



A GLOBAL ACTION FRAMEWORK FOR TB RESEARCH

IN SUPPORT OF THE THIRD PILLAR
OF WHO'S END TB STRATEGY

THE
END TB
STRATEGY



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World Health
Organization

PREFACE

BREAKING THE TRAJECTORY OF THE TB EPIDEMIC THROUGH RESEARCH

Over the last 15 years, there was remarkable progress in the fight against TB. The Millennium Development Goals (MDG) target of halting and reversing TB incidence by 2015 has been achieved and 43 million lives have been saved. This progress has been possible thanks to a number of factors, including adoption and implementation of better strategies for TB care and control in most countries world-wide, associated with economic growth in many countries, as well as advances in research which allowed the roll out of new diagnostics and drugs for the first time in decades. However, TB is the top infectious disease killer alongside with HIV/AIDS, claiming 1.5 million lives every year and causing suffering to millions more.

As a result of the achievements in combating HIV/AIDS, tuberculosis and malaria within the context of the MDGs, the world is now turning its attention towards finishing the job and ending the three epidemics, as part of the new Sustainable Development Goals (SDG), the era of which will start on 1st January 2016. The new WHO End

TB Strategy, adopted by all WHO Member States at the World Health Assembly in May 2014, serves as a blueprint for countries to end the global TB epidemic. It sets targets to reduce TB incidence by 80% and TB deaths by 90% in 2030, and to eliminate catastrophic costs for TB-affected households by 2020.

To reach these ambitious targets, new revolutionary technology including rapid, simple, point-of-care diagnostics for infection and disease, shorter regimens for infection and disease, and eventually an effective vaccine, are needed. This requires much invigorated efforts in research, along a continuum that links upstream fundamental research to discovery and new tool development, and ultimately to operational and implementation research allowing innovative strategic approaches to be adapted to specific country needs. To facilitate this effort, the World Health Organization, under the leadership of Dr Christian Lienhardt, Dr Knut Lönnroth, Dr Richard Menzies and Ms Diana Weil, together with a wide range of experts and partner agencies, has developed this “Global Action Framework for TB Research” that sets the agenda for key stakeholders at global and national levels. The Framework describes how to strengthen TB research

in all countries, with special emphasis on middle-income countries carrying the largest burden of TB, and how to support and facilitate research at global level.

To achieve the vision of an invigorated and expanded TB research globally, every country needs to ensure that the principles contained in this Framework are adopted and put into practice. In practical terms, this means, first, the development of national strategic plans for TB research based on consensus on the top priorities including capacity-building. Second, it requires the establishment of mechanisms to ensure sufficient domestic funding for TB research, that can be complemented by international financing when necessary. Third, it also requires the mobilization of those public and private institutions that can contribute to research and its financing, the definitaion

of novel ways of mobilizing resources, and the expansion of national and global interactions through the establishment of networks of researchers and institutions at national and international levels.

If all the principles that underpin the Framework are transformed into policies and practice in most countries world-wide, then the chances of breaking the trajectory of the TB epidemic and wiping out this ancient killer will increase exponentially over the next several years.

A handwritten signature in black ink, appearing to read 'M. Raviglione', with a long horizontal stroke extending to the right.

Dr Mario Raviglione
Director, Global TB Programme
World Health Organization

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Overall coordination

Christian Lienhardt, Dick Menzies.

Core writing team

Christian Lienhardt, Dick Menzies, Knut Lönnroth, Diana Weil.

Contributors and peer-reviewers

Ibrahim Abubakar, Hannah Akuffo, Stefano Aliberti, Manica Balasegaram, Anurag Bhargava, Delia Boccia, Erlina Burhan, Joseph Cavanaugh, Richard Chaisson, Muhwa Jeremiah Chakaya, Gavin Churchyard, Isabelle Cieren- Puisseux, Daniela Maria Cirillo, Frank Cobelens, Martin Colla, Liz Corbett, Colleen Daniels, Patrice Debré, Tom Evans, Sara Eyangoh, Alberto Garcia-Basteiro, Willem Hanekom, Anthony D. Harries, Norbert Heinrich, Michael Hoelscher, Sven Hoffner, C. Robert Horsburgh, Gunilla Källenius, Nadia Khelef, Gilla Kaplan, Alison Kraigsley, Afranio Kritski, Ajay M.V. Kumar,

Christoph Lange, José Roberto Lapa e Silva, David Lewinsohn, Davide Manissero, Harriet Mayanja-Kizza, Ruth McNerney, Charles S. Mgone, Valerie Mizrahi, Ya-Diul Mukadi, Payam Nahid, James Nicholas Newell, Viet Nhung Nguyen, Anders Nordström, Tom H.M. Ottenhoff, Roxana Rustomjee, Andreas Sandgren, Thomas Shinnick, Christine F. Sizemore, Melvin K. Spigelman, S. Bertel Squire, Beena Thomas, Rony Zachariah, Alimuddin Zumla.

Contributors to case-studies: Afranio Kritski, Andargachew Kumsa, Jeremiah Chakaya, Roberto Lapa, Andrew Ramsay, Roxana Rustomjee, Sudha Srinivasan.

WORLD HEALTH ORGANIZATION:

WHO Regional Offices: Karam Shah, EMRO; Colleen Acosta, EURO; Mirtha del Granada, AMRO.

Health Service Research:

Abdul Ghaffar.

Global TB Programme:

Hannah Monica Dias, Dominique De Santis, Ernesto Jaramillo, Christian Lienhardt, Knut Lönnroth, Alberto Matteelli (now at

University of Brescia, Italy), Dick Menzies (on sabbatical from Montreal Chest Institute, McGill University), Mario Raviglione, Mukund Uplekar, Diana Weil.

Special Programme for Research and Training in Tropical Diseases (TDR):

Corinne Merle, Rob Terry.

Overall guidance was provided by the Director of the Global TB Programme, Mario Raviglione.

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SUMMARY

The World Health Organization's (WHO) End TB Strategy aims to end the global tuberculosis (TB) epidemic by 2035. It targets a 95% reduction in TB mortality, a 90% decline in TB incidence (to below 10/100,000 population) and zero catastrophic costs for TB-affected households. To reach these ambitious targets, intensified research is needed to develop more effective interventions to detect, cure and prevent TB. This constitutes the third pillar of the End TB Strategy, '**Intensified research and innovation**'. It highlights the need for global research at all levels along the research spectrum (from basic science to operational research), as well the need to empower a strong and self-sustained TB research community in low- and middle income countries with high TB burden.

To assist with this, WHO, with contributions from many stakeholders, has developed a *Global Action Framework for TB Research* to foster high-quality national and global TB research over the next 10 years to 2025.

The **first part** of the framework describes how to strengthen TB research in low- and middle-income countries most affected by TB by developing a *national TB research plan*. Key steps include the development or reinforcement of the following: (i) a national TB research network; (ii) a country-specific TB research agenda based on the

characteristics of the TB epidemic and an inventory of resources and activities; (iii) a plan for training and sustained capacity building on TB research; (iv) sustained national TB research funding mechanisms for training, infrastructure and research operations; (v) advocacy for public support and funding of TB research; and (vi) ongoing monitoring and evaluation of the implementation of the framework. A checklist is provided to guide countries in assessing their research capacity and preparedness prior to developing a national TB research plan.

The **second part** of the framework describes how to enhance TB research globally by applying efforts to building strong research partnerships and networks and securing robust funding for research. Key steps include (i) mobilising more funding resources at global and national levels; (ii) holding regular TB research donors' forum; (iii) developing innovative funding mechanisms; (iv) expanding advocacy activities to increase TB research funding internationally; (v) creating international networks and thematic hubs to enhance collaboration on TB research; and (vi) undertaking large-scale, cross-cutting, multi-disciplinary, multi-site, collaborative research projects.

The **third part** of the framework describes WHO's activities in support of the

framework. These activities include the development of guidance tools and documents to provide technical assistance to countries implementing Pillar 3 of the End TB Strategy, as well as work with international, bilateral and national stakeholders to foster TB research. A WHO

Task Force on Global TB Research will guide this work and assist in implementing the Global Action Framework.

A series of milestones and deliverables are provided for the coming 1, 5 and 10 years for these activities.



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INTRODUCTION

The End TB Strategy approved by the World Health Assembly in May 2014 aims to end the global tuberculosis (TB) epidemic by 2035 (1). It targets a 95% reduction in TB mortality, a 90% decline in TB incidence and zero catastrophic costs for TB-affected households.

The strategy (*Figure 1*) relies on three fundamental pillars:

- **PILLAR 1:**
Integrated, patient centred care and prevention
- **PILLAR 2:**
Bold policies and supportive systems
- **PILLAR 3:**
Intensified research and innovation

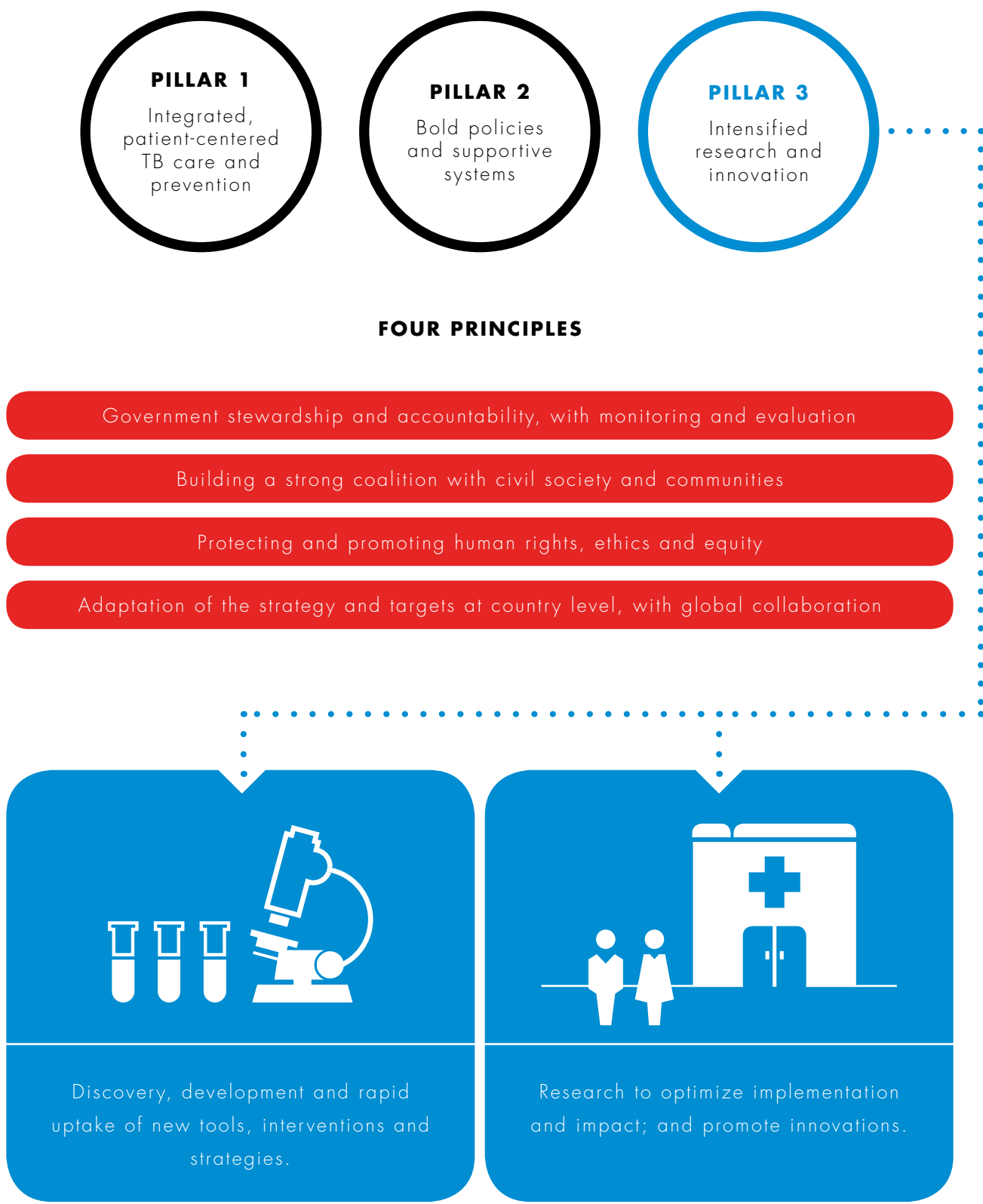
Despite recent advances in the of new TB diagnostics and anti-TB drugs, overall progress in reducing TB incidence and related deaths, burden and costs in the most affected communities is limited by inadequate tools to detect, treat or prevent TB. This inadequacy is compounded by weaknesses in health systems and associated social determinants.

To reach the ambitious targets set by the WHO End TB Strategy, intensified research is needed into better interventions to detect, cure and prevent TB. This should be part

of a global research effort along the entire research spectrum from basic science to operational research (*Box 1*).

