FUNDAÇÃO PARA O DESENVOLVIMENTO CIENTIFÍCO E TECNOLÓGICO EM SAÚDE (FIOTEC)

TOWARDS ELIMINATION OF CONGENITAL TRANSMISSION OF CHAGAS DISEASE IN LATIN AMERICA

EXPECTED PROJECT DATES: 1 MAY 2021 – 31 OCTOBER 2025

Annex 1

Project Plan

Version number: 1.5

Version date: 17 March 2021

Consortium Logos:

Ministério da Saúde

FIOCRUZ
Fundação Oswaldo Cruz

INLASA

INSTITUTO NACIONAL DE SALUD

SENEPA

FIND

CONTENTS

LIST OF ABBREVIATIONS

Please ensure that all abbreviations used in the Project Plan are listed in this section.

ANVISA	Brazil National Health Surveillance Agency
API	Active pharmaceutical ingredients
BZN	Benznidazole
CAB	Community advisory board
CCSE	Community and civil society engagement
CD	Chagas disease
CIRD	Centro de Información y Recursos para el Desarollo
CRF	Case Report Form
CRIS	Centro de Relações Internacionais em Saúde
CS	Civil Society
CSO	Civil society organization
CUIDA Chagas	Comunidades Unidas para Innovación, Desarrollo y Atención para la enfermedad de Chagas; Comunidades Unidas para Inovação, Desenvolvimento e Atenção para a doença de Chagas
DALY	Disability adjusted life year
DNA	Deoxyribonucleic acid
DNDi	Drugs for Neglected Diseases initiative
EAB	External advisory body
EC	Executive committee
ELISA	Enzyme-Linked Immunosorbent Assay
EMTCT	Elimination of mother-to-child transmission
ERB	Ethical Review Board
FDA	Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
FINDECHAGAS	International Federation of Associations of People Affected by Chagas disease
Fiocruz	Fundação Oswaldo Cruz
Fiotec	Fundação para o Desenvolvimento Científico e Tecnológico em Saúde
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HSR	Human Subject Research
IEC	Information, education and communication
IFF	National Institute of Health of Women, Children and Adolescents Fernandes Figueira
IFI	Indirect immunofluorescence
INI	Evandro Chagas National Institute of Infectious Diseases
INLASA	Instituto Nacional de Laboratorios de Salud "Néstor Morales Villazón"
INS	Instituto Nacional de Salud de Colombia
IP	Intellectual property
LAFEPE	Laboratório Farmacêutico de Pernambuco
LMICs	Low- and middle-income countries
LTA	Long-term arrangements
M&E	Monitoring and Evaluation
MCH	Maternal and child health
MoH	Ministry of Health
MoU	Memorandum of Understanding
MSPBS	Ministry of Health and Social Welfare
MSPS	Ministry of Health and Social Protection
MSyD	Ministry of Health and Sports

NFX	Nifurtimox
NGO	Non-governmental organization
NHR	Netherlands Hanseniasis Relief
NTD	Neglected Tropical Disease
PAHO	Pan American Health Organization
PCR	Polymerase chain reaction
PHC	Primary health care
PI	Principal investigator
PMIS	Pharmaceutical management information system
PoC	Point of care
PDA	Plano de Dados Abertos - Open Data Plan
PSM	Procurement and supply management
QALY	Quality adjusted life year
RDT	Rapid diagnostic tests
RFPC	Rede Fiocruz de Pesquisa Clínica - Fiocruz Clinical Research Network
RMNCH	Reproductive, maternal, newborn and child health
RNPC	Rede Nacional de Pesquisa Clínica – National Clinical Research Network
SBCC	Social behaviour change communication
SDGs	Sustainable Development Goals
SME	Small and Medium Enterprises
SENEPA	Servicio Nacional de Erradicación del Paludismo
SOP	Standard operating procedures
STI	Sexually transmitted infection e.g. syphilis
T. cruzi	*Trypanosoma cruzi*
ToR	Terms of Reference
UHC	Universal health coverage
UMICs	Upper- and middle- income countries
UNDP	United Nations Development Programme
WCBA	Women of childbearing age
WHF	World Heart Federation
WHO	World Health Organization

EXECUTIVE SUMMARY

Chagas disease (CD) is a neglected tropical disease (NTD) that mainly affects poor and vulnerable populations in endemic countries in Latin America. Untreated, a significant number of patients will develop severe and sometimes life-threatening clinical complications. Due to the relative success of measures to control vector and transfusion transmission, congenital transmission has become proportionally more relevant in these areas, in addition to being the main source of new cases in non-endemic countries. According to estimates from the World Health Organization (WHO), 6 to 7 million people are infected worldwide, of which 1.12 million are women of childbearing age. An estimated 8,000-15,000 infected babies are born each year in Latin America. Several international strategies and action plans like the elimination of mother-to-child transmission (EMTCT) initiative from the Pan American Health Organization (PAHO) and the road map for neglected tropical diseases from the WHO have been launched to achieve the elimination of congenital transmission of CD, but many countries do not yet have proper programs in place. The barriers impeding access to health-related services for this NTD are profound, especially when it comes to congenital transmission. Endemic countries often do not have adequate reproductive, maternal, newborn and child health (RMNCH) services in place, nor do they systematically carry out congenital transmission surveillance, which results in underestimated data on CD prevalence in pregnant women and newborns. Current treatment options are not recommended during pregnancy, highlighting the need to treat women before they become pregnant. Scarcity of diagnostic tools and treatment options, poor treatment adherence, a lack of knowledge and understanding among health providers and people at risk, socio-economic vulnerabilities of endemic areas, and low social mobilization only aggravate the problem, as does the current COVID-19 pandemic. CD patients are at a greater risk of complications due to COVID-19, and time and resources that have been shifted away from primary health care to attend to the effects of the pandemic has meant an even further decrease in attention for NTDs such as CD. The COVID-19 pandemic has impacted the countries in the region in different ways and to different degrees. The project will establish the necessary monitoring and mitigation actions to be able to adjust to the changing circumstances and its execution will be adapted to local conditions and regulations for COVID-19.

This consortium consists of key players in the public health landscape from Bolivia, Brazil, Colombia and Paraguay, and is endorsed by the ministries of each respective country. The selection of countries was finalized following extensive consultations with key stakeholders and is based on factors beyond disease burden, such as replicability, potential impact on regional sustainable change, and political commitment. Led by Brazil's Fiotec/Fiocruz, the consortium includes other government organizations as implementers such as Instituto Nacional de Laboratorios de Salud "*Néstor Morales Villazón*" (INLASA) from Bolivia, Instituto Nacional de Salud (INS) from Colombia, Servicio Nacional de Erradicación del Paludismo (SENEPA) from Paraguay, and the international non-governmental organization Foundation for Innovative New Diagnostics (FIND). The project will be implemented in a total of 32 municipalities in Bolivia (10), Brazil (5), Colombia (12) and Paraguay (5), selected by the four countries according to public health priorities, ensuring geographically and epidemiologically diverse contexts, with primary health care (PHC) as the central focus of interventions, integrating with existing initiatives most relevant to each country context, such as health and vaccination campaigns and EMTCT-plus. The most cost-effective strategy to reduce congenital cases is the etiological treatment of women of childbearing age before pregnancy, the target population of this project. Approximately 234,000 women of childbearing age, their infants and children and their household contacts will be actively and systematically tested throughout the duration of the project.

Through a combination of implementation and innovation research, this project, co-funded by MoH Brazil, will seek to present a comprehensive and integrated approach to address its **goal** of contributing to the elimination of congenital transmission of Chagas disease by scaling up and enhancing access to diagnosis, treatment and comprehensive care, through innovative and sustainable approaches in Bolivia, Brazil, Colombia and Paraguay. This goal will be achieved through two **outcomes**: (i) increased access to and demand for effective diagnostics, treatment, and care for CD, and (ii) improved diagnostic tools and treatment options validated, and access conditions ensured. These outcomes will be achieved through carefully designed activities under five **outputs**: (i) evidence generated on effective test, treat, and care approaches through implementation research, (ii) community and civil society engaged at local, national and regional levels to increase demand for services and advocate for integration of recommended approaches for Chagas disease in policies, strategies and plans, (iii) diagnostic algorithms validated for chronic and congenital CD, (iv) evidence generated on improved treatment options, and (v) market shaping and supply chain interventions to ensure equitable access to innovative products. Throughout its implementation, the project will work with project and non-project national programs and initiatives, PAHO and WHO to generate evidence towards national, regional and global recommendations and guidance. PAHO will support the project through an 'enabler grant', under Unitaid's direct oversight. Their role will be to participate in research protocol consultations in order to ensure that the planned research addresses key evidence gaps, accelerate policy development and access to new products, technologies and approaches emerging from the project and other on-going research under the same scope, and amplify public health impact within project countries and beyond through evidence dissemination & guideline development.
The project will have a total budget of approximately 19 million USD, and will be financed by Unitaid (15 million USD) and the Brazilian MoH (4 million USD). The Brazilian co-funding has been assigned solely to the Brazil budget, and include all expense groups under output 2 and 5, expense groups 3, 4, 5 and 6 under all outputs and expense group 1 under output 1. In addition, three project staff members under output 0 have been included in the co-funding.

The CUIDA Chagas project (**C**omunidades **U**nidas para **I**nnovación, **D**esarrollo y **A**tención para la enfermedad de Chagas / **C**omunidades **U**nidas para **I**novação, **D**esenvolvimento e **A**tenção para a doença de Chagas) will commence with a six month inception phase, where it will focus on preparatory and ethical-regulatory activities, such as: setting up the central and local teams, establishing the different external advisory board (EAB) and the community advisory board (CAB), develop human subject research (HSR) standard operating practices (SOPs), submit the research protocols for ethical approval, develop the equitable access landscape and strategy, establish procurement memoranda of understanding (MoU) with each consortium country and the PAHO strategic fund, develop procurement and supply management (PSM) plans for each country, and initiating the formative research in each of the project territories to identify important stakeholders on local, provincial/state and national levels and existing social behavior change communication (SBCC) as well as community and civil society engagement (CCSE) tools and approaches. An assessment will be made of COVID-19 situation in all project countries to confirm that project activities can start and be fully implemented as planned or have to be reprogrammed. In addition, during this inception phase, the different study sites will be prepared and project staff will be trained.

In order to achieve **output 1**, the project will conduct implementation research in each of the 32 territories selected by the countries' MoH. The diagnostic and treatment guidelines of each country will be followed, allowing the expansion of access through the updated integral strategy of 'test, treat and care' in the local existing structure of PHC, ensuring the use of rapid diagnostic tests (RDT) for screening chronic CD patients, polymerase chain reaction (PCR) to diagnose congenital CD cases, and

the provision of counseling services by capacitated health professionals. Formative studies will be carried out in each territory, in order to better understand the local context, design context appropriate interventions and assess the performance of the local health system, the influence of socio-demographic descriptors and the existence of systemic and psychosocial barriers. Health professionals will be trained on the integrated theme of RMNCH, provision of pre- and post-counseling services, and the use of (new) diagnostic algorithms and treatment schemes as well as CD surveillance, clinical management and counseling, parasitological diagnosis and molecular biology. The 'test, treat and care' service provision will be piloted and a monitoring and evaluation protocol specific to the implementation research will be generated in order to demonstrate the effectiveness of these interventions. Output 1 will have a Unitaid investment of approximately 6.2 million USD and an investment of the Brazilian MoH of approximately 1.4 million USD.

In order to achieve **output 2** local, national and international civil society (CS) will be mapped, as part of the formative research, and strategies for improved networking will be developed. CS is critical for both the success of the project as well as the sustainability of the outcomes, which is why they will be engaged from the beginning through the community advisory board (CAB) and specific project activities. Information, education and communication (IEC) strategies and campaigns will be developed for each country that are contextualized to different territories and target groups, and where relevant include the broader group of communicable diseases included in the EMTCT-plus strategy. Local leaders will be trained on detection of CD signs and symptoms, potential adverse reactions of treatment and the need for referral to primary care posts, and a leadership training with community leaders and civil society organizations representatives will be conducted on interrelated modules with the aim of strengthening their capacity to represent their communities and influence policies. Output 2 will have a Unitaid investment of approximately 900,000 USD and an investment of the Brazilian MoH of approximately 850,000 USD.

To achieve **output 3 and 4**, innovation protocols have been developed for three of the four countries included in this consortium (Bolivia, Brazil and Colombia) with the aim of overcoming barriers to obtain diagnosis and treatment. Diagnosing the different forms of CD is complex and results in limited access to treatment; e.g., (i) chronic CD (women of childbearing age, pregnant women and the general population) requires at least 2-laboratory based tests, and (ii) congenital CD diagnosis requires a diagnostic algorithm combining direct parasitological exams at birth and 2-serologies over a 9-12 months period, when there are no more antibodies from the infected mother. For chronic CD, RDTs provide only screening information and have not been widely implemented in public health systems in Latin America. The performance of the RDTs vary across endemic regions due to *Trypanosoma cruzi*'s genetic variability and local prevalence. Evidence suggests that RDTs could simplify algorithms for diagnosis of chronic CD in PHC, however, this requires additional validation. The project will therefore conduct a study to demonstrate that RDT-based algorithms (single or multiple tests) can be implemented to diagnose chronic CD at health care facilities, as an alternative to the current (laboratory-based) diagnostic algorithms, considering the *T. cruzi* genetic variability and the epidemiological diversity in Chagas endemic regions. In addition, the project will implement a new algorithm in the pilot 'test, treat and care' service provision for the diagnosis of newborns based on PCR. Currently, diagnosing CD in newborns is complex and usually only possible at the end of the first year of life. This leads to loss of follow-up as many families do not return to the health center. The access to PCR in the first trimester of life reduce losses from follow-up and providing more treatments.

Another important barrier is related to current treatment regimens, which are lengthy (60 days) and entail frequent side effects, causing approximately 20% of patients to drop out of treatment,

discouraging others from starting. A shorter treatment regimen has the potential to greatly increase treatment adherence, which is why this project will conduct a double-blind, phase III study, where 918 patients will be randomly assigned to receive the standard-dose of benznidazole (300 mg daily for 60 days) regimen or the short experimental regimen (300 mg daily for 2 weeks). Efficacy will be assessed considering a non-inferiority design and through the detection of parasite DNA through molecular biology (PCR). Meanwhile, safety will be evaluated through a superiority design, with the aim of finding the new regimen as effective as the standard one, but superior in terms of safety. The study population will include adult patients of 18 years or older, who have been diagnosed with chronic Chagas disease in its indeterminate or mild cardiac form, and who have received a positive diagnosis through two serological assays. The trial will be conducted in a total of seven sites, in Bolivia (2), Brazil (2), and Colombia (3). The primary endpoint will be parasitological response determined as sustained negative qualitative PCR from the end of treatment until 24 months of follow-up. The proportion of patients with positive qualitative PCR will also be measured at 6, 12, 18, and 24 months from end of treatment. The frequency of adverse events leading to treatment discontinuation will be compared. Outputs 3 and 4 will have a Unitaid investment of approximately 4 million USD and an investment of the Brazilian MoH of approximately 750,000 USD.

