clarify this major issue.

Several vaccine candidates[88] are – or will be soon - available against the most prevalent diarrheal pathogens cited above, *Shigella*, ETEC and against Vibrio cholerae. Some of them were supported at their conception, R&D stages, and even clinical stages by EU, but never made it yet to phases 2b and 3 in endemic areas, thus they should all naturally be tested in later phases in dedicated sites (see above) in sub Saharan Africa. In addition, one should consider developing a proper "environment" to vaccine testing encompassing the development of companion tools for immune-monitoring of clinical trials and identification of correlates of protection, and for optimization of the routes and mode of administration.

3. **Diagnostics**[89]

Short to middle term need to develop point of care, multiplexed diagnostic tools that may allow quick and reliable modes of detection.

4. **Operational and implementation research (health services and systems optimization research)** Activities on implementation research will be planned throughout the entire period of EDCTP2, starting with selection and capacity building of relevant sites. In the short term, global implementation of the current rotavirus vaccines is warranted. In the short to midterm, current candidate vaccines against *Shigella* & ETEC should be undergoing phase II trials in order to evaluate their immunogenicity in endemic zones.

9.6 Lower Respiratory Tract Infections (LRTIs)[8]

Lower respiratory tract infections (LRTIs) caused by a range of pathogens in community or hospital settings are among the top four causes of mortality in children and adults globally. HIV-infected adults and children also have LRTIs due to opportunistic infections and have an increased risk of LRTI hospitalization and death. The conventional management of LRTIs with empiric antibiotic therapy may not cover the range of common pathogens responsible for community acquired pneumonia. Limited autopsy studies from Africa show LRTIs as major causes of death and reveal that a substantial proportion of patients autopsied were on inappropriate antibiotic therapy. Co-infections of bacterial and viral LRTIs with TB lead to an increased mortality rate. The lack of resources for proper management of hypoxemia results in very high case fatality rate of severe LRTI in children. An increase in LRTIs caused by antimicrobial resistant Gram-positive and Gram-negative bacteria, multidrug-resistant *Mycobacterium tuberculosis*, and multiazole-resistant fungi makes it more difficult and more expensive to treat LRTIs.

Despite availability of vaccines for type b Haemophilus influenzae, *Streptococcus pneumoniae*, and Influenza viruses, these pathogens remain important causes of LRTIs. In children and in the elderly, Respiratory syncytial virus (RSV) is a leading cause of LRTI and vaccines for RSV are under development.

For detecting the specific aetiology of LRTIs, microarray-based multiplexing and nucleic-acid-based deep-sequencing methods now allow for development of diagnostic platforms which can simultaneous detect pathogen specific nucleic acid and antibiotic resistances in respiratory tract samples. However the use of these methods remains challenged by the difficulty to collect adequate respiratory specimens, especially in children, and by the difficulty to distinguish infection from colonisation of the respiratory tract.

The lack of ecological data to guide the choice of the best empirical antibiotic for treatment of both community and hospital acquired LRTI, the misuse of antibiotics (over-prescription, inadequate duration, self-administration) and the issues with the quality of antibiotics in some countries are likely to have major impact on the proper management and outcomes of LTRI in limited resources countries.

EDCTP2 will support research which focuses on current knowledge gaps and challenges for improving management and control of LRTIs in both HIV-infected and HIV-uninfected adults and children across all health-care settings. This will include the need for more accurate clinical diagnostic and management algorithms, criteria of selecting patient groups who would most benefit from antibiotics, rapid accurate diagnostics identifying the exact microbial aetiology of LRTI and their antibiotic sensitivities, rational and optimal use of existing antibiotics, development of new treatment interventions, impact evaluation of available and new vaccines for preventing bacterial and viral LRTIs evaluation of optimised and alternative imaging methods; simplification of tools aimed at controlling hypoxemia in children with severe LRTI; and strengthening health systems and their surveillance capabilities. EDCTP2 will support epidemiological and operational research to optimize delivery and scaling-up of new diagnostics, new treatments and vaccines for LRTIs as well as research to maximise the management of co-infections with LRTIs.