Basic research will help elucidate fundamental mechanisms in the pathogenesis of tuberculosis as a first step in the discovery of new control tools: rapid and sensitive point-of-care diagnostic tests; short, effective and safe regimens for the treatment of drug-sensitive and resistant TB disease and latent TB infection; and an effective vaccine or other preventive interventions. Clinical and translational research will evaluate safety and efficacy of these new diagnostic, treatment and preventive tools. Epidemiologic research will provide a more complete understanding of the determinants and consequences of TB and of the natural course of infection and disease. Enhanced surveillance is relatively simple and inexpensive and will contribute to understanding the epidemiologic situation in each country, as well as facilitate operational and implementation research. Behavioural, operational and implementation research will help identify setting-specific barriers to access care and to adherence, to encourage the use of new diagnostic and treatment tools, and to determine locally appropriate innovative policies and approaches for TB prevention and care. Finally, health systems and social science research provide an understanding of fundamental elements of health and social service functioning, financing and delivery.

FIGURE 1 / **WHO END TB STRATEGY**



BOX 1 / THE SPECTRUM OF RESEARCH

Basic/fundamental research:

investigation of the characteristics of the germ and analysis of the host-pathogen interaction to decipher the basic mechanisms of transmission, infection, latency and disease, including response to therapy and to vaccination. This includes disciplines such as molecular biology, immunology and biochemistry.

Clinical and translational research:

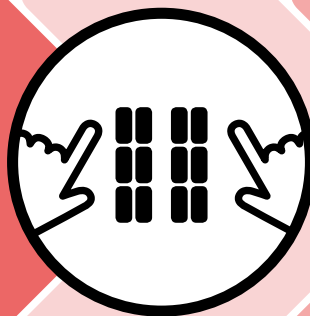
assessment of the safety, efficacy and validity of new interventions or approaches (algorithms) in patient populations. This includes research on new diagnostics, new drugs or regimens and vaccines (Phase 1 to 3 randomized trials).

Operational and implementation research:

research into strategies, interventions, tools or knowledge which can improve programme performance and/or health care delivery. It is generally the simplest, quickest and least costly research methodology. This research examines the conditions, requirements and barriers to implementation, as well as interventions to enhance the use of new or existing tools and strategies by patients and health systems. It also contributes to documenting the safety profile of new interventions (drug, regimens, vaccines) during routine use in large populations. To be successful, this type of research requires identifying clear questions that are amenable to study, have a direct impact on major policy and implementation issues, and can be answered by low-cost research methods.



**FUNDAMENTAL
SCIENCE**



**TRANSLATIONAL
STUDIES**



**PRECLINICAL
STUDIES**

Epidemiologic research:

examination of the natural course of TB infection and disease and the various determinants and consequences of TB. This includes analysis of surveillance and population-level data (such as prevalence surveys or drug resistance surveys), as well as personal, medical and social determinants of TB transmission, infection, progression to active disease, drug resistance, and disease outcomes. This also includes studies to estimate the socioeconomic consequences of TB for the individual, households and society.

Policy, health and social system research:

investigation of the interplay of social, population and personal factors that affect health-seeking behaviours, and wider health systems organization and dynamics. This research also investigates the effectiveness of policy and regulatory interventions on TB prevention and care, particularly the means to ensure universal health coverage, through social protection and actions on the social determinants of health.



**CLINICAL
STUDIES/TRIALS**



**DEPLOYMENT AND SCALE UP
IMPLEMENTATION /
OPERATIONAL RESEARCH**

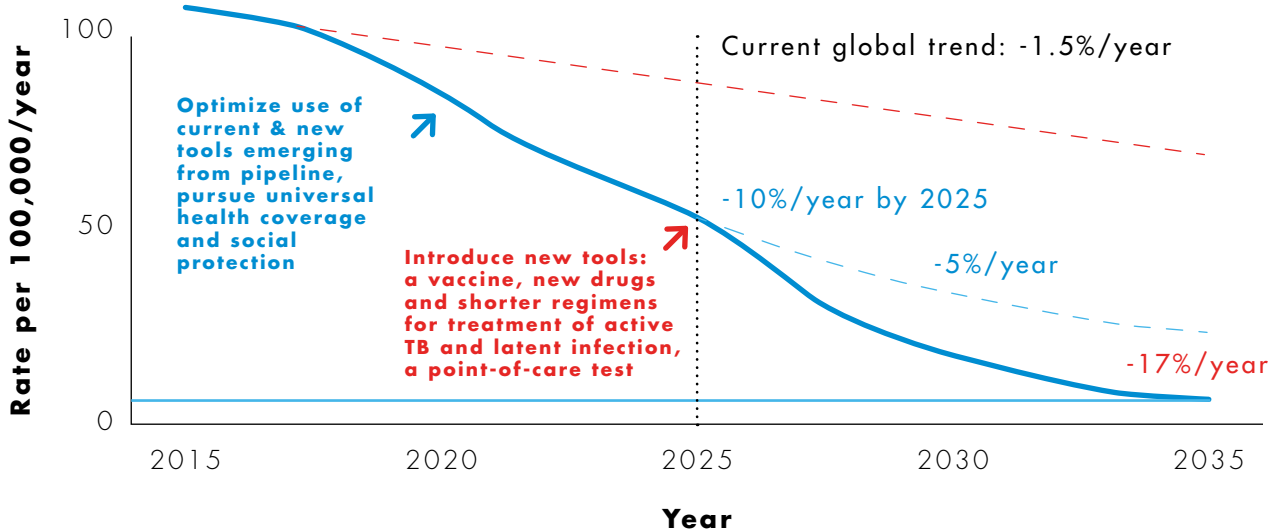
Clearly the need to expand TB research and innovation worldwide is urgent and requires the creation of research-enabling environments where the TB burden is greatest: in low- and middle-income countries. Over the next decade, it is expected that these countries will progressively establish their leadership in TB research by strengthening their own research capacity through domestic funding. This strengthened capacity will not only help achieve the End TB Strategy's goals but will contribute to global research efforts to eliminate TB (**Figure 2**). In parallel, high-income countries, international agencies and philanthropic organisations are also expected to increase their investments in TB research and training.

The challenge of the next decade will be twofold. First, the next generation of

scientists in high-burden countries will have to be trained and equipped to find solutions to ending TB both in their countries and globally. Second, research results will require wider dissemination, especially to policy-makers, ensuring these results are actually used and that investment in research continues.

The *Global Action Framework for TB Research* was developed by WHO in collaboration with a broad range of stakeholders to foster high-quality TB research, both nationally and globally, for the next 10 years (2016-2025). The framework builds on the outcomes of a *Global consultation on research for TB elimination* organized in Stockholm by the WHO Global TB Programme, the Swedish Government and the Karolinska Institutet in November 2014, that proposed the following 10-year vision for TB research.

FIGURE 2 / PROJECTED ACCELERATION OF TB INCIDENCE DECLINE TO TARGET LEVELS





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THE 10-YEAR VISION

To achieve the targets set by the WHO End TB Strategy for 2030/2035, there is a need for intensified research to deliver new tools and strategies to combat the disease, including rapid and sensitive point-of-care diagnostic tests, short regimens for the treatment of TB disease and latent TB infection, and an effective vaccine. These novel tools, as well as any innovation, must be linked with relevant epidemiological, health systems, and operational research to ensure their adoption and implementation to scale. To achieve this vision it is essential that, over the next decade, countries with substantial TB burden progressively establish their leadership for TB research by ensuring the necessary funding through domestic public investments (especially in the middle-income high burden countries, including the BRICS) and by building strong domestic capacity with the necessary international collaboration within the larger context of health research. It is also crucial that high-income countries and their institutions enhance their engagement and investments in TB research overall, including multidisciplinary TB research, to address specific barriers impeding TB elimination, and that they collaborate with, and support, institutions in high-incidence countries. This vision also relies on ongoing global commitment to addressing health as a development priority and to research and innovation across the globe.

The **Global Action Framework for TB Research** has been designed to help achieve this 10-year vision, with two fundamental objectives:

1

To promote, enhance and intensify TB research and innovation at country level, with a focus on low- and middle-income countries, through the development of country-specific TB research plans and strong research capacity.

2

To promote, enhance and catalyse TB research at global level through advocacy, sharing innovations, discussion of global priorities in TB research and development of regional and international networks for research and capacity building.

It sets the principles for action on TB research and recommends the roles, responsibilities and deliverables for major stakeholders, both global and national. It is designed for use by a wide range of groups and individuals including ministries of health and their national TB programmes, ministries of science and technology, national research institutes, academia, researchers, international and national donors and technical agencies, NGOs and civil society.

The Framework is composed of three parts:

Part I:

Strengthening TB research in low and middle-income countries most affected by TB

Part II:

Supporting and facilitating research at global level

Part III:

The role of WHO

GLOBAL ACTION FRAMEWORK

MILESTONES AND DELIVERABLES AT A GLANCE

Countries

2020

All countries with high TB burden will have:

- Established a national TB research network;
- Integrated TB research within the National TB Strategic Plan;
- Developed a list of national TB research priorities;
- Initiated in-country research training.

It is expected that:

- At least three new cross-national TB research networks will be established;
- At least three large multicentre and cross-cutting collaborative studies will be initiated;
- At least two new innovative financing mechanisms will be implemented;
- Full funding of TB research will be ensured at least in the BRICS countries.

WHO

WHO will have:

- Worked with at least three model countries to develop and implement a national TB research plan;
- Organized a multi-country meeting on lessons learned from model countries;
- Published an updated version of the Global Action Framework for TB Research;
- Published TB research investment case studies;
- Included progress in TB R&D at country level within the WHO Global TB Report.

2025

All countries with high TB burden will have:

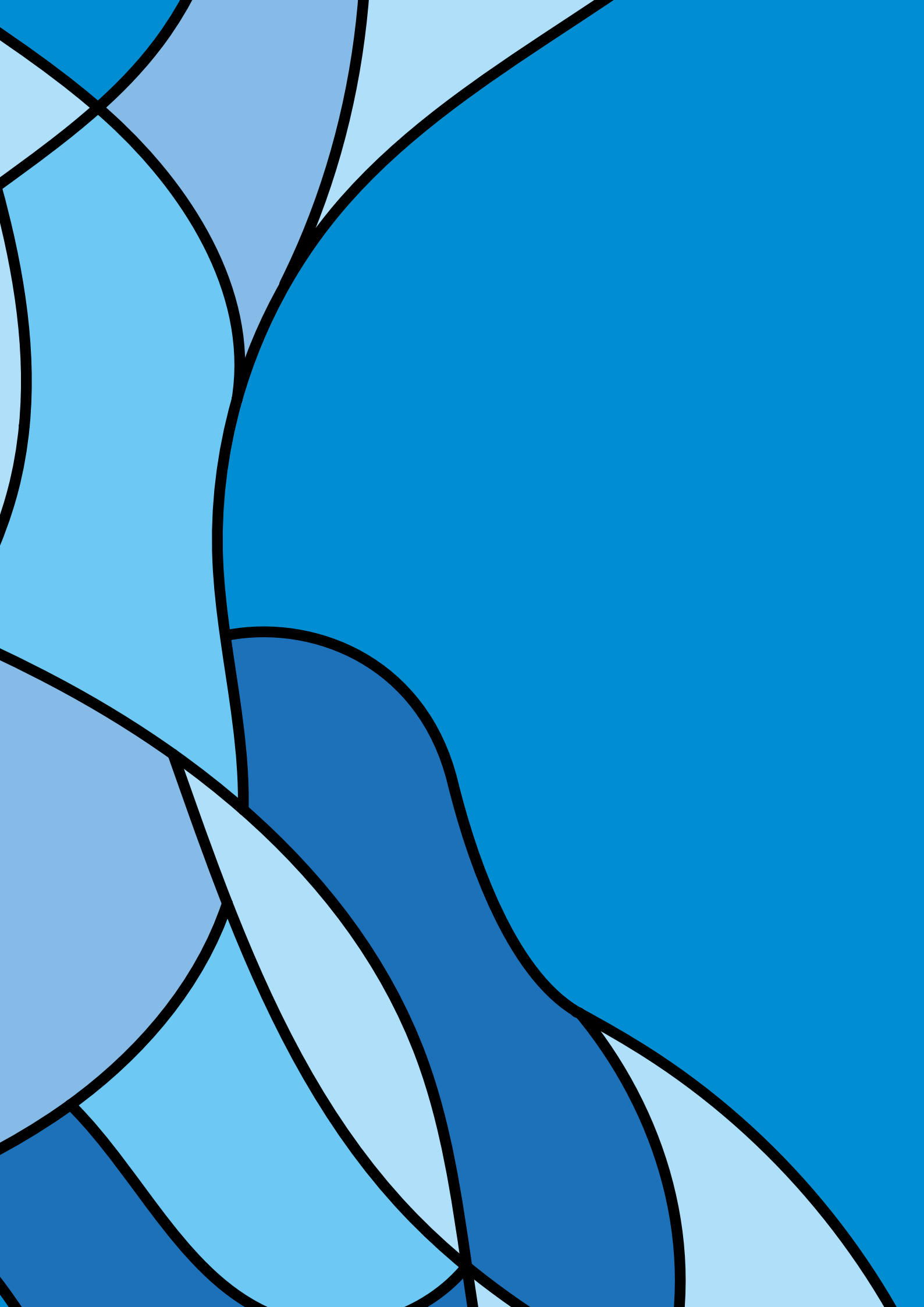
- Developed and implemented a national TB research plan;
- Established sustained mechanisms for national TB research funding;
- Created a strong TB research capacity;
- Empowered a strong and self-sustained TB research community.