All the proposed (innovation) strategies aim to shorten the time that is needed for diagnosis and treatment, thereby lowering the costs and making strategies more accessible and cost-effective. This will increase access to dedicated health care at primary level, covering a larger population, reducing losses in follow-up, and increasing case detection, while at the same time providing patients with proper care. A cost-effectiveness study evaluating both new implementation strategies and innovation protocols will be conducted to provide additional evidence that will feed into strategies for scale up of the project's interventions and recommendations. Furthermore, product landscape assessments and other market preparatory activities will be conducted to inform the development of product roadmaps that contain manufacturing/supply-side information, suggested go-to-market strategies in each country, regulatory pathway and procurement strategies, with the aim to reach **output 5**. Output 5 will have a Unitaid investment of approximately 480,000 USD and an investment of the Brazilian MoH of approximately 130,000 USD.

Throughout the project's development period regional collaboration will be strengthened and stimulated, not only between countries included in this project but also with other countries endemic for CD and those where CD forms a public health challenge. The project will undertake a stakeholder mapping on regional and global level, in order to better understand the different players that will need to be influenced in order for the project's results to be further scaled up and promote peer exchanges between government officials, health professionals or civil society organizations through collective advocacy campaigns. Stakeholders will be convened from the start of the project to ensure optimal alignment and strong collaboration. A collaboration platform will be established to provide template protocols, communication and advocacy materials, SOPs, lessons learned and all relevant tools for non-project countries to consult or adapt, in an effort to catalyze the project's scope. The last nine months of the project will be reserved for result dissemination with the aim of updating national, regional and global guidelines to include the project's interventions and/or best practices.

By the end of this project, this consortium together with Unitaid will have made significant strides towards elimination of congenital transmission of CD in Latin America, producing solid evidence and scalable solutions to tackle this particular public health problem. The project's indirect impact is projected to enable treatment of an additional 131,400 people in the five years following the project, preventing 31,600 cases of cardiomyopathy and 5,005 future congenital infections, with savings to the

health systems of the four countries of USD 203 million in net annual healthcare costs, and a reduction in annual disability adjusted life years (DALYs) of >53,820. However, these reductions cannot be achieved without first validating the effectiveness of new diagnostic and therapeutic tools and piloting test, treat and care models in different contexts. This project therefore represents the first necessary and important step toward achieving elimination of congenital transmission of CD.

1. PROJECT RATIONALE

Chagas disease (CD), a neglected tropical disease (NTD) also known as American trypanosomiasis, is a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*). *T. cruzi* parasites are mainly transmitted through contact with feces/urine of infected blood-sucking triatomine ('kissing') bugs. Other forms of transmission include: consumption of contaminated food; transmission from an infected mother to her newborn during pregnancy or childbirth; blood or blood product transfusion from infected donors; organ transplants using organs from infected donors; and laboratory accidents. (1) CD has an acute phase, which can last up to a few weeks or months and is usually mild or asymptomatic, and a chronic phase. An estimated 30-40 % of infected people will develop severe and sometimes life-threatening medical problems over the course of their lives, including cardiac alterations, digestive manifestations, and neurological or mixed alterations, which may require specific treatment. If untreated, infection is lifelong. (2)

CD is mainly found in endemic areas of 21 continental Latin American countries, with approximately 65 million people at risk of contracting the disease. An estimated 6 to 7 million people worldwide are infected with the *T. cruzi* parasite, of which the large majority resides in Latin America. Every year, over 10,000 CD-related deaths are reported. (1,3,4) Symptomatic CD imposes a substantial financial burden on healthcare systems and societies. (5) With an estimated USD 690 million in healthcare costs and USD 8 billion in annual economic losses, the CD economic burden equals or exceeds that caused by other prominent infectious diseases, such as zika (USD 3.7 billion). (6,7) However, despite the high morbidity and mortality of CD and the significant associated economic burden, only 7% of people with CD have been diagnosed and only about 1% receive etiological treatment. (8) Timely identification and treatment of CD has important benefits, including prevention of future congenital transmission in treated mothers, serological cure in infants and children, and reduction of progression to advanced forms of the disease in adults. (9–13) However, once the disease has progressed to an advanced phase with severe cardiac or digestive disease, etiological treatment does not appear to have clinical benefits. (14) This supports the need for improved diagnostics and early access to safe and effective treatment. (15) An estimated 1.12 million women of childbearing age are infected with the *T. cruzi* parasite (4), and the congenital transmission rate approaches 5%, with higher rates in high-risk endemic areas. (16) Congenital infection could perpetuate CD indefinitely, even in countries without vector transmission. (17) The incidence of congenital *T. cruzi* infection is an estimated 8,000 to 15,000 cases per year in Latin America. (18) In the wake of progress in vector transmission control, congenital transmission has become proportionately more relevant, accounting for about one-third of new infections in 2010. As maternal and child health (MCH) services do not routinely screen mothers or newborns for CD in most endemic areas, prevalence in pregnant women and newborns may be underestimated. Efficacy of treatment in congenitally infected infants exceeds 90%, preventing morbimortality in babies and future chronic stages of the disease. (19) *T. cruzi* infection is curable if treatment is initiated soon after infection, which is why the screening of newborns and children of infected mothers that have not yet received antiparasitic treatment has become an essential strategy. The benefits of universal screening for *T. cruzi* as part of routine prenatal testing in endemic countries far outweigh the program costs. In a recent study, maternal screening, infant testing, and treatment of CD are cost saving for all rates of congenital transmission greater than 0.001% and all levels of maternal prevalence above 0.06%. Rapid diagnostic tests make universal screening cost-saving with maternal prevalence as low as 0.008%. (20) However, the most cost-effective strategy is the etiological

treatment of women of childbearing age before pregnancy, which would allow for a reduction of congenital cases.

Despite diverse geographical, socio-economic and cultural contexts, several common barriers impede effective and efficient diagnosis, treatment, and aftercare of persons affected by CD. These barriers are: a lack of verified data on the burden of CD; a lack of integrated actions on surveillance, control and care at primary health care level; geographic distance of patients from facilities; an often cumbersome, time-consuming and costly diagnostic process; a lack of integration in reproductive, maternal, newborn and child health (RMNCH) policies and practices; a disproportionate impact of the disease on vulnerable populations; limited knowledge on CD in both the general population as well as health professionals; limited media attention; limited health education initiatives; limited availability of tools and materials at (peripheral) health centers; fear; stigma and discrimination against persons affected by CD; low social mobilization; and a limited political voice of persons at risk of CD. (21,22)

Access to diagnosis is the main barrier to CD treatment. This is key in preventing congenital transmission as (i) diagnosing and treating girls and women in endemic areas before pregnancy significantly reduces the risk of congenital transmission, (ii) diagnosing *T. cruzi* infection in pregnant women allows for early screening for infection in the newborn and (iii) diagnosing *T. cruzi* infection in children born to infected mothers allows for the implementation of a highly efficacious and safe treatment. However, diagnosing the different forms of CD is complex. As an infected mother's antibodies to *T. cruzi* can persist in her infant for up to 9–12 months, serologic testing has major drawbacks for detecting congenital infection in neonates. Current methods miss a substantial number of congenital CD cases. Although rapid diagnostic tests (RDTs) have been developed for CD, they provide only screening information, and have not been widely implemented in public health systems, nor are they recommended in national or regional guidelines in Latin America. These complexities result in limited access to and demand for treatment as chronic CD requires at least 2-lab based serological tests and congenital CD diagnosis requires implementing a diagnostic algorithm combining microscopy at birth and serology over a 9-12 months period. Polymerase chain reaction (PCR) in the first trimester of life increases the sensitivity of the diagnosis of congenital CD. However, PCR is not a widely available tool and is usually not accessible in primary health care. Evidence suggests that new point of care (PoC) tools could simplify algorithms for diagnosis of CD in primary health care through the use of two RDTs, but this requires additional validation.

The treatment landscape for CD is plagued by a multitude of barriers preventing widespread access. There are only two drugs available for the treatment of CD, benznidazole (BZN) and nifurtimox (NFX). Both drugs have been proven to be effective in treating patients for acute disease, reactivation in immunosuppressed hosts, congenital disease, and most cases undergoing chronic phase of infection. However, both drugs require long periods of administration (60 days for BZN and 60-90 days for NFX) which causes frequent unwanted drug-related adverse reactions and treatment discontinuity. (23) These side effects add to affected persons' and physicians' reluctance to initiate treatment in the first place. Extensive laboratory monitoring is required, which can add to patients' out-of-pocket costs, and side effects can limit patients' ability to work or care for children. In addition, neither drug can be administered to pregnant women or patients in the late stage of the disease with severe cardiac or digestive disease. In many countries, BZN is the preferred first line of treatment because of its lower incidence of adverse events and shorter treatment duration. (24) Recent evidence suggests that a shorter 15-day treatment course of BZN would have the same effectiveness as the regular treatment course, but with less adverse effects. (25) However, the results of this study should be verified through an additional clinical trial. BZN is produced by two companies: Elea-Phoenix, an Argentine

pharmaceutical company (26), and Laboratório Farmacêutico de Pernambuco (LAFEPE) (27), a Brazilian public enterprise. The Elea-Phoenix adult and pediatric formulations are registered at the Food and Drug Administration (FDA) and in several Latin American countries (excluding Brazil), while the adult and pediatric versions of the LAFEPE product are approved for use in Brazil by its National Health Surveillance Agency (ANVISA). Based on the last Pan American Health Organization (PAHO) Strategic Fund tender, the cost of the Elea-Phoenix product is USD 90 ex-works for a complete adult 60-day treatment. The cost for the LAFEPE product is USD 65 ex-works for the same treatment duration in the adult version. NFX is produced by Bayer, and donated annually to the PAHO strategic fund, therefore being the preferred treatment in a number of countries despite its higher frequency of side effects. (28) Despite being registered in most countries in the Americas, BZN and NFX are not routinely available in sufficient quantities at primary healthcare facilities for several reasons, ranging from suboptimal ordering patterns, repressed demand, limited supply/production, and in-country supply chain issues.

Bolivia, Brazil, Colombia and Paraguay are all countries where CD remains a key public health challenge. Bolivia has the highest (6.1%) and Paraguay the third highest (2.1%) prevalence of CD in the world, accounting for an estimated number of 791,855 people (see Table 6 in chapter 5). (29) In Brazil and Colombia, despite lower national prevalence, there are an estimated 1.66 million people living with *T. cruzi* infection. The four countries combined have an estimated number of 3,015 congenital CD infections per year, however, only Bolivia and Paraguay have a significant historical experience with a national program addressing congenital transmission. (29) In all four countries, the disease is concentrated among vulnerable populations including rural-urban and transnational migrants, the rural poor, and indigenous communities. While they have made significant advances in vector control and transmission through blood transfusions or transplants, and have to some extent implemented national surveillance programs for CD, congenital transmission remains a neglected area. (30) However, health authorities in each country have manifested a strong willingness to participate in a collaborative project to eliminate congenital transmission. Through the diversity that is included in project, both in terms of differing health systems, as well as geographical and populational diversity, in combination with the regional collaboration initiatives, this project will be able to provide best practices and lessons learned that can be replicated to other contexts.

Global and Regional Chagas disease priorities and project alignment

On the 24th of May 2019, at the 72nd session of the World Health Assembly, the World Chagas Disease Day was instituted. World Chagas Day is now one of 11 World Health Organization (WHO) global public health campaigns, which provides a great opportunity to raise awareness on the disease, and recognizing it as an international public health problem. This recognition provides the perfect opportunity for the development and execution of this project. In addition, WHO, in their newly presented NTD Roadmap, has identified three critical actions for the elimination of CD (31):

Critical action 1: Advocate with high-level national ministries to recognize CD as a public health problem, and establish effective prevention, control, care and surveillance in all affected territories.
Critical action 2: Improve medical care for CD, from training health care workers in-service to integrating training at all levels of health services.
Critical action 3: Ensure that countries in which domiciliary vector transmission is still registered in certain territories comply with prevention, control and surveillance.

PAHO, in their framework for elimination of mother-to-child transmission (EMTCT) of Human Immunodeficiency Virus (HIV), Syphilis (STI), Hepatitis B (HBV) and Chagas disease (32), has identified the following lines of action:

Line of action 1: Integrate HIV/STI/HBV/Chagas interventions within sexual and reproductive health, antenatal care, maternal and child health, and family and community health policies, programs, and services.
Line of action 2: Intensify strategic information on HIV, syphilis, HBV, and Chagas disease in maternal and child health services.
Line of action 3: Improve the laboratory network and quality and supply chain management.

Although access to prenatal care and childbirth for pregnant women is high in the context of the Americas, problems persist in relation to screening for mother-to-child transmission diseases, which requires the integration of surveillance actions with those of care. Recommended interventions to control congenital CD are available in all endemic countries, but data on health service coverage are limited. Based on the limited information from a few countries that reported to PAHO, screening for CD in pregnant women varies widely from just over 5% to almost 60% among the few countries that have reported it. (32)

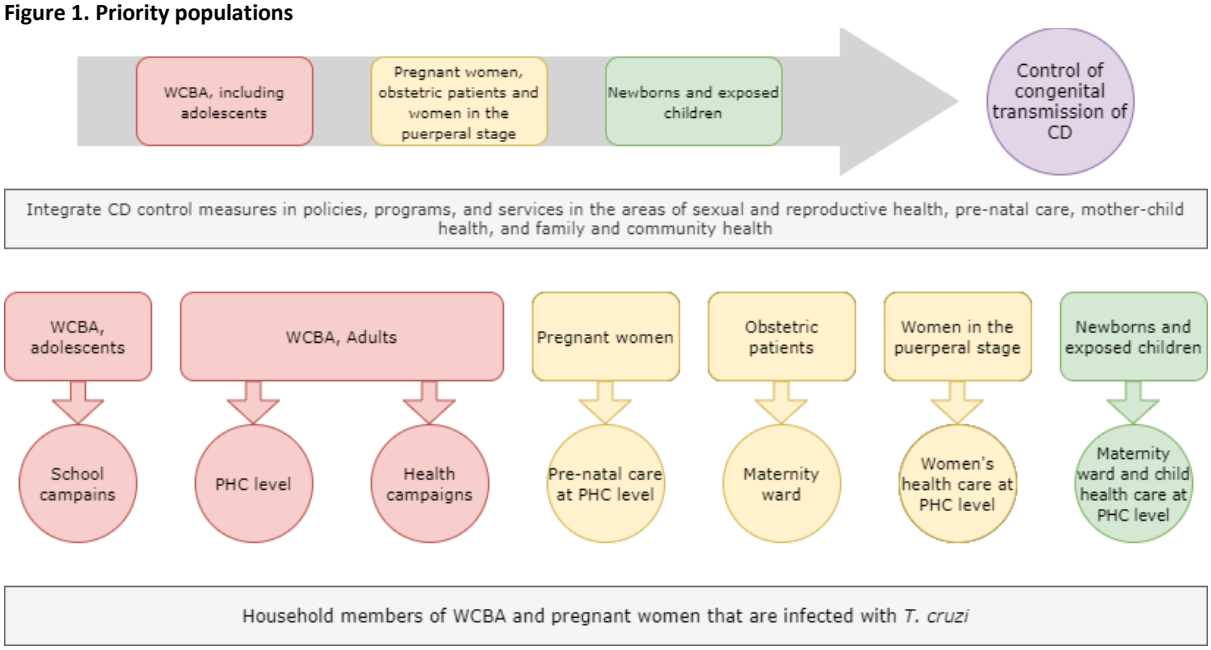
Strategic actions for the elimination of congenital CD should be focused on prenatal, childbirth, puerperium and monitoring of the mother-child binomial. Just like the prevention of congenital syphilis, HIV or hepatitis B, the early diagnosis of the pregnant woman during prenatal care, timely treatment (when indicated), definition of the safest way of delivery, laboratory and clinical investigation of the newborn with treatment and surveillance of partners and other children are necessary routines to be carried out by reproductive, maternal, neonatal and child health systems in an integrated manner with primary health care. For HIV infection and syphilis, despite this high screening coverage, no progress has been made in recent years, which has generated stability in mother-to-child transmission of HIV and a consistent and paradoxical increase in syphilis. This fact reinforces the importance of seeking even more consistent and integrated strategies for disease control for this mode of transmission. (32)

According to the EMTCT plus initiative, the elimination of CD as a public health problem is defined as ≥90% of infected children treated, cured and supported by screening, ≥90% of pregnant women in prenatal care and treatment after delivery, and ≥90% testing on exposed neonates (with *T. cruzi* seropositive mothers), milestones that have not yet been achieved in any Latin American country. As part of the implementation of the EMTCT plus initiative, Latin American countries are encouraged to review and update their information systems to monitor the programmatic indicators for CD control. This scenario opens a window and provides an additional and excellent opportunity for the development of this project, with a view to contribute to decision-making based on the best available evidence, within real scenarios.