[8] See Annex 2 for References

9.6.1 Prioritisation of Call for Proposals for LRTIs

1. **Treatment**

The mainstay of effective treatment for childhood pneumonia remains treatment with appropriate antibiotics and supportive care. This will be included in the short, medium and long-term plans during the period of EDCTP2.

Immediate/short term priority will be on research which will 1) Develop and evaluate a) more accurate clinical management algorithms; b) criteria for selecting patient sub-groups who would most benefit from antibiotics; c) identify which patients are likely to experience an unusual or prolonged illness course; and d) define rational and optimal use of existing antibiotics. 2) Evaluate the efficacy of short duration antibiotic treatment regimens for LRTI in the community 3) Evaluate simplified tools for management of hypoxemia for children with severe LRTI in resource limited settings.

Medium/Long term priorities will be 1) Development and evaluation of new antibiotic treatment regimens for LRTIs, 2) Use of adjunct 'host-directed therapies' with nutritional products, micronutrients, probiotics for prevention of LRTIs in children. It is anticipated that these interventions will improve on the use of the current pneumonia case management strategy in the World Health Organisation Integrated Management of Childhood Illness (IMCI) programme. , 3) Evaluation host-directed therapies improving treatment outcomes for LRTIs and co-morbidities of LRTI with NCDs and preventing long term pulmonary functional disability[90,91].

Apart from HIV-infected individuals, target populations will include children and the elderly and those hospitalized with LRTIs. Most LRTI cases are managed in primary care where an extensive diagnostic work-up for all patients is neither feasible nor cost-effective.

2. **Prevention**

This will be included in the medium and long-term plans during the entire period of EDCTP2.

Short-term priority will be on clinical trials evaluating the:

- Impact of available vaccines (type b Haemophilus influenzae, Bordetella pertussis, Streptococcus pneumoniae, and Influenza) on the rates and aetiologies of LRTIs.
- Adjunct 'host-directed therapies' with nutritional products, micronutrients, probiotics for prevention of LRTIs in children.

Medium/Long term priorities for preventing bacterial and viral LRTIs:
EDCTP2 will support epidemiological and operational research to optimize delivery and scaling-up of new vaccines (e.g. RSV) for LRTIs. This will be in partnership with others as determined at the stakeholder meetings. GSK maternal and paediatric RSV programs are in early stage of development (Phase I/II) Active immunization of pregnant women during the third trimester of pregnancy to prevent RSV (subtypes A and B)-associated LRTI in infants.

Trials evaluating the impact of current recommendations of the use of antibiotic prophylaxis (co-trimoxazole) for preventing bacterial infections including LRTIs in HIV-infected individuals will be supported in light of the growing AMR problem.

3. **Diagnostics**

Short-term priority will include a call for proposals on research which will 1) Develop and evaluate more accurate clinical diagnostic algorithms for LRTIs according to age groups, comorbidities and severity, 2) Evaluate currently available rapid diagnostic platforms for bacterial causes of RTIs. 3)

Evaluate innovative specimen collection methods that are easy to perform at lower level of health facility and well tolerated to improve the etiologic diagnosis of LRTI in children and adults, 5) Evaluate new imaging technology to improve the feasibility and reliability of chest X-ray for diagnosis of LRTI (digitalised mobile X-ray, thermal imaging and computerised readers).

Medium and Long term priorities will include a call for proposals on research which will evaluate (their sensitivity, specificity and impact on management outcomes) of new rapid diagnostic platforms for the rapid diagnosis of the specific microbial aetiology, and co-infections in patients with all clinical forms of LRTIs (Community acquired, Hospital Acquired and Opportunistic).