It is expected that:

- High-income countries will have enhanced their commitment and investments in Research and Development (R&D) for TB;
- Mechanisms will be in place for global networking on TB R&D;
- Novel funding mechanisms will be implemented to enhance TB R&D;
- At least five large scale, multicentre, cross-cutting collaborative research projects will be conducted.

WHO will have:

- Assisted high TB burden countries to develop and implement a national TB research plan;
- Worked with countries and donors at national and international levels to expand the funding base for TB research along the continuum;
- Assisted countries to create a strong TB research capacity;
- Supported the creation of regional hubs and international networks for TB research;
- Included progress in TB R&D at country level within the WHO Global TB Report.



STRENGTHENING TB RESEARCH IN LOW- AND MIDDLE-INCOME COUNTRIES MOST AFFECTED BY TB

THIS CHAPTER DESCRIBES HOW TO STRENGTHEN TB RESEARCH IN LOW- AND MIDDLE-INCOME COUNTRIES MOST AFFECTED BY TB THROUGH THE DEVELOPMENT OF A NATIONAL TB RESEARCH PLAN.

The six key steps in developing and implementing the national TB research plan are described in detail:

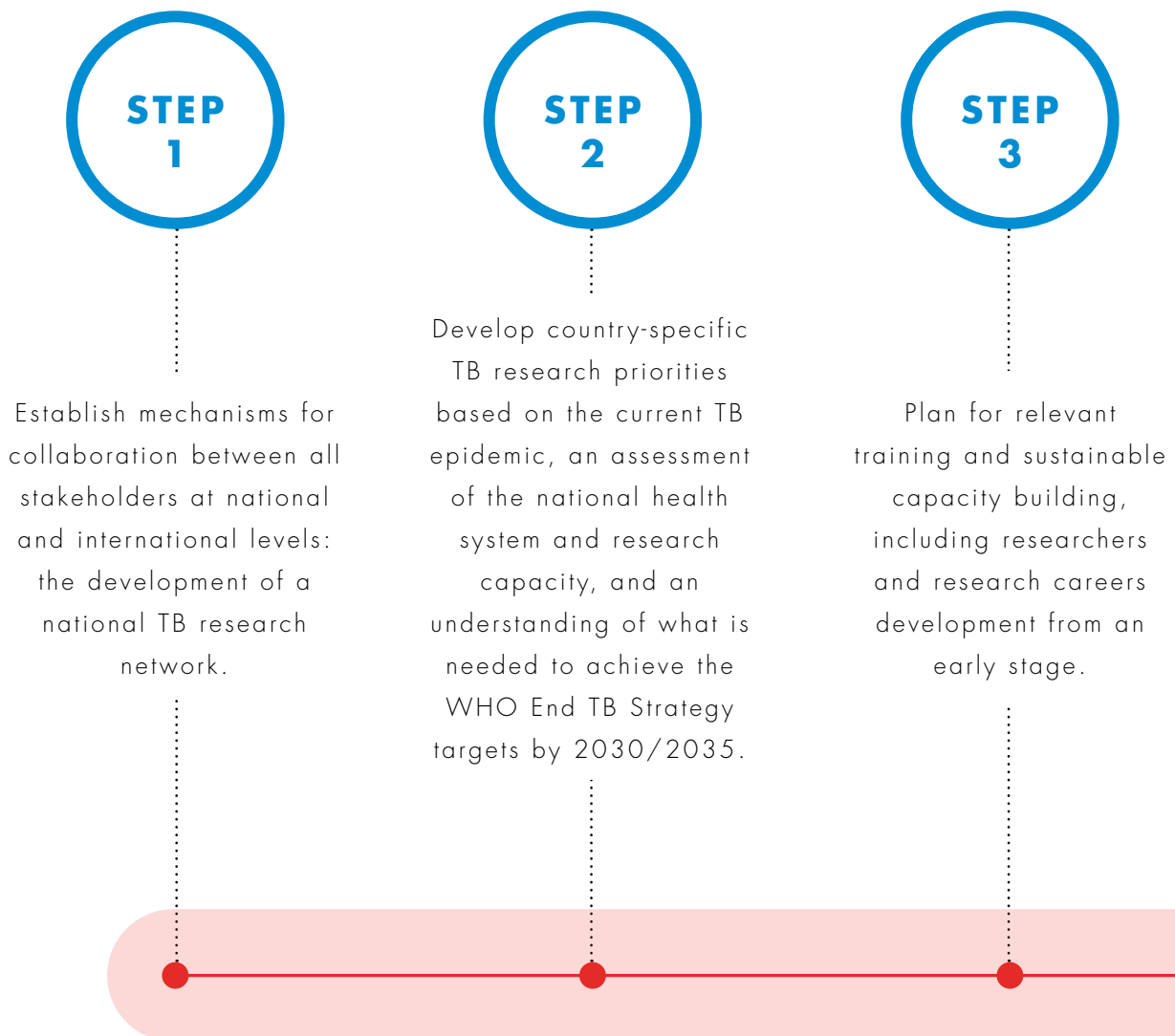
1. Develop (or reinforce) a national TB research network;
2. Develop a country-specific TB research plan based on the characteristics of the TB epidemic and an inventory of resources and activities;
3. Develop a plan for sustained capacity building on TB research;
4. Establish sustained national TB research funding for training, infrastructure and research operations;
5. Advocate for public support and funding of TB research; and
6. Undertake monitoring and evaluation of the implementation of the framework.

A checklist is provided to guide countries in assessing their research capacity and preparedness prior to developing a national TB research plan.

To substantially expand TB-related research, each country should develop a comprehensive *national TB research plan* integrated within the *National TB Strategic Plan* (NSP) to promote and catalyse TB research in the country over the next 10 years.

The plan should identify research considered essential to achieving the 2030/2035 End TB Strategy targets. Each country's financing and pace of implementation will vary, depending on its current TB burden, research capacity, and political and financial support. The plan is expected to

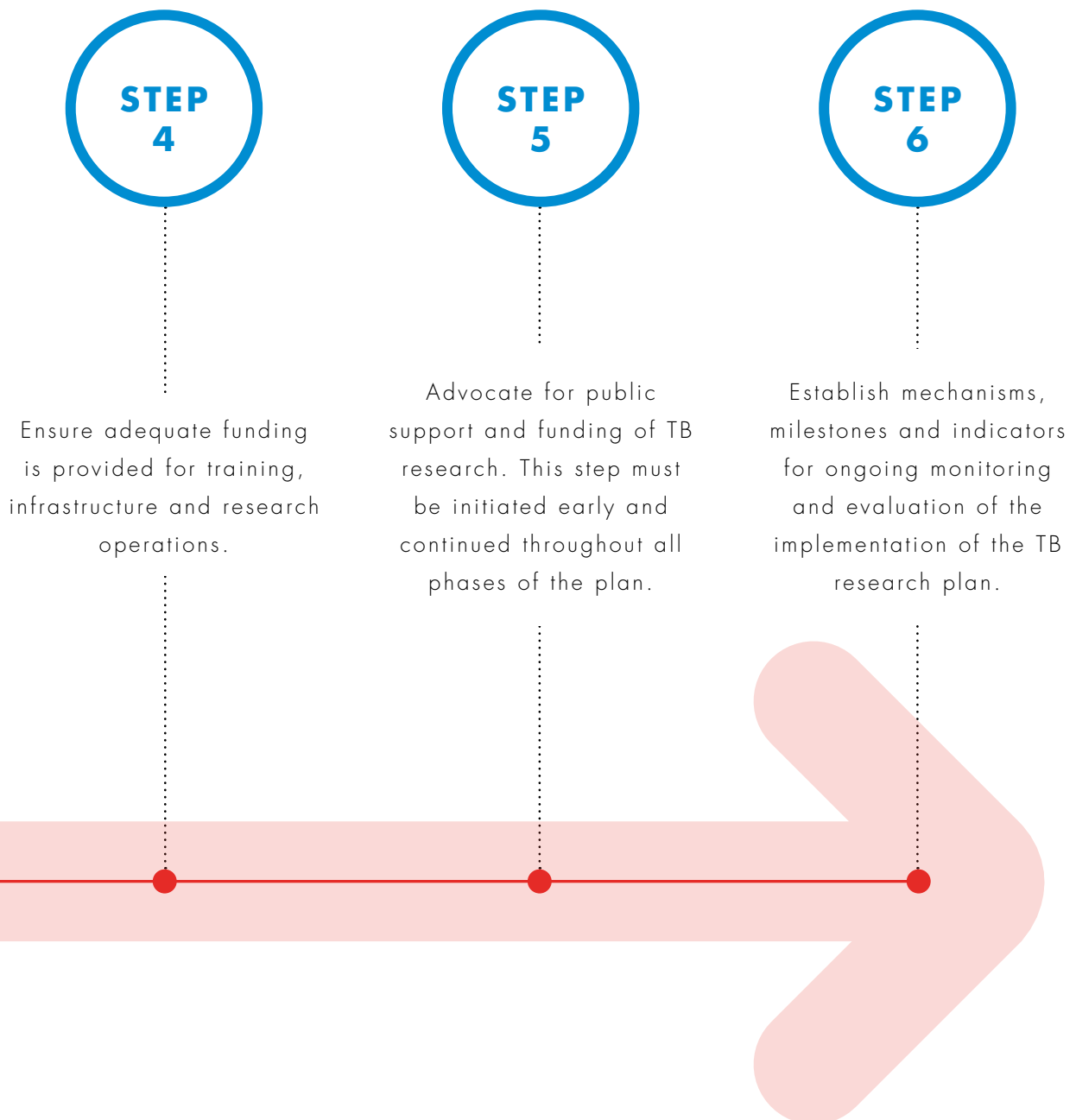
FIGURE 4 / **KEY STEPS IN DEVELOPING AND IMPLEMENTING A NATIONAL TB RESEARCH PLAN**



be fully implemented in many countries by 2020 and in all countries by 2025.

A few countries already have substantial TB research capacity and may be able to develop and implement a national TB research plan rapidly. These countries will

achieve milestones more quickly and will serve as 'path-finding', or model, countries for TB research. **Figure 3** below summarizes proposed key steps for a national TB research plan and the potential activities, roles and responsibilities of different stakeholders.



KEY STEPS IN DEVELOPING AND IMPLEMENTING A NATIONAL TB RESEARCH PLAN

1 / ESTABLISH MECHANISMS FOR COLLABORATION BETWEEN ALL STAKEHOLDERS AT NATIONAL LEVEL: THE DEVELOPMENT OF A NATIONAL TB RESEARCH NETWORK

To make best use of a country's limited human, physical and financial resources, TB-related research should be coordinated with researchers in all disciplines and the National TB Programme (NTP) collaborating closely.

Establishing or strengthening an existing national TB research network is an important early step towards a national TB research plan. The network should be seen as a partnership between public and non-government sectors in which health practitioners and researchers from government agencies, particularly the NTP^a of the Ministry of Health (MoH), should collaborate closely with TB researchers from

various disciplines at national universities, research institutions, and associations. Where possible, collaboration should extend to other government agencies or ministries, such as the Ministry of Science and Technology (MoST).

A truly effective network also requires the participation of research beneficiaries, including community and civil society representatives. Every effort should be made to include representatives from Non Governmental Organizations (NGOs) and the private sector, including professional associations, practitioners and industry. The network should be as inclusive and multi-disciplinary as possible, for example involving researchers and institutions not currently doing TB research but addressing cross-cutting related research questions. International research expertise would also be helpful, including from WHO, international NGOs or universities in high-income countries. The network should be able to help in the inventory and in the formulation of the national TB research agenda, including national research priorities (see below). **Box 2** gives an example of a TB research network in Brazil (2).

^a It is suggested that each NTP designates a TB research focal point, ideally with a background in research. Domestic research institutions would similarly designate one of their researchers (ideally with a clinical or public health background) to be the TB focal point so as to encourage ongoing dialogue and exchange.

BOX 2 / MULTI-DISCIPLINARY AND MULTI-CENTRE NATIONAL TB RESEARCH NETWORKS – THE EXAMPLE OF THE BRAZILIAN TB RESEARCH NETWORK

Before 2001, Brazil had substantial research capacity but very little cooperation and no coordination between industry, universities, the various research institutes, health services and the NTP. In 2001 the Ministry of Science and Technology launched a call for applications to promote the creation of research networks in all areas. The TB network was created and funded, entitled *REDE-TB*. *REDE-TB* is a multi/interdisciplinary group of researchers and students from health sciences, engineering and education, with civil society partners and health service representatives from all levels of TB and AIDS programmes (federal, state and municipal). The main objective of *REDE-TB* is to promote research and educational activities in an integrated manner to contribute to TB and TB/HIV control. *REDE-TB* researchers were invited by the Ministry of Science and Technology and the Ministry of Health to help define a national TB research agenda in 2004, 2007 and 2010. Research topics were identified by *REDE-TB* researchers, TB and AIDS Programme coordinators, representatives from the Oswaldo Cruz Foundation (Fiocruz) and civil society. In 2004, *REDE-TB* initiated a project for research training with US National Institutes of Health (NIH) funding. The creation of *REDE-TB* helped build bridges between university-based researchers, the public health system (and particularly the NTP), industry and civil society. The university-based researchers helped produce scientific knowledge that responds to local demands, through operational and health system research approaches. The network helped the NTP by conducting studies of strategic importance to the NTP, and through expert guidance committees on specific technical issues (such as diagnosis and treatment of latent TB infection (LTBI)).