To achieve these goals, a robust interprogrammatic planning for these diseases with strategic interventions at different levels of national health systems must be developed, with the objective of eliminating preventable communicable diseases, as described in Figure 1. In the case of CD, the following interventions are included in this project:

- Adolescence and pre-pregnancy (sexual and reproductive health): diagnosis and treatment of girls infected with *T. cruzi* and women of childbearing age (WCBA) in endemic areas and adequate care, referral and monitoring of pregnant women and infected sexual partners;
- Pregnancy: increased early access to antenatal care; appropriate provision of actions during prenatal care, including promoting partner involvement; routine serological screening for CD and; monitoring of pregnant women with CD, defining referral when necessary (for example, risk pregnancy with chronic Chagas cardiomyopathy).
- Childbirth: parasitological and serological screening for *T. cruzi* in newborns of infected mothers.
- Postnatal - Mothers: treatment of *T. cruzi* seropositive mothers after pregnancy.
- Postnatal - Newborns: serology for *T. cruzi* of newborns with infected mothers (at 8 months); treatment of *T. cruzi* seropositive children before one year of age and clinical / serological follow-up until a negative result; immediate treatment of all newborns with positive parasitological results for *T. cruzi*.
- Cross-cutting interventions: health campaigns involving information, education and communication; support for social mobilization and community engagement; consider the serological test of siblings of children infected with *T. cruzi*.

Figure 1. Priority populations



CD: Chagas disease; PHC: primary health center; *T. cruzi: Trypanosoma cruzi*; WCBA: women in childbearing age.

Through a combination of implementation and innovation research, this project seeks to present a comprehensive and integrated approach to address WHOs critical actions 1 and 2, and PAHOs lines of action 1, 2 and 3, thereby tackling the following barriers: a lack of efficient diagnostic algorithms, lengthy and difficult treatment options leading to poor linkage and adherence, a lack of knowledge and understanding of CD both by people at risk as well as health professionals, a lack of integrated surveillance, control and care; a lack of efficient and effective policies; insufficient supply of necessary therapeutic and diagnostic tools; low social mobilization; and a limited political voice of persons at risk of CD. In the next chapters, the theoretical frameworks as well as planned interventions and activities will be explained in detail.

2. POTENTIAL IMPACT OF THE PROJECT

Theory of Change

The project foresees two types of inputs: financial input from Unitaid and the Brazilian Ministry of Health (MoH), and human and material resources (inputs) through the country health systems of Bolivia, Brazil, Colombia and Paraguay. The financial input will be received by the lead grantee Fundação para o Desenvolvimento Científico e Tecnológico em Saúde (Fiotec) who will in turn sign contracts with the consortium members, based on the division of activities and the corresponding budgets. Fiotec will be responsible for the financial monitoring of these contracts, and will undertake the necessary actions to ensure full financial accountability.

The project foresees a number of carefully constructed activities that will result in a total of five outputs, each one addressing different barriers and corresponding to key actions that have been identified by major international health organization WHO and PAHO. These five outputs combined will bring about two major changes, which are (i) increased access to and demand for effective diagnostics, treatment and care, as well as (ii) improved diagnostic tools and treatment options that have been validated and will be accessible in an equitable way. However, the success of the project in achieving these outputs and outcomes is anchored in a number of assumptions. First, the project assumes that because the consortium is made up of institutions that are directly linked to the MoHs of each respective country, a form of government buy-in is secured, access to the identified territories will be properly facilitated, and if proven successful governments will be willing to scale up the interventions to non-project areas. A second assumption is that because of the strong working relationship with PAHO on different aspects of the project, the uptake of best practices and recommendations generated through the different studies that are included in the project will be facilitated within project countries, the region and beyond. These assumptions inherently present a number of risks: national governments may not be able to finance a scale-up due to competing public health challenges (for example the COVID-19 pandemic), there might be delays in the uptake due to heavy vetting of the recommendations and best practices. However, the project will put mitigation strategies in place that should reduce the chances of this happening. These can be found under the chapter risk management.

Problem	**Public Health Need**	Chagas disease (CD) remains a public health problem in many Latin American countries, with congenital transmission being an important source of new cases. An estimated 6-7 million people worldwide are infected with the *T.cruzi* parasite and approximately 65 million people are at risk of contracting the disease. Every year around 10,000 CD related deaths are reported and an estimated 30 to 40% of people will develop severe and sometimes life-threatening medical problems due to CD. Congenital transmission is estimated to account for 22% of new cases, making it the second most important form of transmission. The CD economic burden is estimated at USD 690 million in healthcare costs and USD 8 billion in annual economic losses. However, despite the high morbidity and mortality and the significant economic burden, only 7% of people with CD have been diagnosed and only 1% receive antiparasitological treatment.
	Access barriers	While the access barriers in CD are many, the main barriers that this project will address are: a lack of efficient diagnostic algorithms, lengthy and difficult treatment options leading to poor linkage and adherence, a lack of knowledge and understanding of CD both by people at risk as well as health professionals, a lack of integrated surveillance, control and care; a lack of efficient and effective policies; insuffient supply of necessary therapeutic and diagnostic tools; low social mobilization; and a limited political voice of persons at risk of CD.

Pathway to impact	**Input**	**Outputs**	**Outcomes**	**Impact**
	• Unitaid Funding • Brazil government co-funding • Contributions from country health systems in Bolivia, Brazil, Colombia and Paraguay	1. Evidence generated on effective test, treat and care approaches through implementation research 2. Community and civil society engaged at local, national and regional levels to increase demand for services and advocate for integration of recommended approaches for Chagas disease in policies, strategies and plans 3. Diagnostic algorithms validated for chronic and congenital CD 4. Evidence generated on improved treatment options 5. Market shaping and supply chain interventions to ensure equitable access to innovative products	**Outcome 1: Increased access to and demand for effective diagnostics, treatment, and care for Chagas disease** Demand and adoption Evidence on impact and cost-effectiveness of test, treat and care approaches used for national/sub-national policy changes, communities mobilized to demand access to health care and improved understanding of CD by key stakeholders and target groups Supply and delivery Improved supply chain management and integration into maternal child health procurement plans **Outcome 2: Improved diagnostic tools and treatment options validated, and access conditions ensured** Innovation and availability validated diagnostic tools and improved treatment options reducing the time between screening, diagnosis and treatment completion. Affordability: through increased demand and better planning price reductions od key CD tools will be negotiated	**Direct impact:** Prevention of >2000 future cases of cardiomyopathy Prevention of >290 congenital infections Net reduction in health care costs of USD 15 million Reduction in annual DALYs >3,500 **Indirect impact Latin America, after 5 years:** Prevention of an additional >71,570 future cases of cardiomyopathy Prevention of an additional >11,300 congenital infections Net reduction in healthcare costs of USD 456 million Reduction in annual DALYs >121,700

Key Risks	- The COVID-19 pandemic and its impact on economies and health systems in the target countries - Insufficient offer or delays in procurement of strategic supplies that are needed for the validation studies - National governments lack the financial resources for scale-up, for instance due to competing priorities in public health - Delays in the uptake of project recommendations and best practices in global health organizations' guidelines

Impact

Due to its complex nature, WHO considers CD one of the most neglected diseases, even among the larger group of NTDs. PAHO describes CD as "an intricate plot of sociocultural, political, biological, environmental, and health aspects", with a particular set of challenges, as it both reflects and exacerbates social inequality in Latin America. The disease afflicts the poorest regions of Latin America, and especially affects vulnerable populations that are often marginalized, have limited political voice, and live in peripheral areas of large urban centers, or remote rural areas. This is why control of CD involves not only improved performance of health services, but also the reduction of social inequalities, thereby promoting equitable care in line with Sustainable Development Goal 3 and the WHOs main objective of Universal Health Coverage. This project will reduce the current heavy burden of CD by tackling several health system and technological barriers.

The project has calculated the potential impact of the interventions, developing different scenarios (counterfactual, worst-case, central and best-case) over different time periods and for different geographical areas. Over the four years of the project, according to a "central scenario" of potential impact, 234,000 people will be screened for CD, including 181,000 women of childbearing age, 37,000 children and infants, and 16,000 other household members. Based on the prevalence of disease in the different communities participating in the project, this would enable treatment of 8,600 people (after accounting for contraindications and loss to follow-up). The direct impact would be potential avoidance of 2,000 cases of cardiomyopathy and 290 congenital infections, with an annual reduction in healthcare costs of US$ 15 million and a decrease in annual disability adjusted life years of 3,500. The central scenario for indirect impact would require countries to screen 40% of estimated women with *T. cruzi* infection by 5 years after the project ends. The worst-case and best-case scenarios show the potential impact if 12% and 75% of women were screened respectively by 5 years after the project ends. The impact summary table below shows this potential scale-up impact in the four project countries and in Latin America more broadly.

Table 1. Impact summary table

Indicator	Direct impact central scenario	Indirect impact difference between the central and the counter factual scenario	
	Project countries	Project countries	Latin America
Women screened	181,000	1,975,000	4,440,000
Babies screened	4,000	36,420	82,100
Other children screened	33,000	329,000	742,500
Household members screened	16,000	190,300	430,300
Total no people screened	**234,000**	**2,530,720**	**5,694,900**
Range worst to best-case	*132,000 - 410,000*	*353,300 - 5,989,300*	*800,900 - 13,550,900*
Women treated	5,800	99,490	225,600
Babies treated	170	1,770	4,000
Other children treated	1,330	13,810	31,275
Household members treated	1,300	16,330	37,150
Total no people treated	**8,600**	**131,400**	**298,025**
Range worst to best-case	*1,740 - 34,800*	*10,630 - 481,830*	*16,325 - 1,088,075*
Cases of cardiomyopathy avoided	**2,000**	**31,600**	**71,570**
Range worst to best-case	*400 - 8350*	*1,070 - 130,600*	*2,410 - 294,320*
Future congenital infections avoided	**290**	**5,005**	**11,300**
Range worst to best-case	*65 - 890*	*515 - 15,400*	*1,160 - 34,700*
Net savings for health system in USD	**15,000,000**	**203,000,000**	**456,250,000**
Range worst to best-case	*900,000 - 75,000,000*	*10,100,000 - 982,000,000*	*-4,950,000 - 2,218,250,000*
Additional savings due to new treatment regimen in USD	**n/a**	**14,800,000**	**33,000,000**
Range worst to best-case		*1,200,000 - 54,000,000*	*2,700,000 - 122,000,000*
Annual reduction in DALYs	**3,500**	**53,820**	**121,700**
Range worst to best-case	*710 - 14,200*	*1,820- 221,220*	*4,000 - 501,500*

As demonstrated in Table 1, the range between different scenarios is quite big. As CD is an NTD, there is a lack of systematically collected data on important variables such as prevalence, the number of people that are tested, the number of people that initiate treatment, and the number of people that complete treatment. The information that is available, is either slightly dated or comes from sources such as project reports. This means that for the calculation of project impact, there is a high degree of uncertainty, which is reflected in the individual variables per scenario. This project will contribute significantly to the systematic collection and analysis of data in each of the project countries, and provide tools to other countries to do the same.

In addition, this project will allow for the validation of new algorithms and strategies for diagnosis of both chronic cases and congenital infections, which can greatly reduce delays in testing. Prompt diagnosis and treatment of CD have proven clinical and epidemiological benefits, in particular in the context of congenital CD. Identifying and treating girls and women will significantly reduce the risk of congenital transmission and *T. cruzi* infected infants identified soon after birth have a very high cure rate and a good tolerance to treatment. All treated individuals are less likely to develop clinical complications, and treatment breaks the chain of *T. cruzi* transmission. The new algorithms and strategies that will be developed and evaluated in this project will allow the integration of CD care in the primary health system in endemic regions, contributing to the sustainability of the disease control programs. A shorter treatment regimen with fewer side effects will also be validated, reducing treatment time from the current 60 days to 15, with reduced needs for monitoring and patient visits and a subsequent increase in net healthcare savings of 33 million USD (central scenario for indirect impact in Latin America). Improving the diagnosis and treatment of CD will improve access to care and strengthen primary health care. The empowerment of the primary health system in CD endemic communities will allow the advancement of universal health coverage (UHC).

In all, the project will:

- Validate new diagnostic algorithms to greatly speed up and simplify testing via primary healthcare;
- Validate a new, substantially shorter treatment regimen with a better safety profile and fewer laboratory monitoring requirements during the treatment course;
- Develop collaborative action plans involving RMNCH and primary healthcare for addressing access barriers in each country;
- Develop a simplified roadmap of patient care piloted in each country, facilitating scale-up;
- Develop a SBCC toolkit in each country to increase demand for testing;
- Build capacity of healthcare personnel, using a system that can be replicated throughout each country;
- Work towards an equitable market for diagnostics and treatment;
- Strengthen local civil societies and mobilized communities;
- Strengthen regional collaboration on CD;
- Advocate for elimination of congenital CD transmission.