4. **Epidemiology**

   Short, medium and long priorities during the entire period of EDCTP2 will include calls for proposals on 1) defining the burden, severity and aetiology of LRTIs and antimicrobial resistance (AMR) amongst HIV-infected and -uninfected children and adults; 2) evaluating the impact of starting earlier ART initiation on LRTIs and 3) reduction of burden and change of the aetiology of LRTIs with more access to vaccination against influenza and pneumococcus.

   EDCTP2 will support epidemiological and operational research to optimize delivery and scaling-up of vaccines for LRTIs.

5. **Operational research (health services and systems optimization research)**

   Long term priority will focus on implementation research will be planned as medium to long term period of the EDCTP2 programme. Priority will be on delivery methods and research on the use of new diagnostics, drugs and vaccines after they have been tested successfully and in a cost-effective manner. This will also include the scale up and integration within acute medical services. The integrated management of several diseases (such as malaria, pneumonia, diarrhoea and malnutrition) has rarely been evaluated.

   Activities on implementation research will be planned throughout the entire period of the EDCTP2 programme starting from the mid-period. This will also include the integration of LRTI management with HIV/TB/Malaria/diarrhoea treatments and services, innovative use of existing strategies to diagnose and manage RTIs, TB, MDR-TB and TB/HIV co-infections. Further efforts should be made towards the development of adequate surveillance programs to better clarify the epidemiology, ethology, antimicrobial susceptibility patterns and the effectiveness of the preventives and curatives strategies in place against paediatric LRTIs.

Antimicrobial resistance is a global health security threat that requires concerted cross-sectional action by governments and society as a whole and aligned to the Global Respiratory Infection Partnership (GRIP).

10 Programme Monitoring and Evaluation

10.1 Scientific outcome and strategic impact

The evaluation of the programme will be linked to its primary objectives and a results based management system will be implemented. The most important evaluation criteria will be the ability of the EDCTP programme to develop new or improved products that will be used in clinical practice to improve the health and lives of people in the countries affected by HIV, tuberculosis, malaria, respiratory tract infections, diarrhoeal diseases and NIDs. Individual projects will submit final reports on the outcomes of the study. These will form the basis of the assessment of project impact. It is in the nature of clinical trials that not all newly developed products will prove to be effective or necessarily safe for use, but it is important that studies have been designed to give clear definitive answers. EDCTP will not have succeeded if the results of projects are inconclusive. However, studies providing conclusive evidence, will demonstrate the effectiveness of the programme. Where studies have shown a positive effect, the immediacy of the impact on health will depend on the phase of the trial and how the results are taken forward. For phase 3 and 4 trials the results may inform clinical practice directly but for earlier phase trials, the results may identify the specific directions in which the field should develop. The programme may therefore be evaluated against progression of product in the development pathway. Indicators of success will therefore include:

- Successful completion of clinical trials
- Progress of products along the pipeline from early to later stage trials
- Introduction of new or improved products or regimens
- Introduction of new disease management policies.

At the end of each three-year term EDCTP will conduct an internal evaluation to assess the progress of the programme and determine its impact on health issues such its influence on health policies, healthcare, capacity strengthening, strengthening of partnerships and synergy with other programmes. EDCTP, via its outreach activities, will interact with like-minded research and development organisations to identify best practices for monitoring and evaluation of similar activities. In order to further develop the standards for the evaluation of impact of research activities, EDCTP will also work with these organisations. To this effect for instance, EDCTP together with other like-minded funding organisations, through the ESSENCE on health research initiative (Enhancing Support for Strengthening the Effectiveness of National Capacity Effectiveness) have developed a tool for monitoring and evaluation of capacity building projects[92]. This has been adapted by EDCTP and is currently being used to monitor and evaluate EDCTP funded Networks of Excellence for conducting clinical trials and other capacity building activities. This will also be used to monitor and evaluate all capacity development activities under EDCTP2.