(REDE-TB - www.redetb.org.br)

The network should undertake broad outreach. Initially, researchers and institutions can be limited, but the network should soon reach out and connect with other stakeholders nationally, as well as donors and groups from other countries involved in collaborative research activities. This should help create regional networks and foster regional projects in TB research. Finally, the network could also participate in international TB research networks addressing specific research themes.

2 / DEVELOP COUNTRY-SPECIFIC NATIONAL TB RESEARCH PRIORITIES

A key component of the TB research plan is a prioritized list of a country's most important research questions. These priorities should be based on a thorough understanding of the current TB epidemic, the research most needed to achieve the

End TB targets, and an inventory of existing TB research capacity at country level. The list should be developed by members of the network with and within broader national health research strategies. Inevitably the timing and intensity of this process will vary substantially by country.

The steps needed to develop these priorities are outlined below.

2.1 INITIAL SITUATION ASSESSMENT

A baseline assessment of the TB epidemic and of a country's TB research capacity is highly recommended to establish the basis upon which activities to promote and enhance TB research will be built and identify potential bottlenecks and opportunities to address them. This assessment is a major requirement within the overall End TB Strategy and can be undertaken by using a checklist developed for this purpose (see **Annex 1**).

2.1.1 DESCRIPTION OF THE CHARACTERISTICS OF THE TB EPIDEMIC AT COUNTRY LEVEL

This description should be based on the following factors: estimated incidence, prevalence, case detection and mortality, and TB case notification and treatment outcomes by type of TB (drug-susceptible, MDR-TB, TB/HIV) and age/sex. These data are

generally available at national level, as well as submitted by national sources to the WHO for its Global TB Report (3) and presented in individual TB country profiles which are part of WHO's global TB database^b. Available data on subnational geographical distribution, particular situations (such as transmission 'hot spots') or vulnerable groups (e.g. migrants, refugees, prisoners, indigenous populations) should also be reviewed. Finally, data from national or subnational prevalence or drug resistance surveys and surveys on TB/HIV co-infection, as well as other determinants of the TB epidemic (smoking, malnutrition, diabetes etc.) can provide important additional information (4).

2.1.2 THE BROADER HEALTH CONTEXT

Information on the structure and financing of the national health system and national health research should be reviewed, along with strengths and weaknesses. This process could be strengthened by applying lessons learned from research and priority setting in other health or disease research areas. (Note: good practices in priority setting are reviewed in the WHO World Health Report 2013) (5,6,7)

2.1.3 THE INVENTORY OF TB RESEARCH CAPACITY

An inventory of the *existing capacity for TB research* (in terms of human resources, physical

^b See: <http://www.who.int/tb/country/data/profiles/en/>

infrastructure and operations) should be carried out and include the following areas:

(i) Mapping the institutions involved in TB-related research and their productivity

The inventory would include key government agencies, public or private research entities and NGOs in the country, international bodies with substantial involvement in the country, institutions conducting research on cross-cutting themes relevant for TB and, more specifically, the NTP's engagement in research. The inventory should describe physical infrastructure and equipment and available human resources (including details about type of training/positions). Ideally the inventory would cover the strengths and challenges of the different institutions and their recent TB-related publications.

(ii) TB-related research training

Available or planned training courses should be listed, including the training institutions, disciplines and types of training available (fundamental, epidemiologic, clinical, laboratory, health system, social sciences, or operational research), level of training (undergraduate, Master's, PhD, or Post-Doc), and funding to support trainees. Links with international training courses should be mentioned.

(iii) TB-related research funding

National sources of funding should be identified, whether from public (national, provincial or state governments) or private sources (industry, philanthropic institutions,

NGOs). External sources, such as international agencies, bilateral agencies, industry or philanthropic donors should also be mentioned, as well as potential partnerships with international investigators (for example from multi-centre studies).

(iv) Research ethics

Capacity should exist within the country for a timely, multi-disciplinary and knowledgeable research ethics review to ensure rapid approvals for research projects, as appropriate.

A thorough inventory can be time-consuming, however, and require frequent updates. For this reason, the inventory's rationale, objectives, planned use and level of detail should be agreed by all stakeholders beforehand.

2.2 DEVELOPMENT OF TB RESEARCH PRIORITIES

On the basis of the above activities, a list of country-specific TB research priorities will be developed by the TB Research Network (described above), (see **Boxes 3 and 4** for examples from Ethiopia and Kenya). This prioritized list of research questions should be those viewed as essential to address the national as well as the global TB epidemic.

The development of these priorities should respect three key principles:

BOX 3/USING THE NATIONAL TB RESEARCH NETWORK IN A LOW INCOME COUNTRY AS A KEY PART OF THE NATIONAL RESEARCH PLAN: THE TUBERCULOSIS RESEARCH ADVISORY COMMITTEE (TRAC) IN ETHIOPIA

Background: In 2001, the TB and Leprosy Control Team (TLCT) of the Federal Ministry of Health organized a landmark TB Research Workshop (with support from TDR/WHO and the Ethiopian Science and Technology Commission) during which TRAC was appointed to conduct research within the country, based on national priorities and needs. TRAC is a voluntary network of NTP and other relevant MOH departments, public research institutions, major national universities, professional associations and other key TB stakeholders. It is a core technical advisory body to the NTP that sets TB research priorities and builds national capacity to conduct TB research. Over the last 14 years TRAC has been actively engaged in the promotion, conduct and dissemination of operational research in TB control and has been a forum for dialogue and interaction between researchers and NTP staff in Ethiopia. The NTP acts as the Secretariat for TRAC, while the chairperson rotates each year among member institutions.

Objectives: 1) Define national TB research priorities; 2) Create a conducive environment for TB research; 3) Review current status and problems of operational and other forms of TB research in the country; 4) Recommend effective and efficient mechanisms for coordination, management, and evaluation of TB research, as well as dissemination and uptake of results; 5) Identify potential TB research funding institutions or organisations; 6) Identify needs for capacity building to facilitate TB research in Ethiopia; 7) Promote TB research and innovation at all levels of the health system.

Activities: TRAC has organized annual research conferences for the past 10 years during which the number of participants and papers presented has significantly increased. Consultations and side meetings are held on selected thematic areas of national implication for programmatic design and scale-up of services and a list of priority research projects are discussed and endorsed by all conference participants. To date, TRAC has organized 12 rounds of operational research methodology training for 240 experts working at all levels of the health system from across the country. TRAC has also provided operational research training courses and developed an operational research grant mechanism to provide funding for researchers from public institutes and universities and health care delivery systems working collaboratively. As part of ongoing monitoring and evaluation, TRAC, in collaboration with the NTP, has initiated mapping and review of TB operational research activities and publications in Ethiopia.

- (1) they should be tailored to the country's needs and capacity;
- (2) they should include the full continuum of research – from fundamental to operational that is being or could be conducted in that country; and,
- (3) they should capitalize on countries assets.

The actors most involved in setting priorities may vary depending on a country's capacity for different types of research:

- Clinical (translational), epidemiologic, implementation and operational research usually attempt to address a country's need for data to guide its TB control interventions and evaluate their impact. Identification of country-specific research priorities that fit within these types should be made collaboratively by the National TB programme, other public health representatives and academic stakeholders (8).

- Conversely, priorities for fundamental research as well as drug, diagnostic or vaccine development are more likely to be based on the potential of a country's research capacity and funding options, as well as the global TB research agenda (9). For this type of priority-setting, the Ministry of Science and Technology, the country's academic institutions and national industry will likely be involved, whereas the involvement of the NTP might not be essential.

The list of priorities should also be *realistic*. Rather than a long 'shopping list' which represents the interests of each stakeholder, only a few priorities should be selected to ensure efforts and resources are tightly focused. This will enhance the likelihood of success. Priorities should be established for the next five years and a process put in place for periodic review and revision of the agenda.

BOX 4 / SETTING A NATIONAL TB RESEARCH STRATEGY IN KENYA

TB remains a major public health concern in Kenya. In 2013 Kenya notified close to 100,000 cases of TB (about 250 TB cases/100,000 population). Although Kenya has made tremendous progress in its war against TB, many challenges remain, including: inability to detect all incident cases of TB, delays in TB diagnosis, inadequate uptake of interventions to rapidly identify and prevent TB in persons living with HIV, prevention, care and control of drug-resistant TB and systematic screening of vulnerable groups for TB. The solutions for many of these challenges will only come from programme-based operational research to identify the most affordable, sustainable, effective and efficient approaches. To achieve this, Kenya formed a multi-stakeholder national TB research task force in 2008 which was charged with several responsibilities including to:

- Identify the TB programme's research priorities, and develop a strategic plan for multi-year operations research;
- Guide and support the development and review of research proposals;
- Organize forums for dissemination of research findings to all stakeholders and the integration of research findings into routine programme activities;
- Design and evaluate training programmes for operations research;
- Maintain an inventory of planned, ongoing and completed TB research projects;
- Mobilize resources for TB and TB/HIV research, and coordinate all TB and TB/HIV research activities to ensure conformity with identified national research priorities;
- Develop guidelines and ethical standards for TB and TB/HIV research.

The task force organized a workshop in October 2008 in which Kenya's TB research priorities were identified. These research priorities were updated at a second workshop in March 2013.



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3/PLAN FOR RESEARCH TRAINING AND CAPACITY BUILDING

Strong and self-sustained TB research capacity within countries is a pre-requisite to achieving national targets towards ending TB. The national TB research plan should include the mechanisms and activities that will strengthen and maintain infrastructure and human research capacity, including detailed country plans for research training (national and international) in TB, recruitment and retention of investigators, and the necessary funding commitments. The research plan should take advantage of international funding mechanisms and training opportunities, and include formal agreements with international universities or research institutes wherever possible. **Substantial and sustained national funding** is essential to the plan's long-term success and impact.

3.1 HEALTH RESEARCH TRAINING

TB research training should aim to fulfil a country's need for high-quality researchers. It should be part of a larger *national plan for health research training and capacity building*, since strengthened health research generally can benefit TB research. Training should be available at undergraduate and postgraduate levels (MSc and PhD) in fundamental, clinical,

epidemiological, bio-statistical, social, behavioural, health system and operational research methods. While these training programmes will not exclusively target TB research, they should incorporate adequate opportunities for supervision of students involved in TB research.

Many stakeholders are involved in TB research training. The roles and responsibilities of government agencies, universities, medical schools, research institutions and other health professional training programmes should be well defined. Additionally, the diversity provided by private sector and NGO participation will enhance opportunities, support and collaboration. Countries should also expand regional and international partnerships through links with international universities or research institutions, which will help promote student and faculty exchanges and enrichment.

Public funding should be made available for a broad range of training, from a few months to several years, depending on academic level. Funding will be needed to support trainees and to develop or strengthen research training programmes in national universities. While countries should take advantage of all available international training and funding opportunities, the importance of **sustained national public funding** for training cannot be underestimated (see **Box 5**). It is the best mechanism to ensure training is aligned with national research priorities and available for the longer term.

BOX 5 / NATIONALLY-FUNDED RESEARCH CAPACITY BUILDING: SCIENCE WITHOUT BORDERS, A BRAZILIAN PROGRAMME FOR ACADEMIC MOBILITY

Particular challenges for Brazilian science include the need to increase the number of PhDs, strengthen interaction between academia and industry, promote international collaboration, and increase the number of discoveries leading to patents. To address these challenges, the Government of Brazil introduced the Science without Borders programme in September 2011. Its main goals were to increase the presence of students and scientists in international institutions, encourage young talents and highly qualified researchers from abroad to come work in Brazil, and increase the internationalization of universities. In its first four years, the programme would provide scholarships to 100,000 Brazilian students for academic studies and research. By September 2014 over 70,000 scholarships had been awarded. In July 2014, the President of Brazil renewed the programme, funding an additional 100,000 positions for 2015-19. In the first four years 64,000 undergraduate students and 15,000 doctoral students received scholarships to attend international institutions for up to one year. Funds were also provided for an additional 4500 students for full doctorates abroad, 6440 for post-doctoral studies and 7060 for technological development and innovation studies. The programme also funded 2000 young talents and 2000 visiting scientists from international institutions to work in Brazil. It provides training in 17 areas with the greatest number of awards in Engineering and Technology (46% of positions), followed by Health and Biomedical Sciences with 17% of scholarships. The USA is the preferred destination, with 29% of students, followed by the United Kingdom (13%) and Canada (9%).

(<http://www.cienciasemfronteiras.gov.br/web/csf-eng/>)



3.2 RECRUITMENT AND RETENTION OF TB RESEARCHERS

Sustaining TB research requires retaining a critical number of in-country TB researchers and ensuring their long-term salary, infrastructure needs and stable national funding support.

3.3 FORMAL LINKAGES TO ENHANCE CAREER OPPORTUNITIES, MENTORING AND COLLABORATION

Developing national health research capacity in low- and middle-income countries is key to strengthening their health systems. Formal links between TB-related researchers, training institutions, national public health/TB control, international research and training universities would all help reinforce national research capacities. For example, links between research training institutions and the national TB programme would facilitate the entry of programme personnel into research training and of research training graduates into the TB programme. These formal links would also support research trainees for field work, and trainees and faculty for knowledge translation activities.