These deliverables will pave the way for system-wide adoption and scale-up. In a central scenario projection of **indirect project impact**, this would enable identification of 40% of the estimated 498,255 women with *T. cruzi* infection, along with and children and other family members, living in the **four countries** in the five years following the project. Using the project model, this would enable treatment of and additional 131,400 people, including 99,490 women, 1,770 congenitally infected infants, 13,810 children, and 16,330 other household members. This would prevent an additional 31,600 cases of cardiomyopathy and 5,005 future congenital infections, with savings to the health systems of the four countries of USD 203 million in net annual healthcare costs, and a reduction in annual disability adjusted life years (DALYs) of >53,820. When looking at the **indirect impact for Latin America** as a whole in a central scenario, this would enable treatment of an additional 298,025 people, including 225,600 women, 4,000 congenitally infected infants, 31,275 children, and 37,150 household members. This would prevent an additional 71,570 cases of cardiomyopathy and 11,300 future congenital infections, with savings to the Latin American health systems of USD 456 million in net annual healthcare costs, and a reduction of 121,700 DALYs. In addition, through the collaboration platform and exchanges with global CD stakeholders and WHO, this project expects to extend its impact beyond the region as well, providing non-endemic CD countries with the necessary tools to address CD in their contexts.

However, these reductions cannot be achieved without first validating the effectiveness of new diagnostic and therapeutic tools and piloting test, treat and care models in different contexts. This project therefore represents the first necessary and important step toward achieving elimination of congenital transmission of CD.

3. DESCRIPTION OF OUTPUTS, ACTIVITIES AND ASSUMPTIONS

By tackling the main barriers to elimination of congenital CD transmission and assuring access, with improved diagnostic tests and treatment regimens at reduced costs, improved provider awareness, preparedness to address CD, and improved access to information about CD and related services in affected communities, this project will deliver the necessary elements to support countries in achieving elimination of congenital CD transmission. Scalable models to improve access will be consolidated in different epidemiological and sociocultural contexts, facilitating replication throughout the region in support of regional initiatives to interrupt congenital CD transmission.

In order for the project to reach its goal of contributing to the elimination of congenital transmission of Chagas disease by scaling up and enhancing access to diagnosis, treatment and comprehensive care, through innovative and sustainable approaches in Bolivia, Brazil, Colombia and Paraguay, two outcomes were developed:

1. Increased access to and demand for effective diagnostics, treatment, and care for Chagas disease.
2. Improved diagnostic tools and treatment options validated, and access conditions ensured.

Providing timely diagnosis and treatment is a critical part of eliminating CD as a public health problem. This means ensuring: (i) good quality, easy-to-use diagnostic tests and treatment options are widely available, (ii) healthcare professionals proactively offer information and counseling on Chagas disease, and (iii) the population recognizes the importance of getting tested and feels comfortable seeking diagnosis and treatment. This project will strengthen available evidence on testing and treatment strategies and contribute new evidence on simplified diagnostic tools and a shortened drug regimen. This includes not only clinical evidence but also operational feasibility and cost-effectiveness. The project will disseminate this data to key stakeholders, including governments, and both advocate for and support adoption of new policies based on the latest evidence. In order to meet the demand that this project will generate, countries need to be able to secure a steady supply of good quality drugs and diagnostic tools. This project will support health systems in Bolivia, Brazil, Colombia and Paraguay in addressing supply chain issues, assuring proper registration of necessary tools, and strengthening capacity of providers in primary healthcare to administer testing and treatment to patients.

In order to achieve the project's outcomes and goal, the following outputs and activities have been designed. Please find the complete overview of activities, including the distribution amongst countries and responsible organizations in Annex 1.1.

Inception phase: the project will start with a six-month inception phase in which key milestones will be met to further refine activities, indicator targets and milestones. These key milestones are related to both general grant management and individual outputs and include:

- Contract signed with Brazilian MoH on the co-funding, including activities and timelines
- Contract between Fiotec and Fiocruz renewed
- Contracts signed between Fiotec and each individual consortium member
- MoUs for each project country in place
- Development of a terms of reference (ToR), including membership criteria, to guide the selection of participants of the external advisory board (EAB) and the community advisory board (CAB) and outline roles and responsibilities in order to avoid potential conflicts of interest

- Selection of members and set-up of the EAB and CAB
- Develop HSR SOPs
- Ethical approval obtained for each study (outputs 1,3 and 4)
- Formative research, desk studies initiated in each country (output 1)
- National, regional and country stakeholder and civil society mappings completed (output 1 through 4)
- Desk review of SBCC and CCSE tools and approaches completed (output 2)
- Site preparation initiated (outputs 1, 3 and 4)
- Key staff trained (outputs 1, 3 and 4)
- Key finance, procurement, market access staff hired
- Procurement and supply management (PSM) country plans and budgets finalized and approved by Unitaid for all project countries, based on assessments and discussions with national and regional stakeholders
- PAHO Strategic Fund MoUs signed
- Product landscape and equitable access strategy finalized and approved by Unitaid (output 5)
- Finalization of project management manual, policies on conflict of interest/ compliance manual, wrongdoing guidelines
- Assessment of the Covid-19 situation in all project countries and confirmation that project activities can start and be fully implemented as planned or reprogramming submitted.

Output 1: Evidence generated on effective test, treat and care approaches through implementation research

A patient's ability to obtain diagnosis and treatment, is subject to more than just the availability of tools and treatment options. It also relates to the patients' understanding of and beliefs around the disease, as well as the time, travel and out-of-pocket costs involved in seeking treatment, and the ease of adhering to treatment guidelines. Low provider awareness, low availability of CD services in primary healthcare, and lack of public information currently suppress demand for CD testing and treatment, thereby discouraging patients. By engaging communities and civil society, and by employing targeted IEC interventions, this project will boost patient demand. At the same time, capacity building of health professionals and integration of interventions into PHC will ensure an increase of proactive screening via the health system while ensuring patient requests for CD testing and treatment are effectively met. By generating solid evidence, demonstrating best practices, and generating tools and resources to support implementation, recommendations may be included in WHO, PAHO and national guidelines. This, combined with a strong emphasis on regional linking and learning promoting cross-country collaboration throughout all phases of the project, will facilitate the replication and scale up of this project's interventions.

Through carefully designed implementation research that will be executed in each of the countries included in this project, this consortium will generate evidence on the feasibility and effectiveness of test, treat and care approaches in order to contribute to the elimination of congenital transmission of Chagas disease. It will target women of childbearing age, including pregnant women, their children and household contacts, community leaders, health professionals and health managers and will work through existing primary health and maternity structures, establishing links with existing initiatives such as health and vaccination campaigns and EMTCT-plus. Table 2 summarizes the implementation research target municipalities characteristics.

Table 2. Summary table of implementation research target municipalities

Country	Department / State	Municipality	Population	No. of WCBA	Estimated no. of CD cases	Estimated no. of persons to be screened	Estimated no. of persons to be treated	Estimated no. of PHCs	No. of maternity wards (as part of PHC or stand alone)	No. of laboratories	Current CD testing and treatment approach
Bolivia	Chuquisaca	Padilla	11,067	2,654	2,805	3,600	260	6	1	1	Current approach as described in national guidelines
		Yotala	10,017	2,165	2,539	2,900	210	1	0	1	
		Tarabuco	10,383	2,497	2,632	3,400	240	12	1	1	
	La Paz	La Asunta	42,644	10,413	10,809	14,000	1,025	17	9	1	
	Santa Cruz	Mairana	13,197	2,639	3,345	3,600	260	4	4	1	
		El Torno	63,298	16,196	16,044	22,000	1,595	21	1	1	
		Vallegrande	18,478	5,003	4,684	6,800	490	10	2	1	
	Tarija	San Lorenzo	25,796	6,718	6,539	9,200	660	19	1	2	
		Villamontes	51,916	12,661	13,159	17,200	1,245	25	1	1	
		Uriondo	15,599	4,137	3,954	5,600	405	10	1	1	
Totals			**262,395**	**65,083**	**66,509**	**88,300**	**6,390**	**125**	**21**	**11**	
Brazil	Pará	Igarapé Miri	63,036	19,830	1,169	15,500	140	3	5		Current approach as described in national guidelines
	Bahia	Riachão das Neves	22,334	6,372	414	5,000	45	12	1	2	
	Minas Gerais	Janaúba	72,018	22,674	1,336	18,000	160	16	3	5	
	Rio Grande do Sul	Rosário do Sul	39,314	10,489	729	8,300	75	3	5		
	Goias	Parauna	10,980	3,198	204	2,500	20	7	1	1	
Totals			**207,682**	**62,563**	**3,853**	**49,300**	**440**	**41**	**15**	**8**	
Colombia	Boyacá	Moniquirá	21,182	4,126	1,142	3,600	85	3	1	0	Current approach as described in national guidelines
		Santana	7,605	1,445	410	1,250	30	1	1	0	
		Chitaraque	5,298	1,007	286	850	20	1	1	1	
		Soatá	6,541	1,218	353	1,000	25	3	2	1	
		Boavita	6,442	1,224	347	1,000	25	1	1	0	
		Tipacoque	2,969	564	160	500	10	1	0	0	
		San Mateo	3,304	628	178	550	10	1	0	0	
		Miraflores	9,802	1,893	528	1,600	40	1	2		
		Zetaquira	4,326	822	233	700	15	1	1		
	Magdalena	Guachaca	7,879	1,655	425	1,400	35	1	0		
		Don Diego	1,860	391	100	350	10	0	0		
	Casanare	El Yopal	155,882	43,757	8,402	38,100	910	5	3	1	
Totals			**233,090**	**58,730**	**12,564**	**50,900**	**1,215**	**19**	**12**	**3**	
Paraguay	Cordillera	Caacupe	61,616	12,323	1,596	10,000	120	5	1	1	Current approach as described in national guidelines
	Paraguari	Paraguari	24,164	4,833	626	3,900	45	3	1	1	
	Central	Villa Elisa	81,223	16,245	2,104	13,000	160	5	1	1	
	Boquerón	Mariscal Estigarribia	28,348	5,670	734	4,600	55	7	4	0	
	Concepción	Concepción	87,215	17,443	2,259	14,000	175	15	6	1	
Totals			**282,566**	**56,513**	**7,318**	**45,500**	**555**	**35**	**13**	**4**	

The main elements of the implementation research include:

- **Formative research** aimed at conducting a situational analysis of each of the territories in order to better understand the local context, identify existing barriers and design context appropriate interventions. It will include desk research and rapid assessment elements, in order to collect both in-depth qualitative as well as quantifiable data and will make use of secondary data, open-ended semi-structured interviews with target population members and experts, focus group discussions with community members, as well as conduct a health post inventory. The topics that will be covered under the formative research are: demographic and socioeconomic information on the target municipalities; policy and CD context (national and local), including a stakeholder mapping; local health systems (formal and informal); knowledge on CD; testing for and treatment of CD; stigma and discrimination, including status disclosure; and health professionals and their experiences with CD. The outcomes of this research will inform both activities included under output 1 as well as those included under output 2.
- **Capacity building and training of health professionals** on different topics relevant to this project: training of health professionals on CD surveillance; CD clinical management and counseling; parasitological diagnosis; and a training of laboratory staff on molecular biology. The initial outline of the trainings will be developed by the consortium, and will be further defined and contextualized based on the outcomes of the formative research. The project will

try to align the trainings, where possible, with existing capacity building/training calendars in each country and will advocate for their permanent inclusion in the same. In addition, the training manuals will be made widely available through the project website and collaboration platform.

- **Pilot test, treat and care service provision** in each of the 32 municipalities included in the project. This test, treat and care service provision will find its basis in countries' existing policies, protocols and directives on CD, and will be incorporated in the daily work practices of primary health care and maternity staff, with the aim of turning existing diagnostic and treatment processes more efficient and effective. More specifically, it will include the deployment of CD screening through the use of RDTs, enhance the diagnosis and counseling of target groups, provide treatment to eligible CD positive patients and provide counseling to improve treatment adherence, conduct patient follow-up, provide aftercare and linkages to social or complementary services, strengthen CD surveillance at the local level and establish information flows to provincial, state and national levels, and establish selfcare/self-help groups for persons affected by CD. The different interventions will be accompanied by strong technovigilance, pharmacovigilance and quality control activities.

  The use of rapid tests for the screening of suspected CD patients is foreseen in the national guidelines in Bolivia, Brazil and Paraguay (though not regularly used as such). However, Colombia's guidelines do not include this provision, which is why the project will conduct an additional study to select and validate a rapid test for screening in Colombia, as agreed with the Colombian MoH. This means that the implementation protocol for Colombia will initially not include RDTs for screening, but rather use the diagnostic tools as described in the local guidelines. Upon conclusion of the additional study, the implementation protocol will be modified, and a screening strategy with RDTs similar to the one carried out in the other project countries will be applied.
- **Develop and implement a monitoring and evaluation protocol** specific to the implementation research, both at country as well as project level. The monitoring protocol will be designed to complement and strengthen the existing health management information systems (HMIS) and learnings from the projects will assist countries in strengthening their routine data systems to address data gaps for CD. The data that will be generated through the implementation research needs to be properly captured in order to demonstrate the effectiveness of the interventions that will be implemented. To this end, a monitoring plan including an exhaustive list of indicators has been developed, which will need to be operationalized for each territory.
- **Conduct a cost-effectiveness study** that will compare the interventions that are part of the implementation research with the status quo, taking into account both health effects (DALYs and quality adjusted life years (QALYs)) as well as costs related to the expansion of access to diagnosis and treatment through primary health care. The outcomes of the cost-effectiveness study will feed into the advocacy strategies aimed at scaling up the project's interventions, integrating evidence into national plans and securing funding. In addition, the study will provide costing data that can help governments to adequately budget for the necessary CD resources.
- **Strengthen regional collaboration,** not only between countries included in this project but also with other countries endemic for CD and those where CD forms a public health challenge. During the inception phase, as part of the formative research, an exhaustive mapping exercise will be conducted in each country to identify important stakeholders on local, provincial/state and national levels. This mapping will focus on actors such as governments, donors, producers and CD related drugs and diagnostic tools, civil society and local and traditional leaders. In

addition to the country level mappings, the project will undertake a stakeholder mapping on regional and global level, in order to better understand the different players that will need to be influenced in order for the project's results to be further scaled up. A selection will be made from the twenty plus countries that are either endemic for CD or that face public health problems related to CD to receive additional attention under this project. This selection will be based on criteria such as the impact of (congenital) CD on public health systems, relevance/importance of the country in achieving significant scale up, demonstrated interest in adoption/replication of project interventions, and a country's potential catalyzing effect. The specific activities that will be organized to further promote regional collaboration are peer exchanges between government officials, health professionals or civil society organizations in order to exchange experiences and learn from the project's initiatives; (virtual) linking and learning events on topics relevant to congenital CD; the set-up of technical working groups that aim to improve collaboration between actors conducting different CD related studies in the region; set-up of technical working groups that aim to improve the integration of CD into the EMTCT-plus initiatives; regional conferences on CD, bringing together important stakeholders, increasing CD visibility, both in the mother and child health care realms as well as the NTD world; and organizing collective advocacy campaigns.