10.2 Operational performance

The implementation performance and the effectiveness of the programme will be monitored on a regular basis using key performance indicators (KPIs) that give a clear picture of whether the programme is moving in the right direction and measure progress towards planned goals, grant evaluation and processing procedures, effectiveness of north-north and north-south partnerships and networking, the degree of participation of developing countries, number, outcome and effectiveness of the projects, level of capacity attained; administrative costs and other relevant outcomes. KPIs similar to those in current use will be developed and monitored internally on a monthly basis and updated quarterly on the EDCTP website as is the current practice. These will include:

- Performance of the Secretariat in the processing of grants applications from the time the call is launched to the signing of contracts
- Success in organisation and outcomes of stakeholders' meetings
- Timeliness in the launching of calls
- Degree of participation of third parties

- Degree of participation of Participating States
- Contributions of Participating States.

Monitoring will be a continuous process conducted on a quarterly basis and reviewed annually. This will evaluate strategy effectiveness and whether there is a need for a change in direction or modification. Views of other stakeholders will continue to be solicited through the Stakeholders' meetings and feedback at the EDCTP forums. Monitoring will also be done to see that there is no duplication of projects or waste and to ensure that all areas of research are covered, bearing in mind the changing needs as new discoveries are made and new problems emerge. Furthermore, at the mid-term and end of the programme there will be an impact assessment to determine the effect of programme on key health issues as stated in the mission and objectives of EDCTP.

Therefore, to realise these goals multiple systems will be setup for monitoring and evaluation of the performance of both the programme and research output. Currently, the following targets (deliverables) and indicators conveniently classified according to the five key specific objectives as specified in the EC-EDCTP delegation agreement:

Objective	Deliverable	Indicators
1. Support clinical trials and increase number of new or improved medical interventions for PRDs	• At least one new medical intervention delivered • Contributed to issuing of at least 30 guidelines for improved or extended use of existing medical interventions • Progress the clinical development of at least 20 candidate medical interventions.	• At least one new intervention to receive endorsement by policy makers • At least 1 phase 3 trial initiated every year as of the 2nd year of the programme • Increase number of clinical trials to at least 150 • Sustained or increased proportion of clinical trials funded with African leadership • Reduced time to completion of CTs • Increased number of the peer-reviewed articles published (open access) to three times those of EDCTP1 • Increased number of trial registrations (international / PACTR)
2. Strengthen cooperation with SSA countries, in particular on building their capacity for conducting clinical trials in compliance with fundamental ethics and regulatory requirements (national, EU and international legislation)	Strengthen capacity for conducting clinical trials through fellowships, research training networks, strengthening ethics and regulatory bodies	• Sustain 31 existing SSA in EDCTP2 • Participation of at least 2 new SSA in EDCTP2 • 80% functional national ethics committees in ECTP2 funding clinical trials countries • 50% functional regulatory bodies in ECTP2 funding clinical trials countries • Double the number of fellowships and trainees (MSc, PhDs) in comparison to EDCTP1 N=460) • At least 80% of the recipients from EDCTP2 funding retained in SSA • Increase number of capacity building activities supported for conducting clinical trials in SSA compared to the number (74) supported under EDCTP1
3. Improve coordination, alignment and integration of relevant national programmes to increase the cost-effectiveness of European public investments	Through promoting networking, coordination, alignment, collaboration and integration of national research programmes and activities on PRNDs, at scientific, management and financial level	• Number of new Joint Programme Initiatives • Number of new national programmes that fit into and complement EDCTP initiatives • Number of new programmes integrating national initiatives in the scope of EDCTP • Expanded geographical coverage of new initiatives in terms of countries involved • Scientific Area coverage of new initiatives in terms of expansion/diversification to areas initially not covered by individual constituent members of the initiative
4. Achieve extended international cooperation with other public and private partners to maximise	Through establishing cooperation and launching joint actions with other public and private funders	• Number of IC participants and level of participation • Impact on policy (evidence to practice)

	research impact and synergies in leveraging of resources and investments		• Contribution received from developing countries to at least 30 million Euros versus 14 million Euros in EDCTP1 • Contribution from either public or private partners to 500 million Euros versus 71 million in EDCTP1
5.	Increase impact due to effective cooperation with relevant European Union initiatives, including its development assistance.	• Establishing cooperation and launching joint actions with development partners, including where appropriate WHO initiatives, in order to ensure complementarity and increase the impact of the results of EDCTP2. • Ensuring awareness, endorsement and acknowledgment of the EDCTP2 Programme and its activities through advocacy and communication in Africa, EU and globally.	• One joint cooperation per year • Increased funding by development partners • Increased level of consultation with development partners