Links between national research training and international universities and institutes can also provide opportunities for mentoring by allowing faculty at national universities to refine their research and research training skills and graduate students to expand their

research training in-country and abroad (see 'Science without Borders' - *Box 5* above). In the same spirit, joint PhD partnerships have already been created whereby PhD students receive a single qualification from both a national university and a university in another country (a joint PhD degree), while carrying out research at national level (10). International cooperative efforts in operational research may also play an important role in national capacity building (for example, the 'SORT IT initiative' - *Box 6*).

4/ENSURE ADEQUATE AND SUSTAINABLE OPERATING FUNDING FOR RESEARCH

Middle-income high-TB burden countries have the capacity to invest in the full spectrum of TB research, ranging from fundamental to operational research, and should be encouraged to do so by applying the following principles.

4.1 SOURCES OF FUNDING

Sustained national public funding is key to a long-term and stable national research capacity that investigates a country's national priorities. Funding requires strong political commitment to support TB research as part of general health research, but achieving this commitment means convincing policy-makers and politicians of the importance of TB in the nation's health research strategies.

BOX 6/INTERNATIONALLY-FUNDED RESEARCH TRAINING: THE STRUCTURED OPERATIONAL RESEARCH AND TRAINING INITIATIVE (SORT IT)

Launched in 2012, SORT IT supports countries to: 1) Conduct operational research that addresses their priorities; 2) Develop adequate and sustainable operational research capacity in public health programmes; 3) Increase organisational acceptance of operational research and use of research results to improve programme performance.

This global initiative, led by the Tropical Disease Research (TDR) Programme at WHO, supports operational research in TB, as well as a range of other public health programmes including HIV, malaria and neglected tropical diseases. A number of donors actively support SORT IT including DFID, USAID and the Bill & Melinda Gates Foundation. Implementation of SORT IT activities relies upon a strong international partnership of other organisations with experience in operational research, research capacity-building and knowledge management. These include the International Union Against Tuberculosis and Lung Diseases (The Union), Médecins sans Frontières (MSF), KNCV, the US Centres for Disease Control, the Evidence into Policy Network (EVIPNet) and a number of academic institutions. SORT IT partners work closely with ministries of health and the WHO regional and country offices to implement multi-phase SORT IT Programmes. These phases include: research prioritization and planning of capacity-building; conduct of prioritized operational research by healthcare workers in the context of a one-year modular training and mentorship programme; publication of research and dissemination of research findings; active engagement with stakeholders to promote translation of research into policy and practice; supporting further operational research by trained healthcare workers through small grants; and building leadership through SORT IT operational research fellowships that can lead to higher degrees. As of mid-2015 more than 300 healthcare workers in over 75 countries had received training, conducted operational research and participated in other SORT IT activities.

(http://www.who.int/tdr/capacity/strengthening/sort/about_sort/en/)

As is the case with funding for training and capacity building, domestic public funding could be enhanced by partnering with national or international private industry (for TB diagnostic or therapeutic research, for example) or with international donors, other

governments and international institutions. Additional domestic funding sources could include regional, provincial or municipal governments, or private entities such as industry, philanthropic institutions and NGOs.



At the international level, countries receiving support from The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) should be seeking support for operational research directed at improving TB control activities. This includes evaluating the impact of introducing new technologies or TB control strategies into the health system and would require a clear description of the objectives, methods and expected results of research within the country's National TB Strategic Plan.

Other international sources of research funding include multilateral or bilateral development agencies, industry, philanthropic donors and partnerships with international investigators, for example through participation in multi-centre studies or trials. The annual report of the Treatment Action Group (11) and the GFINDER database are useful sources of information on current international funding sources (source of funding, project funded and countries).

4.2 COMPONENTS SUPPORTED

Funding is needed for human resources, including salaries of investigators, administrative and research personnel such as data managers, statisticians, laboratory technicians, research coordinators, interviewers and research assistants. Personnel with adequate training in regulatory, ethical and quality assurance requirements are also needed.

Successful research requires substantial infrastructure, such as well-established institutions with funding specifically for TB research staff and facilities. These institutions offer clear career paths for researchers, stimulate entry into research and encourage retention of researchers in-country. They include universities, research institutes, or TB programmes and public health agencies, with funding for laboratory facilities, clinical facilities, and general office, computing and storage facilities for clinical, epidemiological and operational and health systems research. Additional infrastructure needs include access to library facilities, other research resources such as non-open access medical journals and payment for open access publications, and costs of presenting research results at national and international meetings.

Much of the national funding for TB research should be directed towards the priorities for TB research identified in the national research agendas. However, there must be some flexibility to allow for novel, investigator-initiated ideas, in response to new research findings and directions.

4.3 FUNDING MECHANISMS AND DURATION

Publicly funded health research should be encouraged through an open and transparent competitive process for time-limited grants with external judging by peer-review committees. Countries should refrain from indefinite or lifetime funding to avoid stagnation.

5/ADVOCATE FOR PUBLIC SUPPORT AND FUNDING OF TB RESEARCH

Effective engagement of all stakeholders can greatly enhance investments in research and development - including public and private donors, the scientific community, national TB programmes and civil society. Strong and carefully focused advocacy activities will increase stakeholder engagement in TB

research as well as the country's research and development funding on TB. Stakeholder engagement is an essential activity that must be initiated early and maintained throughout all phases of the national strategic plan. National NGOs can be of great assistance in advocating for additional funding (see **Box 7**). Advocacy should focus on gaining full government commitment for sustained national public funding of TB research and strengthening community engagement in research, from the design of clinical trials and trial conduct to the delivery and uptake of successful innovations.

BOX 7/THE ROLE OF NGOs AND OTHER CSOs IN SUPPORTING PILLAR 3 OF THE END TB STRATEGY

NGOs and other Civil Society Organizations (CSOs) can be key stakeholders in the promotion of TB research particularly at country level. NGOs could play a salient role in the following suggested areas:

- Focused advocacy activities to emphasize the importance for enhanced engagement of various stakeholders in TB research at national level;
- Catalyzing the establishment / reinforcement of a national TB research network and actively participate in it;
- Advocating the development of the country specific TB research plan and agenda;
- Advocating for obtaining full government commitment for sustained public funding of TB research and research capacity building;
- Engaging in the implementation of the national research plan and agenda and monitoring their implementation;
- Strengthening community engagement in research.

6/INDICATORS AND MILESTONES FOR MONITORING AND EVALUATION

6.1 INDICATORS

Progress in implementing the national TB research plan must be monitored and evaluated with relevant indicators and milestones. These should include 'process' indicators (how TB research is being strengthened) and 'content' indicators (how far the TB research strategy has been developed and its impact on the End TB Strategy targets in each country). Ideally the inclusion of some of these metrics in the WHO Global TB Report would stimulate their adoption by NTPs.

Process indicators (Yes/No) include:

- Whether a national TB research network has been established, receives funding support from national public sources, and meets regularly;
- Whether a plan for TB research has been developed through a multi-stakeholder process, and is integrated within the National TB Strategic Plan;

- Whether national TB research priorities have been developed through a multi-stakeholder process and are widely disseminated;
- Whether a national plan exists for health research capacity building, including mechanisms for national funding of health research training and infrastructure;
- Whether a national mechanism for funding TB research operating costs has been developed.

Content indicators include:

- The number of researchers trained at MSc and PhD levels (in-country and abroad);
- The number of researchers working in research within the country five years after training;
- The type and amount of research operating funds awarded from national public sources;
- The number of publications in international peer-reviewed journals;
- Changes in diagnostic, treatment or preventive policies and strategies of the NTP resulting from domestic research.

6.2 MILESTONES AND DELIVERABLES

MID-TERM MILESTONES AND DELIVERABLES (BY 2020)

Within 5 years, all countries with substantial TB burden will have:

- Established a national TB research network that includes at least leadership from national universities/research institutes, the national TB programme, and civil society;
- Integrated TB research within the National TB Strategic Plan;
- Developed TB research priorities;
- Initiated in-country research training with national faculty (at a minimum, have the capacity to deliver operational research training).

FINAL MILESTONES AND DELIVERABLES (BY 2025)

Within 10 years, all countries with substantial TB burden will have:

- Developed and implemented a national TB research plan with a TB-specific prioritized research agenda within a larger health research agenda, based on mapping of resources and activities, with a process to review and renew it every five years;
 - Established sustained mechanisms for funding a broad spectrum of research efforts on TB (from basic to operational according to the country's resources and research capacity), based on newly developed national research agendas;
 - Created a strong TB research capacity, including training, mentoring and career support, with well-defined roles for government agencies and national TB programmes, universities or research institutions, private sector and NGOs;
 - Empowered a strong and self-sustained TB research community, which is productive, addresses national priorities, and with links to regional hubs and international research networks.
-

MODEL COUNTRIES

A few countries already have substantial TB research capacity and may be able to develop and implement a national TB research plan rapidly. These countries will achieve milestones more quickly and will serve as *model countries for TB research*. The following one and 5-year milestones and deliverables are proposed:

FIRST-YEAR MILESTONES AND DELIVERABLES IN MODEL COUNTRIES (BY 2016)

Within one year, model countries will have:

- Formed a national TB research network that receives funding support from national public sources and meets regularly;
- Integrated TB research within the National TB Strategic Plan using a multi-stakeholder process;
- Developed a list of national TB research priorities through a multi-stakeholder process, and disseminated this widely;

- Established a national plan for health research capacity building, including mechanisms for national funding of health research training and infrastructure support;
- Established mechanisms for regular (such as annual) award of national research operating funds.

MID-TERM MILESTONES AND DELIVERABLES (BY 2020)

Within 5 years, model countries will have:

- Established national funding for TB research capacity including in-country training at MSc and PhD levels in a variety of disciplines, and for infrastructure including salaries for researchers;
- Established annual (or more frequent) national competitions for health research operating funds.

MODEL COUNTRIES MILESTONES AND DELIVERABLES AT A GLANCE



2016

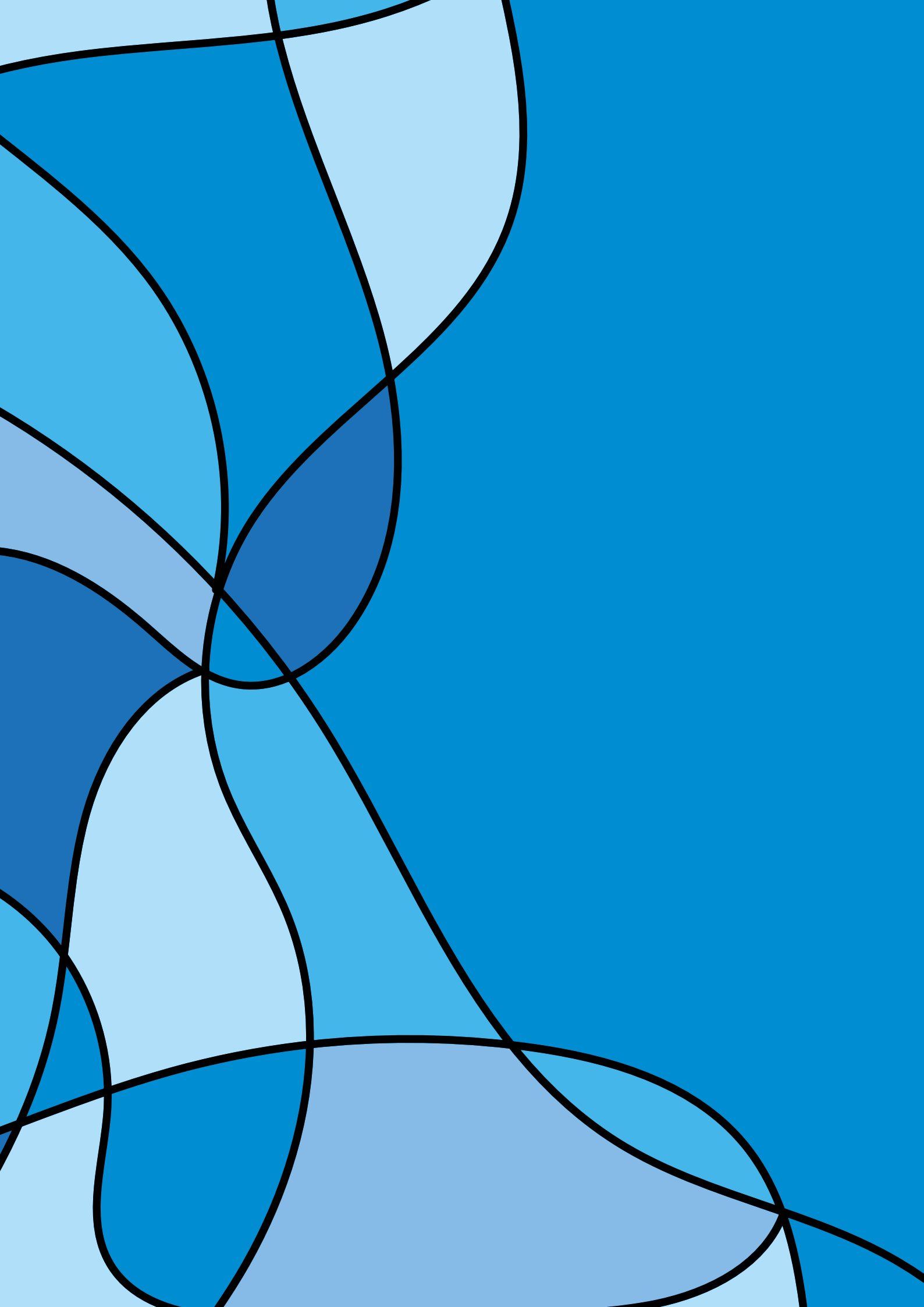
Model countries will have:

- Formed a national TB research network;
- Integrated TB research within the National TB Strategic Plan;
- Developed a list of national TB research priorities;
- Established a national plan for research capacity building;
- Established mechanisms for regular award of national research operating funds.