- **Analysis and dissemination of research results and resources,** with the aim of updating national, regional and global guidelines to include the project's interventions and/or best practices and support further implantation.

The activities under output 1 have been divided amongst the three main phases of the implementation research, which are the preparation, execution and analysis and dissemination phase.

Activity 1.1 Preparation of the implementation research (inception phase)

1.1.1	Development of study protocol including tools in collaboration with national, regional and normative body experts, and submit for approval
1.1.2	Acquire Ethical Review Board (ERB) approval at all levels (national and WHO)
1.1.3	Site preparation, including elaboration of study documentation, SOPs, forms, data system, etc.)
1.1.4	Training of team members
1.1.5	Formative research – desk research
1.1.6	Stakeholder mapping
1.1.7	Preparation of the monitoring and evaluation protocols

Activity 1.2 Execution of the implementation research

1.2.1	Formative research – rapid assessment
1.2.2	Workshop to establish diagnostic confirmation flows, references and clinical management
1.2.3	Capacity building and training of health professionals
1.2.4	Pilot test, treat and care service provision
1.2.5	Monitoring and Evaluation – execution
1.2.6	Conduct a cost-effectiveness study

1.2.7	Strengthen regional collaboration, including the set-up of a platform for sharing of templates of protocols, monitoring and registries, training, communication and advocacy materials and other tools non-project countries can adapt and adopt

Activity 1.3 Dissemination of research results and implementation resources and learning to facilitate scale-up

1.3.1	Analysis of research data
1.3.2	Dissemination of results, reports, implementation resources and lessons learnt
1.3.3	Share data with normative bodies
1.3.4	Publication of scientific articles

The success of output 1 is strongly linked to output 2, where this project will focus on the inclusion and engagement of community and civil society actors.

Output 2: Community and civil society engaged at local, national and regional levels to increase demand for services and advocate for integration of recommended approaches for Chagas disease in policies, strategies and plans

The engagement of communities and civil society is central in any public health intervention, but potentially even more so in settings where there is evidence of inequalities in health. Due to the nature of Chagas disease, the people it affects most, and its classification as an NTD, the focus on community and civil society engagement becomes even more important. Currently, the number of civil society organizations (CSOs) working on CD is limited, especially compared to diseases such as HIV, as is the meaningful engagement of communities and their leaders (traditional, religious, etc.). This project will therefore place special emphasis on: understanding the existing civil society (CS) that is either working on CD or has potential links with CD (such as NTDs, HIV, or RMNCH) in each of the countries (as part of the formative research); understand the international CS that this project can potentially link up with; promote CS networking and set-up or strengthen existing platforms for this purpose; facilitate meetings between CS and local leaders and policy/decision makers; develop joint CS advocacy campaigns in each territory/country, including campaigns for the world Chagas disease day on the 14th of April each year; develop social behaviour change communication (SBCC) strategies and campaigns in each country that are contextualized to different territories and target groups and where possible, include the broader group of EMTCT-plus communicable diseases in these strategies; train local leaders on CD signs and symptoms, potential adverse reactions of treatment and the need for referral to primary care posts; and conduct a leadership training with community leaders and CSO representatives on interrelated modules with the aim of strengthening their capacity to represent their communities and influence policies. These modules include topics such as human rights and public policies in each country, expanded concept of health and citizenship, local health system guidelines and principles, social participation and control, activism and social conquest in each country, types, objectives and performance of leadership, strategies to encourage empowerment and reduce stigma, communication and public narratives, and competencies and skills for building public relationships and citizenship.

Activity 2.1 Community and civil society engagement and demand creation

2.1.1	Civil society mapping (local, national, regional and international) – inception phase
2.1.2	Develop social behaviour change communication (SBCC) strategies in each country for different regions, populations and stakeholders

2.1.3	Develop IEC campaigns and materials for different target groups
2.1.4	Training of local leaders (traditional, religious, etc) on signs and symptoms of CD, potential adverse reactions of treatment and the need to refer patients to primary health posts
2.1.5	Training of Trainers in each country on Leadership training
2.1.6	Leadership training of CSO and local leaders

Activity 2.2 Civil society advocacy and policy influencing

2.2.1	Civil society networking consolidation
2.2.2	Develop and deploy campaigns for the international Chagas disease day
2.2.3	Civil society advocacy campaigns developed and launched
2.2.4	Facilitation of meetings between civil society organizations, local leaders and local policy/decision makers

Activity 2.3 Documentation and dissemination of CCSE engagement and demand creation learning, best practices and resources

2.3.1	Analysis of collected data
2.3.2	Dissemination of lessons learned, best practices and reports

Output 3: Diagnostic algorithms validated for chronic and congenital CD

Diagnosing the different forms of CD is complex and results in limited access to treatment; e.g. chronic CD (women of childbearing age, pregnant women and the general population) requires at least 2-laboratory based tests and congenital CD diagnosis requires the implementation of a diagnostic algorithm combining microscopy and laboratory based tests over a 9-12 months period. CD RDTs are available in endemic countries, but their use is limited. They provide only screening information and have not been widely implemented in public health systems. In addition, they have not been included in PAHO guidelines, which maintains serology as the only tool for the diagnosis of chronic CD. The performance of the RDTs vary across endemic regions due to *T. cruzi*'s genetic variability and other factors (e.g. co-endemicity of cross-reacting parasites with the antibody detection tests). Furthermore, people at risk of suffering *T. cruzi* infection often migrate from rural areas with high prevalence of infection to urban areas where the prevalence is lower. Evidence suggests that RDTs could simplify algorithms for diagnosis of chronic CD in primary health care, through the use of one or several RDTs. However, this requires additional validation of an RDT-based algorithm that could potentially be implemented in a test-and-treat strategy for chronic CD. The project will therefore conduct a study to demonstrate that RDT-based algorithms (single or multiple tests) can be implemented to diagnose chronic *T. cruzi* infection in endemic countries in all populations at risk (including children above 9 months and pregnant women) at health care facilities, as an alternative to the current (laboratory-based) diagnostic algorithms, considering the *T. cruzi* genetic variability and the epidemiological diversity in Chagas endemic regions. A two-phased consecutive multicenter prospective field study will be conducted in 10-11 sites from Bolivia (3-4), Brazil (3) and Colombia (4) to validate a new RDT algorithm for CD diagnosis: (i) phase 1, RDT algorithm identification; and (ii) phase 2, RDT algorithm validation. During phase 1, the performance of 3 RDTs (in series and/or parallel) will be evaluated in each country, using the gold standard diagnosis as a reference (two serologies). The most performant RDT algorithm selected in each country will be evaluated in a second prospective field study compared with gold standard diagnosis to define its accuracy, demonstrating

that an RDT-based algorithm is 98% sensitive and non-inferior than 95% using two-sided binomial test with 5% alpha-level and 90% power. During phase 1, 150 confirmed CD patients and 150 non-infected people will be evaluated, with a necessity to screen a total of 750 people in each country (1/4 of the participants from a low endemic region and 3/4 in high endemic regions). During phase 2, 390 CD cases and the same number of non-infected people are necessary, with around 2000 people screened per country (again, 1/4 of the participants from a low endemic region and 3/4 in high endemic regions). Table 3 summarizes the information of RDT innovation protocols.

In addition, the project will implement a new algorithm in the pilot test, treat and care service provision for the diagnosis of newborns. Currently, diagnosing CD in newborns is complex, as the antibodies of an infected mother to *T. cruzi* can persist in her baby in the first few months of life. Direct parasitological exams are the gold standard for congenital CD diagnosis straight after birth, but these are often not available outside large urban centers.

A good alternative is the use of molecular biology, the Polymerase Chain Reaction (PCR), a method recognized in each of the four project countries for other diseases but not accessible in clinical practices related to CD. By including molecular biology in the diagnostic algorithm of congenital CD in newborns, the project will reduce at least 6 months of the time that is necessary for diagnostic confirmation, thereby decreasing the chances of follow-up losses. This activity will be part of the implementation research in all 32 municipalities, under the pilot test, treat and care provision. The use of PCR will be facilitated through technical support by the Institute of Technology in Immunobiologicals (Bio-Manguinhos), the Fiocruz unit responsible for research, innovation, technological development and the production of vaccines, reagents and biopharmaceuticals. Important to note is that for this project, PCR will have two main uses: (i) allow the diagnosis of early congenital CD and (ii) evaluate therapeutic failure. This last use will be important in the context of the clinical trial (output 4), having been defined as a primary endpoint, which requires a rigorous process of standardization and quality control for a reliable result of the study. For the diagnosis of newborns, samples will be sent to central laboratories in each country, which will have undergone capacity building sessions organized by Bio-Manguinhos to guarantee a high level of quality of the results.

In order to strengthen the evidence base for this output, a cost-effectiveness study will be executed to compare the health effects and costs related to the conventional diagnosis versus the newly validated RDT algorithm. This study will provide evidence that will feed into the work that will be done under output 5, thereby contributing to equitable access. Additionally, as mentioned under output 1, technical working groups will be set up to improve collaboration amongst actors conducting similar types of research in the region. The study under this output will provide sufficient evidence to update both PAHO and national guidelines and its protocols will be made available for use by other research consortia.

Activity 3.1 Preparation of RDT-based algorithm studies (inception phase)

3.1.1	Development of study protocol including tools in collaboration with national, regional and normative body experts, and submit for approval
3.1.2	Acquire ERB approval at all levels
3.1.3	Site selection and preparation, including elaboration of study documentation (SOPs, forms, data system, etc.)
3.1.4	Training of clinical trial team members and laboratories
3.1.5	Procurement RDT studies supplies

Activity 3.2 Phase 1 – RDT algorithm identification

3.2.1	Participant enrolment
3.2.2	Laboratory analyses
3.2.3	Statistical analyses and reporting
3.2.4	Supervision and monitoring

Activity 3.3 Phase 2 – RDT algorithm validation

3.3.1	Participant enrolment
3.3.2	Laboratory analyses
3.3.3	Statistical analyses and reporting
3.3.4	Supervision and monitoring

Activity 3.4 Analysis and dissemination of research results

3.4.1	Set-up and meetings of technical working groups to track on-going relevant trials, discuss challenges and share results
3.4.2	Analysis of research data
3.4.3	Cost-Effectiveness Study in Bolivia, Brazil and Colombia
3.4.4	Dissemination of results and reports
3.4.5	Publication of scientific articles

Output 4: Evidence generated on improved treatment options

Chagas disease is a major cause of heart disease, morbidity, and premature loss of life in Latin America. Antiparasitological treatment of CD has shown to halt future congenital transmission, reduce morbidity from the disease, and cure children, but the current treatment regimens are lengthy (60 days) and entail frequent side effects, causing approximately 20% of patients to drop out of treatment, discouraging others from starting. Recent research has suggested that a shorter treatment duration may still have adequate efficacy. BENDITA, a recent Phase II trial, found that a 15-day treatment of benznidazole eliminated the parasite in >75% of patients with few side effects. A shorter treatment regimen has the potential to greatly increase treatment adherence, which is why this project will conduct a double-blind, phase III study, where 918 patients will be randomly assigned to receive the standard-dose (300 mg daily for 60 days) regimen or the short experimental regimen (300 mg daily for 2 weeks). Efficacy will be assessed considering a non-inferiority design and through the detection of parasite DNA through molecular biology (PCR). Meanwhile, safety will be evaluated through a superiority design, with the aim of finding the new regimen as effective as the standard one, but superior in terms of safety. The study population will include adult patients of 18 years or older, who have been diagnosed with chronic Chagas disease in its indeterminate or mild cardiac form, and who have received a positive diagnosis through two serological assays. The study will not include children or infants, as the current methods of treatment are both effective (with high cure rates) and present little to no side-effects. The trial will be conducted in a total of seven sites, in Bolivia (2), Brazil (2), and Colombia (3). The primary endpoint will be parasitological response determined as sustained negative qualitative PCR from the end of treatment until 24 months of follow-up. The proportion of patients with positive qualitative PCR will also be measured at 6, 12, 18, and 24 months from end of treatment. Parasitic DNA measured with PCR has been widely used to assess CD treatment efficacy among more

recent clinical trials. Its utility as a tool to determine treatment success came from two assumptions: i) To date there are no reliable cure biomarkers, at least not on a reasonable timescale; and ii) a positive result after treatment is a biological proxy of treatment failure. Furthermore, the frequency of adverse events leading to treatment discontinuation will be compared. Table 3 summarizes information about this clinical trial and other innovation protocols.

In order to strengthen the evidence base for this output, a cost-effectiveness study will be executed to compare the health effects and costs related to the conventional treatment versus the validated shorter regimen. This study will provide evidence that will feed into the work that will be done under output 5, thereby contributing to equitable access. Additionally, as mentioned under output 1, technical working groups will be set up to improve collaboration amongst actors conducting similar types of research in the region.