In reference to objective 2 listed above, where percentage indicators are given, the baseline will be determined at the application stage. Progress will be measured by assessing deviations from the baseline through subsequent reporting where elements of functionality can be built into the benchmarking of the capacity being built. The WHO guidelines for the setting up of functional ethics committees will be considered as a starting point for achieving the second objective. For objective 3, the SEC will consider including a platform that helps in achieving this objective, which is primarily an administrative function. For objective 5, the following will considered:

- Strengthen communication with development partners
- Improve consultation framework with these partners
- Increase number of development partners under EDCTP2 in comparison to EDCTP1
- Facilitate alignment development partner programs with the priorities of EDCTP2
- Increase number of joint actions launched with development partners
- Increase co-financing provided by development partners to EDCTP2
- Leverage additional funds from third parties based on the results achieved through the increased interaction with development partners under EDCTP2.

11 Definitions

Co-funding: is the contribution in cash or in-kind that is raised by parties other than the European Union to support the EDCTP Programme.

National programmes: National programmes are defined as country-based publicly funded activities within the scope of the EDCTP programme. These may be at individual, project, institutional or programme level.

Alignment of national programmes: The arrangement of Participating States' programmes to complement and fit with each other and with the needs of their sub-Saharan counterparts and contribute to the EDCTP programme.

Coordination of national programme: The organisation and harmonisation of Participating States' activities and projects within the scope of EDCTP with developing countries into synergistic and efficient joint ventures with common scientific review, oversight and administration including monitoring and evaluation as part of common programming.

Integration of national programmes: is to bring together the European partner countries' national programmes into a common programme under the umbrella of the EDCTP and directed to the objectives of the EDCTP. This is a long-term goal of EDCTP.

EDCTP Participating States: any country joining the European and Developing Countries Clinical Trials Partnership and supporting the EDCTP programme and activities. In EDCTP1, there were 16 European Participating States working in partnership with 46 African Participating States. European Participating States are members of the EDCTP2-IS that has been established for the purpose of implementing the EDCTP and managing the EDCTP activities and funds

Financial contributions to EDCTP:

In-kind contribution: that contribution that is made by Participating States, other than cash, that directly makes it possible for a clinical trial, networking or capacity development activity to be performed with cash funding from the EU.

Cash contribution: restricted or unrestricted funds that are given directly to the Secretariat, projects or other activities within the scope of EDCTP.

Restricted cash contribution: New cash contributions on which the contributing country may impose some limitations on how that money can be spent. E.g. limited to projects in specific research areas, or limited to researchers within same country as the contributor

Unrestricted cash contribution: New cash contributions on which the contributing country does not place limitations and which therefore can contribute to any part of the EDCTP programme.