2020

Model countries will have:

- Established national funding for TB research capacity;
- Established annual national competitions for health research operating funds.



PART II

SUPPORTING AND FACILITATING RESEARCH AT GLOBAL LEVEL

THIS CHAPTER DESCRIBES HOW TO ENHANCE TB RESEARCH GLOBALLY TO BUILDING STRONG RESEARCH PARTNERSHIPS AND NETWORKS AND SECURING ROBUST FUNDING FOR TB RESEARCH.

Key activities are:

1. Mobilise increased funding resources for TB research at global and national levels;
2. Hold regular TB research donors' forum;
3. Develop innovative funding mechanisms;
4. Expand advocacy activities to increase TB research funding internationally;
5. Create international networks and thematic hubs; and
6. Undertake large-scale, cross-cutting, multi-disciplinary, multi-site, collaborative research projects.

Efforts invested at national level must be reinforced and supported at the global level by developing strong research partnerships and networks, associated with reinvigorated funding for TB research and development.

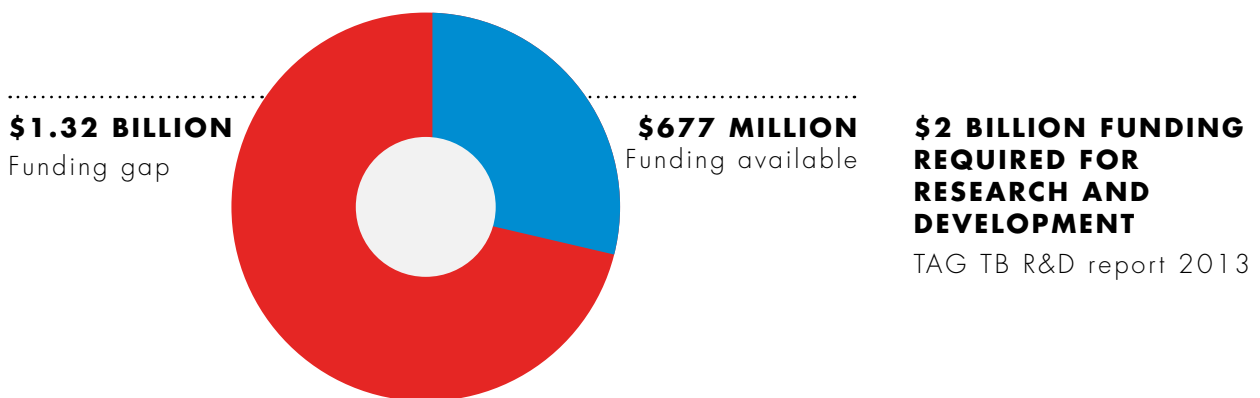
1/MOBILIZE INCREASED RESOURCES FOR TB RESEARCH

Development of new tools and strategies for TB prevention, care and control is hindered by limited investments in TB research. After a significant increase from US\$ 358 million in 2005 to US\$ 637 million in 2009, global funding for TB research and development has remained static for the last five years (11) (*Figure 4*). In 2013, US\$ 676.5 million were spent globally - a

financial shortfall of about US\$ 1.4 billion per year according to the Global Plan to Stop TB 2011-2015 (12).

TB research is highly dependent on a very limited number of donors, including a few government agencies and philanthropic groups based almost exclusively in high-income countries. This creates a fragile resource base, as government donor agencies face many competing demands for funding and are subject to continuous challenges from emerging priorities. There is a risk that current support by major public donors may stagnate or even decline in the near future, and that private pharmaceutical companies are progressively retreating from research and development of TB drugs. There is therefore an urgent need to increase and diversify investment sources. A series of directions are proposed.

FIGURE 4/**FUNDING GAP IN TB RESEARCH**



1.1 EXPAND INTERNATIONAL FUNDING SOURCES TO SUPPORT RESEARCH IN LOW- AND MIDDLE-INCOME COUNTRIES

Funding is needed for a wide range of research, from basic science for the development of new tools to the research required to effectively scale up and implement these new tools. While public, private and philanthropic donors currently contribute to funding of TB research worldwide, almost 90% of global TB research funding comes from fewer than 10 donors. There is a clear need to expand the current base of donors who contribute to TB research.

Promoting operational, health systems or social science research will help improve activities to end TB and contribute to more effective national policies. WHO will therefore advocate with relevant international, bilateral and philanthropic donors^c for increases in TB research funding for programmatic and operational research, prevalence and drug-resistance surveys and health systems research, among others. Parallel discussions should take place with all international research institutions, donors and the private sector to increase their commitment to funding TB research in low- and middle-income countries.

1.2. HOLD REGULAR TB RESEARCH DONORS' FORUM

In addition to seeking additional funding, countries should aim to improve the use of

existing funding through regular discussions with key donors on enhancing the efficiency and impact of current investments. This type of discussion forum could be an opportunity to bring in new potential funders, reveal the gaps in TB research and highlight areas where they could invest.

1.3. STIMULATE THE DEVELOPMENT OF INNOVATIVE FUNDING MECHANISMS

Various new mechanisms are now being explored or implemented to provide incentives for research. One is the 'risk-guarantee' model (exemplified by the Swedish Guarantee Model) designed to complement and stimulate other financial resources that have the potential to contribute to the goal of poverty reduction and sustainable development. Another is the 'Global TB Vaccine Partnership' designed to better align current funders and attract new and innovative funding to support TB vaccine development. Yet another approach consists in matching national and externally raised funding, such as the Strategic Health Innovation Partnerships (SHIP) implemented in South Africa (see **Box 8**). A novel concept for innovative funding, the 'Push, Pull & Pool' mechanism, has been developed by MSF and includes a mix of incentives and collective management of intellectual property for new TB drug development^d. It is proposed that specific model business cases be developed and discussion fora organized to reflect on these innovative funding mechanisms.

^c For example, The Global Fund, European & Developing Countries Clinical Trial Partnership (EDCTP), National Institutes of Health (NIH), US Agency for International Development (USAID), UK Department for International Development (DfID), Bill & Melinda Gates Foundation, the Special Programme for Research and Training in Tropical Diseases (TDR)

^d <http://www.msfacecess.org/push-pull-pool>

BOX 8 / INNOVATIVE FUNDING MECHANISMS: SOUTH AFRICAN MEDICAL RESEARCH COUNCIL - STRATEGIC HEALTH INNOVATION PARTNERSHIPS (SHIP)

Driven by a pressing need to develop new or improved health interventions to address South Africa's major health problems, the South African Medical Research Council (SAMRC) launched Strategic Health Innovation Partnerships (SHIP) in 2013. SHIP utilizes funding from the South African Government to leverage international funding. Funds from both these sources support the National Biotechnology Strategy, which fosters research and innovation. The primary objectives of SHIP are to:

- (i) Seek, fund, and manage product research development from discovery to proof-of-concept.
- (ii) Enhance the South African research capacity for development of novel or improved drugs, vaccines and other biologicals, diagnostics and medical devices – for priority diseases.
- (iii) Facilitate, through partnerships with local universities, science councils and the private sector, the transfer of research outputs from the laboratory to the marketplace, resulting in improved health outcomes or social benefits.

In just over 18 months, this new initiative attracted US\$ 70 million in international funding from the Bill & Melinda Gates Foundation, Wellcome Trust, Grand Challenges, Newton Fund and private sector donors. One example is a fund to which SAMRC committed R30 million over three years and which will be matched by funds from the UK Medical Research Council (MRC) and GSK, as part of a broader collaboration for scientific research between the UK and South Africa. Currently 45 projects are funded, ranging from vaccine discovery to drugs and diagnostics and health systems strengthening in TB, HIV, malaria and maternal and child health.

1.4 ADVOCACY

Advocacy activities should be undertaken at all levels to increase and expand TB research funding both nationally and internationally. At national level, patients' representatives and civil society

organisations (CSOs) should be actively involved. At international level, a similar case should be made to increase national funding for TB research, particularly in the BRICS^e, and to expand international commitment to funding TB research and development. Research funding should be

^e Brazil, Russia, India, China, South Africa

coupled with increased partnership built on joint ownership, leadership and trust with mutual benefit. This will facilitate and enhance research, training, infrastructure development and control efforts in high-TB burden countries.

2 / IMPROVE INTERNATIONAL COLLABORATION

Activities to enhance international collaboration on TB research should also be undertaken. These include mapping the main international actors in TB research, organising meetings to promote research collaboration, developing international research networks and promoting large-scale collaborative projects. These activities are outlined below.

2.1 PURSUE AN INTERNATIONAL MAPPING OF TB RESEARCH

A number of initiatives have been set to map main actors in health research and development (for example the WHO Health R&D Observatory^f) (13) with a focus on TB research and funding (such as the Treatment Action Group annual report on TB R&D financing) (11). This should be expanded by mapping key institutions and programmes involved in TB research globally, and matching them to identified research needs and priorities at international and national levels. A global catalogue of TB research

by discipline, sites, country and other variables will be produced and compared to the research needs described in the International TB Research Roadmap (8), and potential funding gaps identified for specific areas of TB research.

2.2 COMPILE AN INTERNATIONAL COMPENDIUM OF FUNDING OPPORTUNITIES

A funder's compendium, initiated by NIAID and WHO, is proposed to describe available international sources of TB research funding as well as conditions for accessing this funding, with guidance on the conditions and procedures for grant-making by specific agencies, where appropriate.

2.3 STIMULATE THE CREATION OF REGIONAL AND SUPRANATIONAL NETWORKS

Some TB research networks have been organized around specific projects or themes; a few examples include the EDCTP networks of excellence (14), the Southern Africa Consortium for Research Excellence (SACORE) (15), the UK-MRC African investigators schemes^g, the Tuberculosis Vaccine Initiative (TBVI)^h and the NIH Fogarty Fellowshipsⁱ. Based on these and other existing networks, large TB research networks could be created to fill geographic or thematic gaps, linking researchers and

^f http://www.who.int/phi/implementation/phi_rd_observatory/en/

^g <http://www.mrc.ac.uk/funding/science-areas/global-health/arl/>

^h <http://www.tbvi.eu>

ⁱ <http://www.fic.nih.gov/WORLDREGIONS/Pages/SubSaharanAfrica.aspx>

BOX 9 / AN EXAMPLE OF INTERNATIONAL COLLABORATIVE TB RESEARCH: A MULTI-DISCIPLINARY MULTI-SITE RESEARCH STUDY ON TB - REPORT INTERNATIONAL

The National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health (NIH) has long recognized the need for TB research collaboration and coordination, as prioritized in the International Roadmap for TB Research. Partially in response to this need, NIAID and collaborating biomedical research entities in Brazil, India, Indonesia and South Africa initiated **RePORT** (Regional Prospective Observational Research in Tuberculosis) *International*.

The objective of **RePORT International** is to provide a platform for coordinated TB research by establishing a common set of standards and definitions, harmonized observational cohorts with well-characterized populations, consolidated bio-specimen banks, and integrated data collection and analysis strategies. A common protocol with corresponding clinical research forms, a manual of operations, data definitions, and other pertinent standards have been developed. These documents, and the study designs developed by **RePORT International** may eventually serve as templates for global collaborative TB clinical research. It is envisioned that each participating country will support local research teams to develop RePORT cohorts, which will be available for clinical studies to address questions of local, regional and international importance. Investigators are encouraged to work with colleagues developing national RePORT networks in other countries to undertake jointly-developed common protocols, using common standards and practices. Such an approach will enable large clinical research projects and trials (as the need arises) that cannot be undertaken by a single group. In essence, the strategy is to create a multi-faceted, collaboratively funded global TB research network that can address important questions with locally and globally relevant answers, which could expand to include additional collaborators in the future.

institutions with programme managers and public health specialists at regional and supranational levels and stimulating *multi-site research*. This would in turn improve efficiency based on local experience and enhance capacity building and knowledge

transfer. *Hubs* centred around institutions with a particular expertise or capacity-building competence could further stimulate collaboration, coordination and learning, creating a powerful opportunity for enabling platforms that could be used across the



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world. As an example, this could be a TB-centric bio-informatic platform allowing access to TB-related data (such as array or RNAseq) and providing the tools needed to look at these data. Other data sets, such as epidemiological data sets, might also be housed in such a platform. These tools could provide researchers with modest infrastructures to access sophisticated technologies.