Activity 4.1 Preparation of the clinical trial (inception phase)

4.1.1	Development of study protocol including tools in collaboration with national, regional and normative body experts, and submit for approval
4.1.2	Acquire ERB approval at all levels
4.1.3	Site identification
4.1.4	Procurement of drugs
4.1.5	Site preparation, including elaboration of study documentation (SOPs, forms, data system, etc.)
4.1.6	Training of clinical trial team members

Activity 4.2 Clinical trial implementation

4.2.1	Participants screening and enrolment
4.2.2	Patients treatment
4.2.3	Patients follow-up
4.2.4	Supervision and monitoring of clinical trial
4.2.5	Data systematization and analysis
4.2.6	Development of study report and scientific article

Activity 4.3 Analysis and dissemination of research results

4.4.1	Set-up and meetings of technical working groups to track on-going relevant trials, discuss challenges and share results
4.4.2	Analysis of research data
4.4.3	Cost-Effectiveness Study in Bolivia, Brazil and Colombia
4.4.4	Publication of scientific articles
4.4.5	Dissemination of results and reports

Table 3. Summary of Innovation Protocols

	Study design	Primary outcome	Sites per country	Sample size	Target population
RDT algorithm identification (RDT phase 1)	Prospective field study (3 RDT vs. gold standard serologies) evaluated in series and/or parallel	Identify the most performant RDT algorithm to diagnose chronic CD in each country	Bolivia (3-4); Brazil (3); Colombia (4) (shared sites with clinical trial and another 1-2 sites in high endemic areas)	750 screened per country to reach 150 CD cases and 150 non-infected people; total screened=2250	Patients at risk of chronic *T. cruzi* infection attending the study sites, including children and pregnant women; 1/4 recruited in a low and 3/4 in a high endemic region
RDT algorithm validation (RDT phase 2)	Prospective field study (algorithm selected in RDT trial 1 vs. gold standard serologies)	Accuracy of RDT-algorithm to diagnosis chronic CD in each country		2000 screened per country to reach 400 CD cases and 1600 non-infected people; total screened=6000	
Clinical trial	Phase III, double-blind, randomized, placebo-controlled study (60 days vs. 15 days BZN treatment)	Sustained negative qualitative *T. cruzi* PCR from the end of treatment until 24 months of follow-up	Bolivia (2) Brazil (2) Colombia (3)	n = 918; 306 per country, representing genetic parasite variances TCV (BOL), TCII (BR) and TCI (COL)	Adult patients, ≥18 years-old, chronic CD (indeterminate or mild cardiac form) with no previous treatment, excluding pregnancy

Output 5: Market shaping and supply chain interventions to ensure equitable access to innovative products

The market for CD diagnostic tools and treatment options suffers from a number of important barriers that impede efficient and often effective procurement. There are currently no diagnostic products or treatments that are WHO pre-qualified. The adult and pediatric formulations of BZN that is produced by Elea-Phoenix have FDA approval, but no other diagnostic tools or treatment options do. A number of products have registration with local regulatory institutions, but their registration alone does not mean that they are actually available on the local markets, least of all in sufficient numbers. In addition, repressed demand leads to insufficient procurement of the necessary tools to diagnose and treat the disease, further contributing to fragmented markets. The aim of this output is therefore to develop a healthy, competitive and transparent market for diagnosis and treatment of CD, with affordable prices for quality diagnostic tools and treatment options, increased market volumes, increased numbers of registered manufacturers and sustainable procurement strategies. During the project's inception phase, market landscape and market shaping strategy documents will be developed, setting out the key barriers to equitable access to diagnostics and treatments, as well as proposed activities to address those barriers. The documents will include: an analysis of the relevance of including NFX in the market strategies for CD treatment, information on intellectual property (IP)/

patent status for relevant treatment and diagnostics in the project countries and any other country relevant for scale-up; proposed activities to address market barriers including details of any proposed incentives and/or market interventions (long-term arrangements (LTA)), volume guarantees, pooled procurement etc); demand forecast for diagnostics CD programmes, including procurement groups, implementation agencies, normative bodies, and manufacturers, which could provide the market intelligence needed to inform appropriate CD control targets; roles and responsibilities for implementation of activities and any market interventions; rationale for potential incentives or support to manufacturers, how they will be selected and the proposed commitments of the manufacturer to ensuring equitable access to the product (i.e. commitments to affordable pricing and sufficient volumes); and details on the rationale for market interventions, including the process for selection of the recipient, the structure of the intervention, proposed key terms and commitments to access of the recipient/manufacturer. Upon Unitaid's approval of the plans, indicators, targets and milestones, the project will start with the implementation of the proposed activities.

Activity 5.1 Develop market landscape and market strategy documents (inception phase)

5.1.1	Develop a market landscape and competitive analysis of Chagas therapeutics available/in the pipeline in Latin America and globally
5.1.2	Develop a market landscape and competitive analysis of Chagas diagnostics available/in the pipeline in Latin America and globally
5.1.3	Develop a market strategy

Table 4 highlights the main products to be generated and disseminated.

Table 4. Products for dissemination

Output	Result/finding	Recipients	Approximate timeline
Output 1 - Evidence generated on effective test, treat and care approaches through implementation research			
Clinical database	*Presentations, informal reports*	*WHO, general stakeholders*	*Q3 2022*
	Peer-reviewed published reports & related datasets	*General (consumers of open access journals)*	*Q1 2023*
	Individual patient dataset	Curated data repository, partners under consortium agreement	*2024-2025*
Programmatic data	*Presentations, informal reports, implementation resources*	*WHO, national governments, general stakeholders*	*2024-2025*
Formative Research	*Presentations, informal reports*	*WHO, general stakeholders*	Q4 2022
	Peer-reviewed published reports & related datasets	*General (consumers of open access journals)*	Q2 2023
Primary analysis	*Peer-reviewed published reports & related datasets*	*General (consumers of open access journals)*	*2024-2025*
Output 2 - Community and civil society engaged at local, national and regional levels to increase demand for services and advocate for integration of recommended approaches for Chagas disease in policies, strategies and plans			
Clinical database	*Presentations, informal reports*	*WHO, general stakeholders*	*Q3 2022*
	Peer-reviewed published reports & related datasets	*General (consumers of open access journals)*	*Q1 2023*
Programmatic data	*Presentations, informal reports, SBCC and advocacy resources*	*WHO, general stakeholders*	*2024-2025*
Formative Research	*Presentations, informal reports*	*WHO, general stakeholders*	Q4 2022
	Peer-reviewed published reports & related datasets	*General (consumers of open access journals)*	Q2 2023
Output 3 - Diagnostic algorithms validated for chronic and congenital CD			
Primary analysis	*Presentations, informal reports*	*WHO, other Guideline developers; general stakeholders*	Q1 2025
	Peer-reviewed published reports & related datasets	*General (consumers of open access journals),* potential future funders, manufacturers	Q3 2025
Clinical database	*Individual patient dataset*	Curated data repository, partners under consortium agreement	*2024-2025*
Output 4 - Evidence generated on improved treatment option			
Interim analysis	*Presentations, informal reports*	*WHO, other Guideline developers; general stakeholders*	*Q2 2023*

	Peer-reviewed publication & related dataset	*General (consumers of open access journals)*	*Q4 2023*
Primary analysis	*Presentations, informal reports*	*WHO, other Guideline developers; general stakeholders*	Q1 2025
	Peer-reviewed published reports & related datasets	*General (consumers of open access journals),* potential future funders, manufacturers, Regulatory agencies.	Q3 2025
Clinical database	*Individual patient dataset*	Curated data repository, partners under consortium agreement	*2024-2025*
Output 5 - Market shaping and supply chain interventions to ensure equitable access to innovative products			
Primary analysis	*Presentations*	*WHO, other Guideline developers; general stakeholders*	*Q2 2023*
	Peer-reviewed publication & related dataset	*General (consumers of open access journals)*	*Q4 2023*
Programmatic data	Presentations, informal reports	WHO, general stakeholders	2024-2025
Market Intelligence data	Forecast and demand data	Country and general stakeholders, manufacturers, Regulatory agencies.	2024-2025

COVID-19 precautions

CD patients are at a greater risk of complications due to COVID-19, and time and resources that have been shifted away from primary health care to attend to the effects of the pandemic has meant an even further decrease in attention for NTDs such as CD. (33) COVID-19 precautions will be taken throughout every phase of the project, and will be monitored and revised according to changing circumstances in each of the countries involved. Overall, the project execution will be adapted to local conditions and regulations for COVID-19 and until the numbers of cases according to each locality are at an acceptable control figure, international recommendations will be followed for the reduction of exposure and transmission, as well as the local standards that regulate the mobility of people.

During the inception phase, the majority of the planned activities such as signing of contracts, developing protocols and ToRs and initiating desk research may all be done remotely. The project will keep travel and field work to a bare minimum, carefully discussing and planning activities that do require any travel or in-person contacts with our consortium members who are best placed to advise on the possibilities given the current contexts. Throughout the inception phase, the grant PI and project director, together with the consortium members, will continue to monitor the local COVID-19 conditions on the ground, define the right time to initiate field activities, and come up with detailed and agile plans to mitigate any negative impacts on the project. However, field activities may be halted at any time, should epidemiological circumstances dictate. In that case, plans will be adjusted quickly, and shared with Unitaid. It is important to note that part of the mitigation strategy already lies in the fact that the consortium will recruit local teams in the municipalities (therefore eliminating the need for constant travel) and make use of existing structures and staff for the execution of the studies. In addition, the project will ensure that adequate protective measures are taken throughout all activities that require physical contact (the use of PPE when attending to patients or when conducting trainings, maintaining appropriate distance where possible, etc.). In addition, where possible, the project will use remote communication platforms, and visits will only be made when it is considered essential. For the studies that involve patient visits, appointments might need to be rescheduled, but this can only be appropriately assessed once ethical approval has been obtained and the studies may officially commence (currently projected for October 2021). In the event of prolonged restrictions in local travel due to COVID-19, patients may be asked to report adverse event data via telephone, while sample collection will remain postponed. As mentioned, COVID-19 precautions will be reviewed with investigators and site personnel at the beginning of the study, and information will be provided to patients accordingly. The patient inclusion sites must have adapted protocols for the diagnosis and management of patients with suspected and/or confirmed COVID, and their personnel must be trained.

COVID-19 contexts and perspectives in Bolivia, Brazil, Colombia and Paraguay

Bolivia

The Bolivian Government confirmed the first case of COVID-19 in the country on March 10, 2020, and responded quickly by cancelling events, closing schools and borders, and implementing a national lockdown on March 22, 2020. During the first outbreak, the Bolivian government adopted a rigid quarantine. The relaxation of restrictions in some departments coincided with the nationwide surge in COVID-19 deaths in June and July, 2020. However, deaths declined in September and October, 2020, despite the post-confinement relaxation. The second outbreak started in January 2021 and the government adopted punctual restrictions instead of a national lockdown. According to the Ministry of Health and Sports (MSyD), the current situation of COVID-19 in Bolivia presents a total of 242,292

accumulated infections, and 11,441 deaths nationwide. The MSyD publishes periodic bulletins on the country's pandemic situation on its website.

The National Vaccination Plan provides for immunization in two phases. In the first phase, the following criteria for prioritization are maintained: risk due to exposure and strategic function (health personnel prioritization according to the work area); risk of serious disease (adults 60 years and older, adults 18-59 years with underlying diseases); criteria of vulnerability (indigenous peoples, people deprived of liberty, migrants). In the second phase, the following prioritization criteria will be maintained: vaccination of persons over 60 years old; vaccination of persons with underlying disease; vaccination of 18 to 59 year old's that are otherwise healthy. The vaccines will be obtained through different mechanisms: agreements with individual manufacturers; regional supply agreements through the PAHO revolving fund (Fondo Rotatorio); and the global mechanism for obtaining and accessing COVAX products, an international initiative to provide equitable global access to COVID-19 vaccines. So far, the Bolivian government has received 20,000 doses, inoculating 10,167 health professionals that are at the front line dealing with the pandemic. The Bolivian government has signed an agreement with China and will receive 500,000 doses from Sinopharm on 24 February. Once in Bolivia, these doses will be distributed among the departmental health services of the 9 departments immediately. The Bolivian government expects to receive 15 million doses form different pharmaceutic laboratories in order to immunize 7.5 million people. Government officials expect immunization to reach 100% of the population by the end of 2021.

Brazil

The first case of COVID-19 in Brazil was reported on 26 February 2020 and by March 22, the coronavirus had spread to all 26 Brazilian states. In 2020, 7,716,405 cases of COVID-19 and 195,725 deaths were reported. According to the Brazilian government, on February 22, 2021, the country had 10.195,160 confirmed cases and 247,143 deaths caused by COVID-19.

On December 16 2020, the Federal Government launched the National Vaccine Operationalization Plan against COVID-19. The Brazilian government will acquire vaccines through the following mechanisms: 1) Fiocruz / AstraZeneca - 102.4 million doses expected by July / 2021 and around 110 million doses (national production) between August and December / 2021; 2) COVAX Facility: 42.5 million doses expected; 3) Butantan Institute / Sinovac: 46 million doses are expected in the first half of 2021 and 54 million in the second half of this year; 4) Memoranda of Understanding: non-binding MoUs will be defined and adjusted according to the schedules and quantities negotiated with the pharmaceutical companies that currently offer the product to the national market: Janssen, Bharat Biotech, Modern, Gamaleya, Pfizer, and Sputnik V.

The National Plan prioritizes the elderly, 74 and up, people with disabilities aged 18+ in long-term institutions, indigenous peoples living on indigenous lands, health workers, and traditional riverside and quilombola peoples and communities. Next are elderly people from 60 to 74 years old, people with comorbidities, people with severe permanent disabilities, homeless people, people deprived of their liberties and employees of these institutions, education workers in basic and higher education, security and armed forces.

On January 17, 2021, the National Health Surveillance Agency (Anvisa) authorized COVID-19 vaccines of Sinovac (CoronaVac) and Serum (Oxford) laboratories for emergency use. The National Vaccination Campaign against COVID-19 started on January 18, 2021, when the Ministry of Health delivered 4.6 million CoronaVac doses to state governments. On January 22, the first batch of the AstraZeneca /

Oxford COVID-19 vaccine arrived in Brazil. A month later, another 2 million doses of this immunizing arrived in the country. Until February 22nd, 5,982,640 Brazilians received at least the first dose of the vaccine, which corresponds to 2.83% of the national population. The Government expects to vaccinate 50% of the population until June and the other half by the end of this year.

Colombia

On March 6th 2020, the first COVID-19 case in Colombia was diagnosed in a person who traveled from Italy. Because of the increasing number of cases, on March 12th, the Ministry of Health and Social Protection (MSPS) declared a health emergency in the country because of the COVID-19, and introduced isolation and quarantine measures, banning events with more than 500 people, requesting that state governors and mayors assess transmission risks, and ordering commercial establishments and stores to implement hygiene and sanitation measures for users and workers. On March 13, international tourist ships were banned from docking in Colombia. Four days later, the president declared a state of emergency and added measures such as the closure of schools, restaurants, and bars and the order that people older than 70 years should stay at home unless buying essential food or health products. As in other Latin American countries, the pandemic has particularly impacted poorer communities. The Colombian government has implemented a number of policies toward social protection and economic measures in an attempt to improve the situation.

According to INS, on 21 February 2021 there were 2,226,262 confirmed cases and 58,834 deaths due to COVID-19. The City of Bogotá D.C and the Department of Antioquia concentrate the majority of cases and deaths. These data put Colombia in fourth place in Latin America and the Caribbean in terms of the number of people affected and deaths in proportion to its number of inhabitants.

On February 17th, 2021, Colombia began its mass immunization campaign against COVID-19. So far (February 23), the government has purchased 240,000 doses – 50,000 from Pfizer and 190,000 from Sinovac –, vaccinating approximately 50,000 people (less than 1% of the country's population). The National Government has presented a National Vaccination Plan, which establishes two phases and five stages. In its first phase, the main goal is to reduce mortality and the incidence of serious cases caused by this virus, as well as to protect health workers, while in the second phase it aims to reduce the contagion to generate herd immunity. The Colombian government has managed to buy 20 million doses for 10 million Colombians through Covax, an international initiative to provide equitable global access to COVID-19 vaccines, and 41.5 million doses for 25,250,000 people through bilateral mechanisms. Government officials expect immunization to reach 70% of the population or 35 million inhabitants in 2021.

Paraguay

The first COVID-19 case in Paraguay was confirmed on 7 March 2020. From then on, the health authorities took different measures to contain the epidemic. Paraguay adopted a suppression approach early, on March 11th 2020, which was mainly focused on "buying time". Measures included the suspension of classes at all educational levels (basic, secondary and university) and the creation of temporary shelters, so that people who tested positive for COVID-19 were kept in supervised isolation. Subsequently, these temporary shelters have been used to maintain the temporary isolation (quarantine) of all people from abroad who enter the country by air or land. In addition, "health hotels" were created for those people who would like to have more comfort during the isolation period (14 days).