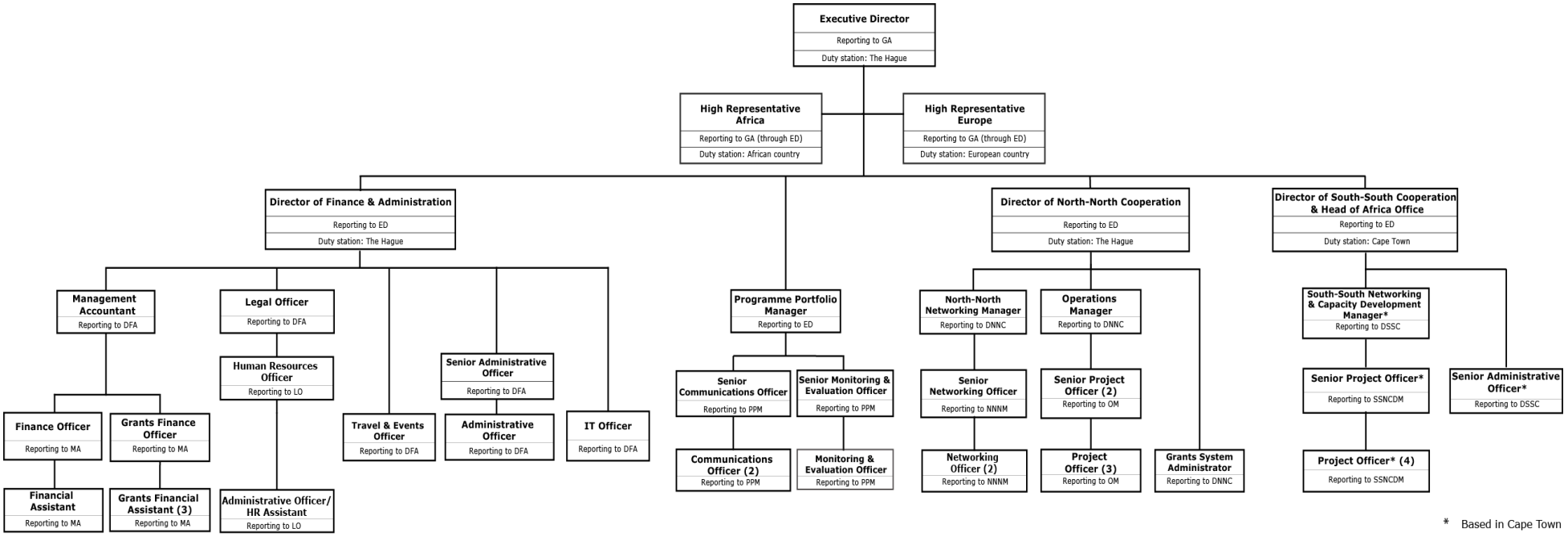
12 Acronyms

AAS	African Academy of Sciences
ACT	Artemisinin-based Combination Therapy
AERAS	Global TB Vaccine Foundation
AESA	Alliance for Accelerating Excellence in Science in Africa
AIDS	Acquired Immune Deficiency Syndrome
AL	Artemether plus Lumefantrine
AMR	Antimicrobial resistance
ANC	Antenatal Care Clinic
ANDi	African Network for Drug and Diagnostics innovation
ART	Anti-Retroviral Therapy
ARV	Antiretroviral Treatment
ASAQ	Artesunate plus Amodiaquine
ASLM	African Society for Laboratory Medicine
AU	African Union
BMGF	Bill & Melinda Gates Foundation
bPI	Boosted protease inhibitor
CAP	Community Acquired Pneumonia
CSA	Coordination and support actions
DALY	Disability-Adjusted Life-Year
DCCC	Developing Countries Coordinating Committee
DFA	Director of Finance and Administration
DHAPQ	Dihydro-artemisinin plus Piperaquine
DMS	Document Management System
DNDi	Drugs for Neglected Diseases Initiative
DNNC	Director of North-North Cooperation
DSMB	Data and Safety Monitoring Board
DSSC	Director of South-South Cooperation
EAC	East African Community
EC	European Commission
ECOWAS	Economic Community of West African States
ECSA	The East, Central and Southern African (ECSA) Health Community
ED	Executive Director
EDCTP	European and Developing Countries Clinical Trials Partnership
EDCTP1	First EDCTP programme (2003-2015)
EDCTP2	Second EDCTP programme (2014-2020/2024)
EDCTP2-IS	EDCTP2 Implementation Structure
EEIG	European Economic Interest Group
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFV	Efavirenz
EIDT	Global Emergency Immediate Disaster Team
EMA	European Medicines Agency
ENNP	European Network of National Programmes
ENO	European Networking Officer
EPI	Expanded Immunisation Programme
ESSENCE	Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts
ETEC	Enterotoxigenic Escheichia Coli
EU	European Union
EVD	Ebola Virus Disease
FDA	USA Food and Drug Authority
FIND	Foundation for Innovative Diagnostics