2.4 ENCOURAGE LARGE-SCALE, CROSS-CUTTING COLLABORATIVE RESEARCH PROJECTS

Researchers should be encouraged to develop large cross-cutting multi-disciplinary research projects combining basic, translational, clinical, operational, health systems, and public health research, conducted by multi-disciplinary consortia of academic and research institutions at national, regional or international levels,

and involving multiple funders (16). For instance, these could be longitudinal studies of patients and households used to identify biomarkers that characterize the various clinically relevant stages of TB, together with studies on how to prevent transmission and disease development (see **Box 9**). Linking training and capacity development closely to research should be encouraged and will empower local scientists to take leadership of TB research.

In addition, *theme-specific scientific meetings assembling* key stakeholders (research teams and financial partners, for example) could be organized to investigate the country's capacity to develop cross-cutting science projects and their funding. Collaborative and inter-disciplinary research could also be stimulated through multidisciplinary scientific meetings (involving the full range of scientists from basic and clinical to epidemiologic and implementation) around specific themes such as preventive treatment or transmission.

3 / MILESTONES AND DELIVERABLES

FIVE-YEAR DELIVERABLES (BY 2020)

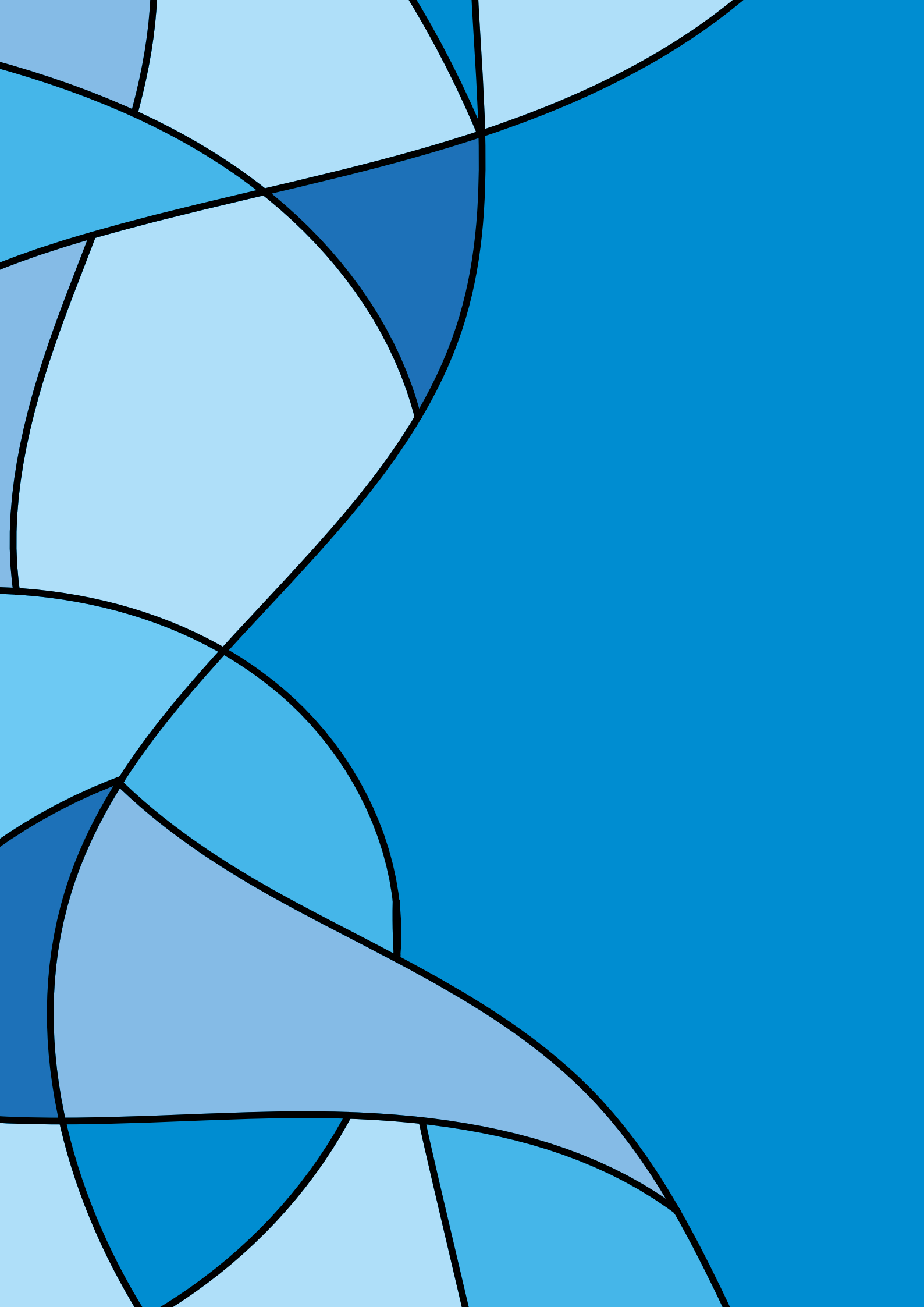
Within 5 years, it is expected that:

- At least three new cross-national TB research networks will be established;
- At least three large multicentre and cross-cutting collaborative studies will be initiated;
- At least two new innovative financing mechanisms will be implemented;
- Full funding of TB research will be ensured at least in the BRICS countries.

TEN-YEAR DELIVERABLES (BY 2025)

Within 10 years, it is expected that:

- High-income countries will have enhanced their commitment and investments in R&D for TB, (including on TB elimination measures in low-incidence countries);
 - Mechanisms will be in place for global networking on TB research and monitoring the global impact of research advances;
 - Novel funding mechanisms will be created and implemented to enhance TB R&D;
 - At least five large scale, multicentre, cross-cutting collaborative research projects will be developed, fully funded and produce relevant results in terms of TB research.
-



THE ROLE OF WHO

THIS CHAPTER DESCRIBES WHO'S ACTIVITIES IN SUPPORT OF THE FRAMEWORK.

Key activities are:

1. Provide technical assistance to countries for the development and implementation of a national TB research plan in line with the End TB Strategy;
2. Develop guidance tools and documents to assist countries in implementing the Pillar 3 of the End TB Strategy;
3. Work with international, bilateral and national stakeholders to foster dissemination of research outputs and uptake by countries;
4. Ensure data sharing;
5. Convene meetings and facilitate communication.

A Task Force on Global TB Research will guide this work and assist in implementing the Global Action Framework.

As requested by the World Health Assembly, the WHO Secretariat, led by the Global TB Programme, is promoting the End TB Strategy and supporting its implementation, including its Pillar 3 on research. WHO is therefore committed to supporting the implementation of this Global Action Framework and will support the activities listed in Part II above by providing direct support to specific countries, as requested.

1 / PROVIDE TECHNICAL ASSISTANCE

WHO will work with countries, other partners and donors to assist in developing and implementing a national TB research plan in line with the End TB Strategy, ensuring that it is well aligned with other national planning documents. This support will include direct technical assistance (TA) to countries. In addition, during National TB Programme reviews, WHO will assist in the monitoring and evaluation of current research efforts and provide recommendations for improvements.

WHO will develop and disseminate guidance tools and documents to be used by key actors in countries (for example, “How to form a TB research network?” or “How to develop a National TB Research Agenda?” – see Annex 2). One such tool to be developed with the model countries will help estimate the costs of a national TB research plan.

WHO will also continue working with other agencies, such as bilateral agencies supporting various forms of national TB research.

2 / FOSTER SUPPORT FOR DISSEMINATION OF RESEARCH OUTPUTS AND UPTAKE BY COUNTRIES

As part of its normative role, WHO conducts independent evaluations of key research outputs and evidence and makes subsequent policy recommendations for the use of new tools and interventions for TB prevention, care and control, such as Xpert MTB/RIF (17), bedaquiline (18), delamanid (19) or treatment of latent TB infection (20). By developing documents and tools for technical assistance, and through collaboration with partners, WHO supports the introduction of these new tools in countries, their uptake under programme conditions, and subsequent monitoring and evaluation.

3 / ENHANCE DATA SHARING

Access to research information in low- and middle-income countries could be expanded by compiling large and reliable databases that all researchers could share. WHO will seek support for, and may host as needed, this type of data sharing infrastructure. These transnational data sharing platforms (with data from large-scale clinical trials and cohort studies, and from genome or RNA sequencing studies) would be available to researchers from all countries. Data might be housed in inter-connected platforms and would include the software needed for access and analysis. This low-cost intervention would

give researchers from low- and middle-income countries access to results generated by highly sophisticated technology.

4/CONVENE MEETINGS AND FACILITATE COMMUNICATION

WHO will convene meetings and fora as described in Parts I & II. WHO will assist with linking countries through the creation of regional and international networks. If requested, WHO will help convene meetings within countries that involve various stakeholders, including national institutions (MoH, MoST), TA agencies, NGOs, financial partners and CSOs.

5/ESTABLISH A GLOBAL TB RESEARCH TASK FORCE

WHO's Global TB Programme will establish a task force to guide WHO in supporting this Global Action Framework. The task force will include national research institute officials, NTP representatives, researchers from low-, middle- and high-income countries, donors, NGOs and CSO representatives. It will meet regularly to review progress and challenges in pursuing this 10-year action framework, as well as assessing the overall role of research progress within the End TB Strategy at country and global levels.

6 / MILESTONES AND DELIVERABLES

FIRST-YEAR DELIVERABLES (BY 2016)

By 2016, WHO will have:

- Posted the Global Action Framework on the WHO/MTB website to serve as a guide for work on TB research promotion and global and national support over the next 10 years;
- Organized a TB Research Symposium at the World Lung Health Conference in Cape Town (Dec 2015), and presented the Global Action Framework and countries' experience at a meeting with NTP managers;
- Established the Global TB Research Task Force, and held its first meeting;
- Developed tools to assist in the implementation of this Global Action Framework (such as "How to develop a

National TB Research Plan", "How to form a national TB research network", and a guide to monitoring and evaluation (M&E) on research at national level, including a 'checklist for national TB research');

- Participated in trainings on the End TB Strategy organized by WHO regional and country offices;
- Initiated work with potential model countries implementing Pillar 3;
- Included progress in TB research and achievement of national milestones for model countries in the WHO Global TB Report.

MID-TERM (5 YEARS) DELIVERABLES (BY 2020)

By 2020, WHO will have:

- Worked with at least three model countries, in close collaboration with key national and international stakeholders, to develop and implement a national TB research plan;

- Organized a multi-country meeting to disseminate lessons learned from model countries;
 - Published an updated version of the Global Action Framework for TB Research based on lessons learned;
 - Published “TB research investment case studies” that will inform the implementation of the End TB Strategy based on estimates of impact and cost-effectiveness of interventions in specific settings;
 - Included progress in TB research and achievement of national milestones for lower- and middle-income countries in the WHO Global TB Report.
- research plan with TB specific research priorities, that is integrated within the National Strategic Plan;
 - Worked with countries and donors at national and international levels to expand the funding base for TB research, including the identification of novel funding mechanisms. This funding will support the full spectrum of TB research (from basic to operational) as appropriate for the national TB research priorities;
 - Assisted countries to create a strong TB research capacity with enhanced regional and international collaboration;
 - Supported the creation of regional hubs and international networks for TB research;
 - Included progress in TB research and achievement of national milestones by country and globally in the WHO Global TB Report.

FINAL (10 YEARS) DELIVERABLES (BY 2025)

By 2025, WHO will have:

- Assisted high TB burden countries to develop and implement a national TB

CONCLUSION

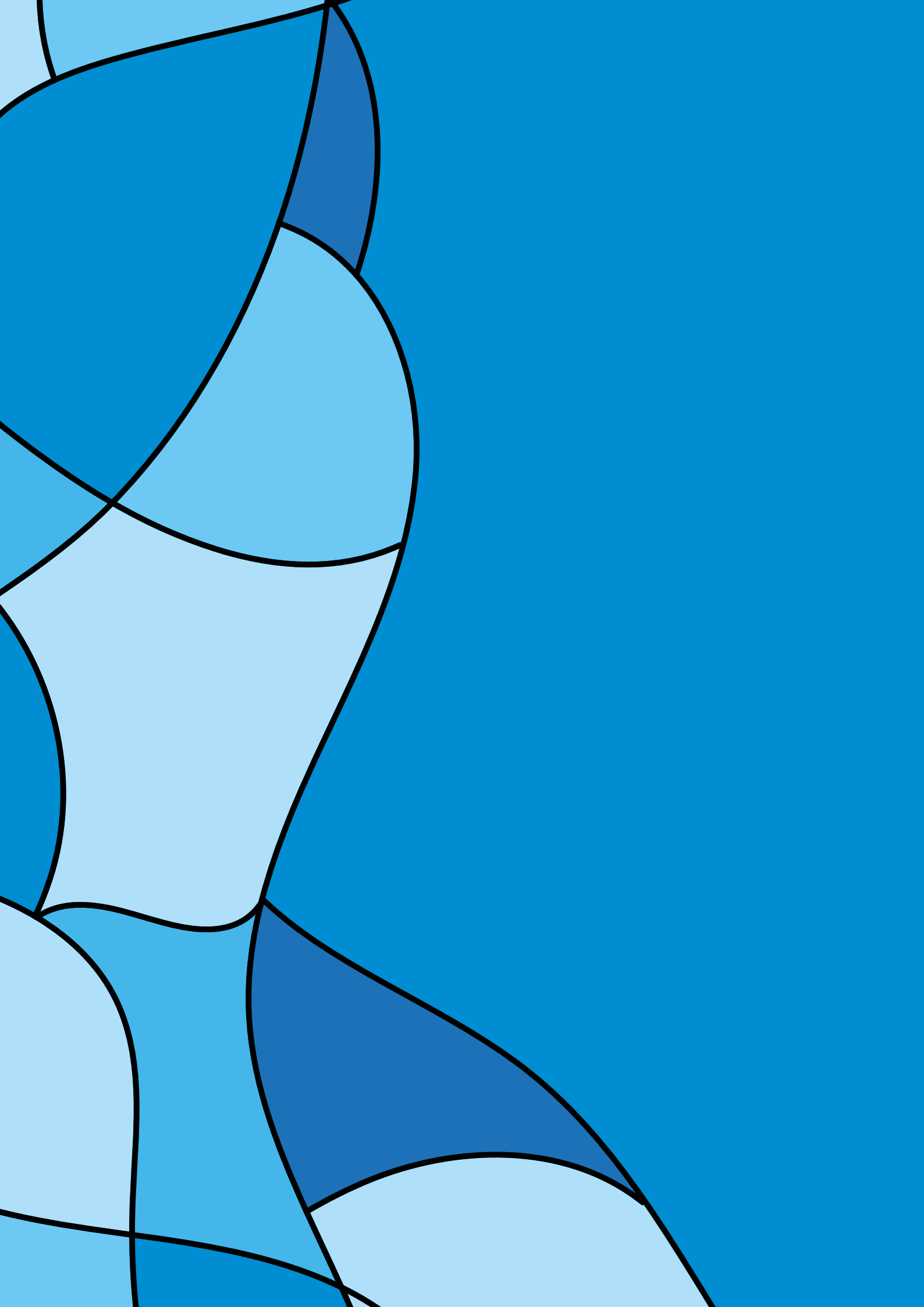
The ultimate goal of research in TB is to discover new tools and develop novel strategies to improve prevention, diagnosis and treatment of TB. This requires close collaboration between all key stakeholders to guide development and implementation of new tools nationally and internationally. The success of the End TB Strategy relies heavily on the potential to create optimal synergies among researchers, funders, programmes, health systems, patients and advocacy groups, so that efforts are effectively carried out worldwide for enhanced, properly funded and sustainable research for TB elimination.

The implementation of the present Global Action Framework for TB Research will contribute to the creation of a research-enabling environment that fosters and rewards high-quality research (from basic to implementation) and strengthens research capacity in countries with substantial TB burden. This, coupled with efforts to expand resources at global level to discover and develop new tools and facilitate their seamless integration into national programmes, represents a crucial step towards ending the global TB epidemic.



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ANNEX 1

SUGGESTED CHECKLIST FOR ASSESSMENT OF TB RESEARCH SITUATION AT COUNTRY LEVEL FOR PREPAREDNESS AND PLANNING

Objective:

This checklist is intended to assist countries in conducting an assessment of the TB research situation in order to inform the development of a National TB Research Plan. It can be used by NTP managers, external consultants, or during a monitoring mission.

Questions can be answered with a simple Yes/No, but some require further explanation. If documents are available to answer some questions, or a section of questions, these should be referred to, or attached.

Domain	Questions / assessment	Yes/No	Yes - to be strengthened	No - to be established
PLANNING AND PRIORITIZATION	1. Has an inventory of current TB research been conducted in the country in the last 10 years ?			
	<i>If yes, did this inventory include the following elements:</i>			
	<ul style="list-style-type: none"> • a research network with links to NTP? 			
	<ul style="list-style-type: none"> • a national health research plan with TB research priorities? 			
	<ul style="list-style-type: none"> • funding – for operating, training, infrastructure, and investigators salary support? 			
	<ul style="list-style-type: none"> • list of researchers and institutions involved in TB research? 			
	<ul style="list-style-type: none"> • national or international TB research training? 			
	2. Is there currently a national TB research network?			
	<i>If yes:</i>			
	<ul style="list-style-type: none"> • does it include national and international TB researchers? 			
<ul style="list-style-type: none"> • does it include public health officials, especially TB programme focal points (or managers)? 				
<ul style="list-style-type: none"> • does it include representatives of the private sector – industry, NGOs? 				
<ul style="list-style-type: none"> • does it focus on all research or is it restricted to certain types (operational, epidemiologic)? 				
<ul style="list-style-type: none"> • is it linked formally with other countries in the region to foster TB/ health research? 				

Domain	Questions / assessment	Yes/No	Yes - to be strengthened	No - to be established
	<p>3. Has a national TB research plan been developed? [If yes - please attach document/report]</p> <p><i>If yes:</i></p> <ul style="list-style-type: none"> • does it include the following aspects? <ul style="list-style-type: none"> • training • funding • development of networks • priority setting • was the plan developed through a 'multi-stakeholder' process? • is there a process for regular review and revision of this plan? <p><i>If yes at what frequency:</i></p>			
	<p>4. Have national TB research priorities been established?*</p> <p><i>If yes:</i></p> <ul style="list-style-type: none"> • by what group? (list stakeholders who were involved) • in what year? 			
RESEARCH CAPACITY	<p>5. How many full-time TB researchers are there in the country?</p> <p>0 1-9 10-19 20-29 30-49 50 or more</p> <ul style="list-style-type: none"> • please list by categories (public institutions, private institutions, pharmaceutical industry, detached/seconded, others) 			

Domain	Questions / assessment	Yes/No	Yes - to be strengthened	No - to be established
RESEARCH CAPACITY	<p>6. Are there institutions within the country that have physical facilities and human resources to conduct TB research?</p> <p><i>If yes:</i></p> <ul style="list-style-type: none"> • how many are there, based in the following? <p>universities:</p> <p>research institutes:</p> <p>TB programmes/public health programmes:</p> <p>Other (specify):</p> <ul style="list-style-type: none"> • how many are considered national centres for TB research? 			
RESEARCH TRAINING	<p>7. Do any national universities offer graduate training in health research?</p> <p><i>If yes:</i></p> <ul style="list-style-type: none"> • at Master's level? • at PhD level? • are any of these specifically targeted to TB research? • is there graduate-level training in clinical/epidemiological/bio-statistical research? • is there graduate level training in basic research (e.g. molecular biology, genetics, immunology)? <p>8. Are there formal links between the TB programme and national universities/institutes for graduate-level research training?</p> <p><i>If yes: with which universities:</i></p>			

Domain	Questions / assessment	Yes/No	Yes - to be strengthened	No - to be established
RESEARCH FUNDING	9. Is there a mechanism for national (public) funding of operating funds for TB research (to which health research and TB researchers may apply)?			
	<i>If yes:</i>			
	<ul style="list-style-type: none"> • is the mechanism competitive and peer-reviewed? 			
	<ul style="list-style-type: none"> • is the competition: annual/twice a year/other? 			
	<ul style="list-style-type: none"> • for how many years has this funding mechanism been in place? 			
	<ul style="list-style-type: none"> • what is the total value awarded annually (amount and currency)? 			
	<ul style="list-style-type: none"> • what is the source of funding (ministry/national agency providing funding)? any other ministry? <i>If yes, specify</i> 			
<ul style="list-style-type: none"> • is there any other mechanism? <i>If yes, specify</i> 				
	10. Are there other sources for health (or TB specifically) research funding?			
	<i>If yes, specify</i>			
	11. Is there national funding for TB research infrastructure (facilities, equipment, human resources)?			

Domain	Questions / assessment	Yes/No	Yes - to be strengthened	No - to be established
	<p data-bbox="411 353 745 488">12. Is there a national (public) programme explicitly for salary support of TB researchers (or health researchers)?</p> <p data-bbox="411 521 485 555"><i>If yes:</i></p> <ul data-bbox="411 566 745 1529" style="list-style-type: none"> <li data-bbox="411 566 745 723">• is it based in universities or research institutes (i.e. block funding to these institutions who then hire researchers on contract)? <li data-bbox="411 734 745 835">• is this national competitive funding for salary support for TB/health researchers? <li data-bbox="411 846 745 902">• is the mechanism open and peer-reviewed? <li data-bbox="411 913 745 992">• is the competition: annual/twice a year/other? <li data-bbox="411 1003 745 1081">• for how many years has this funding mechanism been in place? <li data-bbox="411 1093 745 1171">• what is the total value awarded annually (amount and currency)? <li data-bbox="411 1182 745 1305">• which ministry or department is providing funding? <li data-bbox="411 1317 745 1417">• any other ministry or department? Specify: <li data-bbox="411 1429 745 1529">• other mechanism or department? Specify: <p data-bbox="411 1574 692 1686">13. Is there national funding to support TB (or health) research training?</p> <p data-bbox="411 1720 485 1753"><i>If yes,</i></p> <ul data-bbox="411 1765 745 1977" style="list-style-type: none"> <li data-bbox="411 1765 745 1798">• at Master's level <li data-bbox="411 1809 745 1843">• at PhD level <li data-bbox="411 1854 745 1921">• only at national universities (in-country training) <li data-bbox="411 1933 745 1977">• at national and international universities 			

Domain	Questions / assessment	Yes/No	Yes - to be strengthened	No - to be established
	<p>14. Is there funding available from national industries (drugs/diagnostics/vaccines) to support TB research?</p>			
	<p>15. Does the country receive funding from the Global Fund?</p>			
	<p><i>If yes:</i></p> <ul style="list-style-type: none"> • since what year? • what is the amount for TB? (specify average amount annually, and currency) • is there any funding allocated for TB research in the current Global Fund award? 			
	<p><i>If yes: How much? (specify average annual amount in past 5 years, and currency):</i></p>			
	<ul style="list-style-type: none"> • what percentage of total Global Funds disbursed in the country go to TB research? • is this only for operational research? • if other types of research – specify: 			
	<p>16. Are there other substantial and regular external sources of research funding?</p>			
	<p><i>If yes:</i></p> <ul style="list-style-type: none"> • specify source(s) • average annual amount and currency (if known): 			



MEMBERSHIP AND LEADERSHIP OF THE NATIONAL TB RESEARCH NETWORK

This network should be as inclusive and multi-disciplinary as possible. It should include researchers from a broad range of disciplines (such as clinical, operational, epidemiology, genetics, and immunology). Representatives from universities, research institutions, biomedical associations and government agencies such as public health officials, especially TB programme managers, should be included. Representatives of nursing and other allied health professions should be invited, as well as community and civil society representatives and NGOs. Representatives of the private sector including practitioners and industry should also be invited to participate. The NTP should consider designating someone within the programme to be a TB research focal point; this person should receive training or have a background in research.

The network should also include researchers and institutions from other countries involved in collaborative research activities, as well as donors. Links with TB research networks in other countries should be encouraged or reinforced to create regional networks and foster regional projects in TB research. The network could also be usefully linked to international TB research networks addressing specific disciplines or research themes.

Representatives from different groups should initially be appointed for three to four years and then encouraged to rotate, allowing other persons from their institution or group to participate in the network. Leadership of the network should be rotated regularly and often (for example every two years). It is suggested that leadership should alternate between members from different groups to ensure all major groups are represented at the leadership level. This is best done by writing a brief 'constitution' outlining rules of leadership, and by a leadership vote open to all members of the network.

ACTIVITIES AND RESPONSIBILITIES OF THE NETWORK

In general, the activities of the network will be aligned with its objectives. Each country will have to develop its own terms of reference and mode of operations for the network. The frequency and duration of meetings will depend on practical issues such as resources to support these activities.

To address the specific objectives listed above, the following activities are suggested:

1. Coordinate TB research:

Organization of regular meetings assembling all members of the network who will provide updates on their activities. At

least one scientific meeting annually should be organized to disseminate research results by network members to all other members and discuss scientific questions of interest. Particular emphasis should be placed on presenting results of projects that are cross-cutting or judged likely of interest to others within the network.

2. Facilitate collaboration between different partners, stakeholders and disciplines:

As part of the network's meetings and with the help of the Secretariat, ensure that all members of the network are aware of any potentially relevant call for proposals from national and international sources. Encourage collaboration in responding to these calls. Advocate with policy-makers on the importance and value of multi-disciplinary research (to encourage funding of this type of research).

3. Advocate for increased support for TB research:

Develop strategies to raise awareness at all levels of government and among private funders on the value of health research, and especially TB research. Develop case studies where research findings were applied to clinical practice and led to health or financial benefits.

4. Participate in strategic planning:

An important activity is to assist in the development of the National TB Research

Plan. Even before this can be started, an inventory of TB-related research is needed. The network should be involved, at least in an advisory role, in this activity. Once the inventory is completed and the TB research plan developed, the network will participate in the development of detailed country-specific TB research priorities.

5. Participate in monitoring and evaluation:

The network will also carry out updates of the National Strategic Plan and the research priorities through regular reviews. Revisions should be performed, at minimum, every five years.

RESOURCES FOR THE NETWORK:

Network activities revolve primarily around meetings and communication.

While it is best that members pay their own way to meetings, this may lead to under-representation of certain groups, particularly civil society. As a result, a minimum of funding will be required to support attendance at meetings, and ideally some additional funds for the necessary administrative support for the meeting's organization, correspondence, minutes, etc. This should, however, be seen as a rather low-budget activity to which members volunteer their time and, where possible, their travel.