According to the Ministry of Health and Social Welfare (MSPBS), on February 18 2021 there were 148,622 confirmed cases (52% of women and 48% of men) and 3,008 deaths by COVID-19. As a

consequence of the country's population pyramid, more than half of the confirmed cases are among people under 50 years old. The Departments of Central and Asunción concentrate the majority of cases. It is worth highlighting that neither the public nor the private health services collapsed during the pandemic.

On February 2nd, Paraguayan authorities presented the action plan for vaccination against COVID-19, in which they divided the priority groups into three stages. The first stage includes health professionals and people aged 60 or over. The second stage includes people between 18 and 59 years old with underlying illnesses, teachers of initial and primary level, workers of essential services and indigenous population. The third phase will include workers of airports and entry points to the country, military personnel, police, firefighters and people in detention. The provisional vaccination schedule provides that each of these phases will last between four and six weeks. Paraguay received its first batch of COVID-19 vaccines on February 18, with the government's purchase of 4,000 doses of the Russian Sputnik V vaccine, that will be used to vaccinate 2,000 health professionals. In total, the Paraguayan government acquired 1 million Sputnik V doses and other 2 million CoronaVac doses. Furthermore, Paraguay expects to receive 4.3 million doses of AstraZenaca vaccine, purchased through Covax. Government officials expect immunization to reach 50% of the population in 2021.

4. GOVERNANCE STRUCTURE OF THE PROJECT

The consortium is made up of six members. The lead grantee Fundação para o Desenvolvimento Científico e Tecnológico em Saúde (Fiotec) is a foundation that was created to support Fiocruz's researchers in obtaining and managing research grants and awards. The foundation has a wealth of experience in working with international donors and executing projects and programs. The technical lead, Fundação Oswaldo Cruz (Fiocruz), an institution linked to the Brazilian Ministry of Health, is considered one of the world's main public health research institutions and develops diversified research, teaching methods and actions with the objective of promoting health and sustainable social development, generating and disseminating scientific and technological knowledge. Chagas disease, described in 1909 by Carlos Chagas, a researcher from Fiocruz, was and remains the emblem of this institution that combines innovation and social commitment. The Instituto Nacional de Laboratorios de Salud "*Néstor Morales Villazón*" (INLASA), has been the reference health laboratory in Bolivia, and is a leader in the development of scientific knowledge. The Instituto Nacional de Salud de Colombia (INS) is the national scientific-technical institution dedicated to public health in Colombia. INS contributes to the protection of health through knowledge management, monitoring the health status of the population, and the provision of goods and services of interest in public health. The Servicio Nacional de Erradicación del Paludismo (SENEPA) is a Paraguayan public, normative and operational institution with national coverage. It is in charge of the surveillance and control of vector-borne diseases, with the purpose of improving the quality of life of the population in general. Finally, there is the Foundation for Innovative New Diagnostics (FIND), a global non-profit organization that drives innovation in the development and delivery of diagnostics to combat major diseases affecting the world's poorest populations. Since 2003, FIND has been instrumental in the delivery of 21 new diagnostic tools used in 150 low- and middle-income countries (LMICs).

Due to legal and/or bureaucratic reasons, INLASA in Bolivia and SENEPA in Paraguay have selected administrative agents to be responsible for the financial administration of the project. For Bolivia, United Nations Development Programme (UNDP) will enter as the administrative agent, and for Paraguay this will be Centro de Información y Recursos para el Desarollo (CIRD). Fiotec will sign tripartite contracts with the organizations involved, which will clearly stipulate the roles and responsibilities of each partner.

Fiotec will have the overall administrative and financial responsibility and Fiocruz will have the technical responsibility for the project, overseeing the other consortium members and coordinating the execution of the different studies included in the project. In addition, Fiocruz will design the implementation research and clinical trial, co-design the validation of the RDT based diagnostic algorithm, and conduct market research for therapeutics. INLASA, INS and SENEPA will be responsible for the facilitation of a proper execution of the different studies that will be executed in their respective countries. FIND will co-design and execute the validation of an RDT based diagnostic algorithm and conduct market research for diagnostics. As Fiocruz, INLASA, INS and SENEPA are all locally based organizations, directly linked to the MoHs of their respective countries, they are all authorized to work locally. FIND will work through the local structures, so there is no need for additional authorizations. The sharing of data will be arranged for in the contracts that will be signed between Fiotec and each organization/institute before the start of project implementation.

The consortium will be supported by collaborating organizations, such as Drugs for Neglected Diseases initiative (DNDi), through its Latin America office, which had an important role in supporting the building of the current project and of the consortium. It will take on the role of a strategic collaborator

in the project implementation, supporting implementation, diagnostics, clinical trial, market shaping and monitoring and evaluation (M&E) components.

Governance structure

The project will have two advisory bodies, and three levels of governing bodies. The first advisory body will be an external advisory board (EAB), which will include representatives from the MoH of each participating country, as well as representatives from WHO and PAHO. In addition, the EAB will include a representative from Unitaid as a permanent observer. The EAB will provide political and technical input into the project and will meet online twice a year. During the inception phase of the project, a terms of reference (ToR), including membership criteria, will be developed to guide the selection of participants and outline roles and responsibilities in order to avoid potential conflicts of interest. The second advisory body will be a community advisory board (CAB) which will compose of community members that come from the project's target areas and who share a common identity, history, language or culture with the project's target groups. The CAB will serve as a liaison between study participants and researchers, and may help in the development of materials. The CAB will meet online four times per year. Terms of reference will be developed for both advisory bodies and the selection of participants will be part of the project's inception phase. On the governing level, the project will have an executive committee (EC), which will function as a steering committee and will prioritize issues for the project to address. The EC will also discuss and decide on possible disputes. The EC will consist of the project principal investigator (PI), the project director, and representatives from Fiotec/Fiocruz, INLASA, INS, SENEPA and FIND. The second governing level will be between the central level core team and the country level teams. Country level teams will be put into place in each country, and will be directly responsible for the execution of the research and project activities. The central level core team will oversee the work that is being done in each country. The third governing level will be between the country level teams and the municipal level teams. Please see the visual representation in Figures 2 and 3 and appendix 1 for a further explanation on the teams.

Figure 2 Governance structure

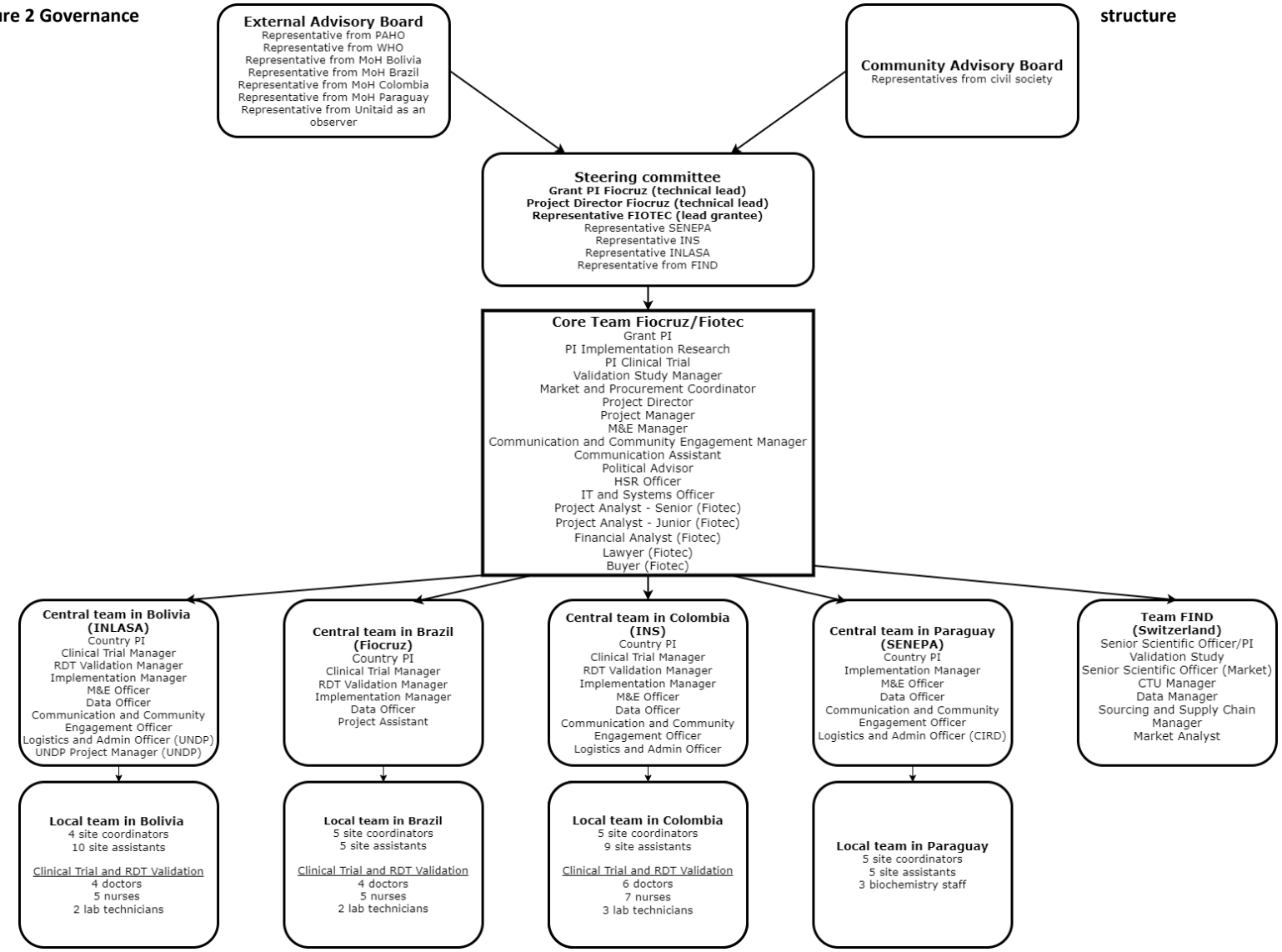
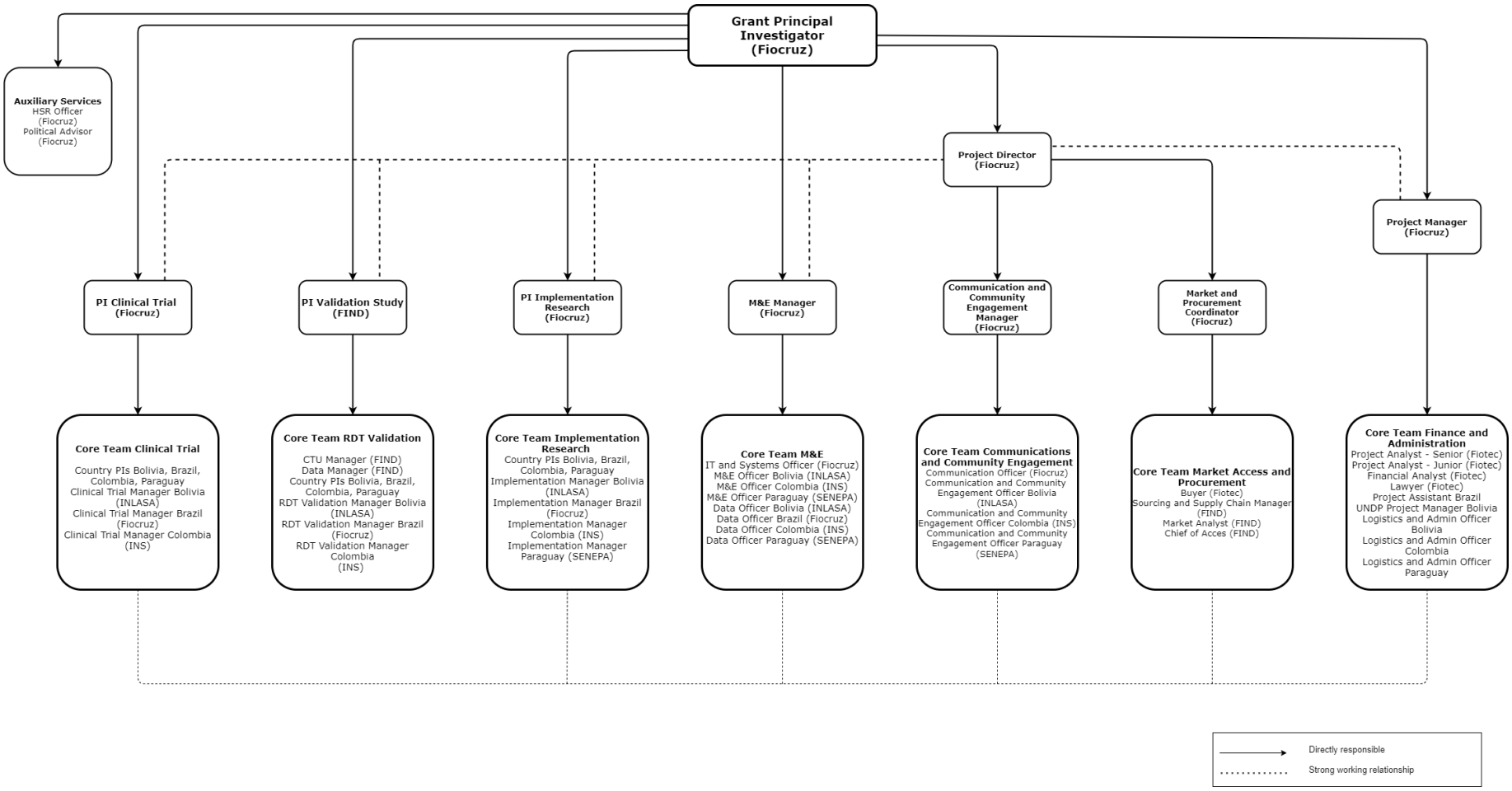