FMAT	Financial Management Assessment Tool
GA	General Assembly of the EDCTP EEIG
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GFAMT	Global Fund to fight AIDS, Malaria and Tuberculosis
GMS	Grant Management System
GRIP	Global Respiratory Infection Partnership
HAART	Highly Active Antiretroviral Therapy
HAP	Hospital Acquired Pneumonia
HCW	Health Community Workers
HDT	Host-Directed Therapy
HIV	Human Immunodeficiency Virus
IAS	International Accounting Standards
IAVI	International Aids Vaccine Initiative
I(C)T	Information (and Communication) Technology
IMCI	Integrated Management of Childhood Illness
IPR	Intellectual Property Rights
IPT	Isoniazid preventive therapy
IRB	Institutional Review Board
ISO	International Organisation for Standardisation
KPI	Key Performance Indicator
LRTI	Lower Respiratory Tract Infection
MAMS	Multi-Arm Multi-Stage
MDA	Mass Drug Administration
MDG	Millennium Development Goal
MDR-TB	Multi-Drug-Resistant Tuberculosis
MERS	Middle East Respiratory Syndrome
MMV	Medicine for Malaria Venture
MRC	Medical Research Council (South African hosting organisation)
MS	Member State
MSM	Men Who Have Sex With Men
MTCT	Mother to Child Transmission
NCD	Non-Communicable Disease
NEC	National Ethics Community
NEJM	New England Journal of Medicine
NEPAD	New Partnership for Africa's Development
NID	Neglected Infectious Disease
NIH	National Institutes of Health (USA)
NOE	Network of Excellence
NRA	National Regulatory Authority
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NWO	Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Dutch hosting organisation)
OCEAC	The Coordination Organisation for the Fight Against Endemic Diseases in Central Africa
OECD	Organisation for Economic Co-operation and Development
ORTI	Opportunistic Respiratory Tract Infection
PACTR	Pan-African Clinical Trials Registry
PB	Partnership Board
PDP	Product Development Partnership
PEE	Paediatric Environmental Enteropathy
PEP	Peri-Exposure-Prophylaxis
PI	Principal Investigator
PMTCT	Prevention of Mother-to-Child Transmission
PPP	Public Private Partnership

PR	Public Relations
PRD	Poverty Related Disease
PrEP	Pre-Exposure Prophylaxis
PRN(I)D	Poverty Related and Neglected (Infectious) Disease
PS	Participating State
PSIA	Participating States Initiated Activity
R&D	Research and Development
RCT	Randomised Clinical Trials
RIA	Research and Innovation Action
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
SAC	Scientific Advisory Committee
SADC	Southern African Development Community
SARS	Severe Acute Respiratory Syndrome
SDG	Sustainable Development Goal
SEC	EDCTP Secretariat
SME	Small and Medium-Sized Company
SOP	Standard Operating Procedure
SRA	Strategic Research Agenda
SRC	Scientific Review Committee
SSA	Sub-Saharan Africa
STI	Sexually Transmitted Infection
TasP	Treatment of Infected People
TB	Tuberculosis
TB-Alliance	Global Alliance for TB Drug Development
TDF	Tenofovir
TDR	WHO Special Programme for Research and Training in Tropical Diseases
TFEU	Treaty on the Functioning of the European Union
TMA	Training and Mobility Action
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV
VAP	Ventilator Associated Pneumonia
VCT	Voluntary Counselling and Testing
WAHO	West African Health Organisation
WHO	World Health Organisation
WHO/AFRO	WHO Regional Office for Africa
XDR-TB	Extensively Drug-Resistant Tuberculosis

13 Annex 1: EDCTP Secretariat (SEC) organogram



* Based in Cape Town

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