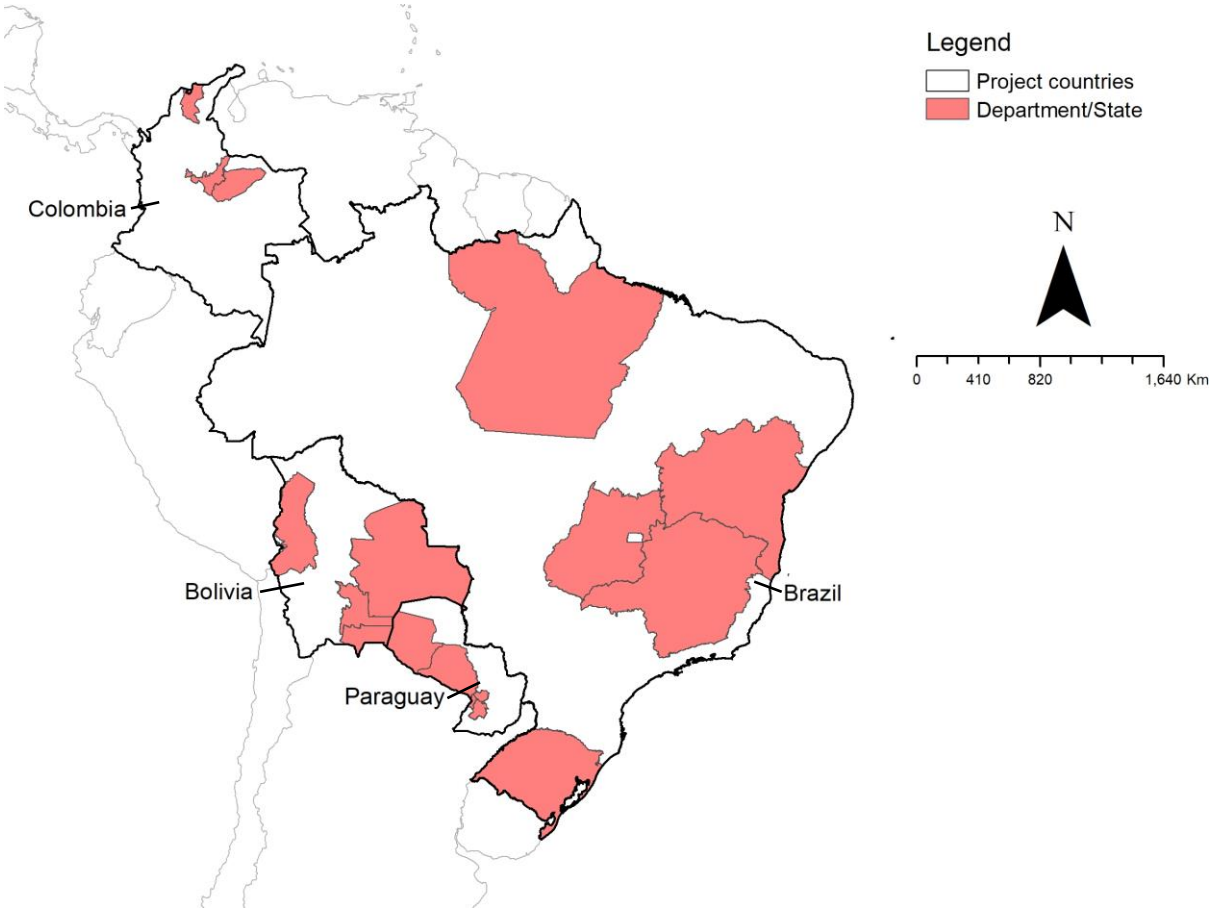
Figure 3 Workstreams



5. PROJECT COUNTRIES

The project will be implemented in four countries: Bolivia, Brazil, Colombia and Paraguay (Figure 4). Detailed overviews of the municipalities that will be included in the project may be found in Annex 1.2 – Annex 1.6.

Figure 4. Project countries including department/states



Project implementation countries have been selected based on a mix of criteria. While the prevalence and burden of CD are important factors, the potential for sustainable and catalytic change in the region was evaluated as whole and the below criteria helped identify the top countries:

- **Prevalence and burden of CD**: countries with high prevalence and/or absolute numbers of people with CD were selected in order to ensure the project benefits a large number of affected people and supports countries where CD is a major public health challenge. In total, the four countries have an estimated 2.4 million people with *T. cruzi* infection, of which an estimated 498,255 are women between the ages of 15-44. The following tables (5-7) demonstrate the ranking of the project countries when it comes to estimated prevalence, estimated total number of people with *T. cruzi* infection and the estimated number of women aged 15-44 with *T. cruzi* infection (29).

Table 5. Estimated *T. cruzi* prevalence per country

	Country	Estimated prevalence of *T.cruzi* infection per 100 habitants
1	Bolivia	6.10
2	Argentina	3.64
3	Paraguay	2.13
4	Ecuador	1.38
5	El Salvador	1.30
6	Guatemala	1.23
7	Colombia	0.96
8	Honduras	0.92
9	French Guyana, Guyana and Suriname	0.84
10	Mexico	0.78
11	Venezuela	0.71
12	Chile	0.70
13	Nicaragua	0.52
14	Panama	0.52
15	Peru	0.44
16	Belize	0.33
17	Uruguay	0.24
18	Costa Rica	0.17
19	Brazil	0.03

Table 6. Estimated number of people infected by *T. cruzi*

	Country	Estimated number of people infected by *T.cruzi*
1	Argentina	1,505,235
2	Brazil	1,156,821
3	Mexico	876,458
4	Bolivia	607,186
5	Colombia	437,960
6	Ecuador	199,872
7	Venezuela	193,339
8	Paraguay	184,669
9	Guatemala	166,667
10	Peru	127,282
11	Chile	119,660
12	El Salvador	90,222
13	Honduras	73,333
14	Nicaragua	29,300
15	Panama	18,337
16	French Guyana, Guyana and Suriname	12,600
17	Uruguay	7,852
18	Costa Rica	7,667
19	Belize	1,040

Table 7. Estimated no of women aged 15-44 years with *T. cruzi* infection

	Country	Estimated no of women aged 15-44 years with *T. cruzi*
1	Argentina	211,102
2	Bolivia	199,351
3	Mexico	185,600
4	Brazil	119,298
5	Colombia	116,221
6	Paraguay	63,385
7	Ecuador	62,898
8	Venezuela	40,223
9	Guatemala	32,759
10	Peru	28,132
11	El Salvador	18,211
12	Honduras	16,149
13	Chile	11,771
14	Panama	6,332
15	Nicaragua	5,822
16	French Guyana, Guyana and Suriname	3,818
17	Uruguay	1,858
18	Costa Rica	1,728
19	Belize	272

- **Political commitment and readiness:** for project success, the political commitment of government is indispensable, and in turn this commitment is reinforced as governments engage in direct, productive actions to help affected people. Each country's government has demonstrated a commitment and readiness to controlling CD through national CD programs, vector control initiatives, research support, and other activities. In addition, each government has put forward a renowned national institute to participate in this project, emphasizing the importance and commitment.
- **Availability of strong implementing partners**: each country selected has historically exhibited a commitment to controlling CD, with recent achievements, and hosts diverse stakeholders in government, academia, and civil society actively working to improve control of CD.
- **Relevance of countries to this project:** Bolivia is the country in Latin America that is most affected by Chagas disease, in terms of prevalence and the estimated number of infected persons. This had led to a large interest of research consortia and a number of important studies being conducted in Bolivian territories (like the TESEO, EQUITY and CHICO studies). (34–36) Although estimated prevalence in Brazil is low, due to the size of the population, the absolute number of estimated cases is high, both for the general population as well as women aged 15-44. In addition, Brazil's government has demonstrated significant interest in supporting interventions that have the potential of contributing to the elimination of congenital transmission. Colombia also has a relatively low prevalence, but relatively high absolute estimated numbers of CD infected persons. In addition, Colombia has a geographic and populational diversity that is important to include in the different studies. Paraguay is the country with the third highest prevalence in the region and a considerable proportion of women aged 15-44 that are estimated to be infected. In addition, the country has played a pioneering role in identifying the relevance of congenital transmission of Chagas disease.
- **Health systems:** each of the four countries has organized their health systems in different ways, with the primary health care (PHC) coverage (defined as % of the population that has access to PHC facilities) ranging from only 7% to 100% in the selected territories. Generally speaking, Colombia has the highest PHC coverage, whereas PHC coverage in Paraguay is very low. This diversity is important to be able to assess the feasibility of especially the implementation research interventions in each territory and ensure maximum replicability to other countries. Annex 1.7 demonstrates detailed overviews of the set-up of the health systems in each country.
- **Socio-economic factors**: according to the World Bank classification, Bolivia is a low- and middle-income country (LMIC), while Brazil, Colombia and Paraguay are upper- and middle- income countries (UMICs) who nevertheless suffer from high income inequalities. In these countries, as in the entire region, CD disproportionately affects marginalized populations, including indigenous communities, poor people in both rural and urban areas, and rural-urban or transnational migrants.
- **Parasitic variance**: the countries included in the project represent the genetic variety of parasitic strains that are responsible for the largest number of clinical manifestations of CD (see Table 8).
- **A strong link with epidemiological and entomological surveillance**: the participating countries have established epidemiological surveillance systems, with particular experience in CD. One aim of the project will be to help these countries strengthen surveillance with updated systems of data monitoring.

Table 8 describes the epidemiological characteristics of Chagas disease in the countries. Please find an overview of criteria for all Latin American countries in Annex 1.8.

Table 8. Epidemiological characteristics of Chagas disease in the countries

Country	Geographical areas at risk	Estimated no. of people infected by *T. cruzi* (2010)	Estimated no of women aged 15-44 with *T. cruzi* infection (2010)	Estimated annual no of cases of *T. cruzi* infection due to congenital transmission (2010)	Estimated prevalence of *T. cruzi* infection per 100 habitants (2010)	Population 2010	Predominant genetic and parasitic variances CD	Existing CD control program (Y/N)	Vector control (Y/N)	Existence of a diagnostic algorithm for Chagas disease	Existence of adequate laboratories for this project (Y/N)
Bolivia	Cochabamba, Sucre, Tarija and Santa Cruz	607,186	199,351	616	6.104	9,947,000	TcI & TcV	Y	Y	Y - see annexes for details	Y
Brazil	Bahia, Goiás, Minas Gerais, Pernambuco, Pará	1,156,821	119,298	571	0.030	190,755,799	TcI & TcII	Y	Y	Y - see annexes for details	Y
Colombia	Arauca, Sierra Nevada de Santa Marta, Casanare, Santander, Boyacá	437,960	116,221	1,046	0.956	45,805,000	TcI	Y	Y	Y - see annexes for details	Y
Paraguay	Chaco and Eastern regions	184,669	63,385	525	2.130	8,668,000	TcIII & TcV	Y	Y	Y - see annexes for details	Y

*WHO published an update on Chagas disease in 2015, however, the data was generated in 2010.

In November of 2019, the Brazilian MoH invited a number of the main organizations and institutions working on Chagas disease to a meeting in Brasilia to discuss the possibilities of forming a coalition to respond to the call of proposals that had just been launched by Unitaid. The organizations that were invited were Fiocruz, DNDi, Mundo Sano, ISGlobal, Instituto Nacional de Salud (Colombia), the Chagas Coalition and CEDIC (Paraguay). The organizations that did participate were asked to present their current work on Chagas, after which the possibility of combining forces and join in one consortium were discussed. DNDi, Instituto Nacional de Salud and CEDIC expressed their interest to participate. Mundo Sano and ISGlobal declined to participate as they were preparing to join a different consortium, endorsed by the Argentine MoH. After the meeting, the Brazilian MoH proceeded to formally contact the MoH of Bolivia, Colombia and Paraguay, as well as the MoH of Mexico to request their participation in a consortium that would be led by Fiocruz. The MoHs of Bolivia, Colombia and Paraguay agreed and formally acknowledged their willingness to participate in the consortium and the project. The MoH of Paraguay selected SENEPA to be their representative organization, substituting CEDIC.

For the regional collaboration, the project will make a selection of three focus countries, to be included in specific activities and interventions. The criteria for inclusion will be defined during the inception phase.

Table 9 presents an overview of the different studies to be executed in each country as well as the official documents and legal instruments that are either already in place or will be developed.

Table 9. Activities, official documents and legal instruments per country

Project country	Type of research to be executed	Details of MoU or legal instrument	Does this document cover the proposed project activities	Details of proposed new MoU or legal instrument to guide project implementation	Timeline
Bolivia	Implementation RDT validation Clinical Trial	Fiotec/Fiocruz have received a formal letter of the Bolivian MoH, confirming the participation in the project	Specific activities are not mentioned, but document is a full letter of support	A contract will be signed with INLASA upon signature of the contract with Unitaid	Inception phase
Brazil	Implementation RDT validation Clinical Trial	The Brazilian MoH has formally confirmed their commitment and support to this project	Specific activities are not mentioned, but document is a full letter of support	n.a.	
Colombia	Implementation RDT validation Clinical Trial	Fiotec/Fiocruz have received a formal letter of the Colombian MoH, confirming the participation in the project	Specific activities are not mentioned, but document is a full letter of support	A contract will be signed with INS upon signature of the contract with Unitaid	Inception phase

Paraguay	Implementation	Fiotec/Fiocruz have received a formal letter of the Paraguayan MoH, confirming the participation in the project	Specific activities are not mentioned, but document is a full letter of support	A contract will be signed with SENEPA upon signature of the contract with Unitaid	Inception phase

Please find the letters of commitment from the MoHs of each country in Annex 1.9 – Annex 1.12.

Figure 5 shows the PIs per protocol and per study, as agreed with consortium members.

Figure 5. Protocols and country PIs

	Protocols			
Countries	**Implementation**	**RDT Validation**	**Clinical Trial**	**Country PI**
Bolivia	Dr. Jorge Aruni Dr. Justo Chungara	Bioq. Enzo Gamarra Alfaro	Dr. Justo Chungara	**Dr. Jorge Aruni**
Brazil	Dr. Eliana Amorim	Dr. Alejandro Luquetti	Dr. Israel Molina	**Dr. Fernanda Sardinha**
Colombia	Dr. Gabriel Parra Dr. Magdalena Wiessner	Dr. Astrid Carolina Florez	Dr. Mario Olivera Dr. Marcela Mercado	**Dr. Gabriel Parra**
Paraguay	Dr. Vidalia Lesmo			**Dr. Hernan Rodriguez**
Protocol PI	**Dr. Andréa Silvestre**	**Dr. Albert Picado de Puig**	**Dr. Israel Molina**	**Dr. Andréa Silvestre**

6. STAKEHOLDER ENGAGEMENT

The stakeholder engagement outlined in this project aims to promote integration at different levels between affected communities and leaders, community organizations and other civil society organizations, local and national government authorities, national and international universities and research institutes, non-governmental organizations (NGOs) with national activities in addition to other global, regional and national institutions and agencies, and other interested or affected parties. Efforts for successful stakeholder engagement and efficient project implementation will take place at the local, regional and national level in each of the participating countries with the mobilization of health professionals, decision-making managers and health professionals, government and legislators, academic and scientific communities as well as NGOs. Meetings are planned in each country with key leaders and stakeholders for discussions at local and regional round tables to consider a unified CD agenda based on national and global needs with a focus on congenital transmission and reproductive, maternal, neonatal and child health, as a necessary first step.

Diverse national scenarios will be found in the four target countries. In general, the theme of CD, although present on the agenda of national governments, tends to be disconnected from reproductive, maternal, newborn and child health actions. The transformation of local agendas, ensuring the integration of surveillance actions with primary care, will be achieved through advocacy actions. Advocacy is a key component to enable the embedding of CD interventions into programs of MoHs and other public institutions. Such a structure favors the sustainability of health programs and promotes better national coordination and financing. NGOs and other stakeholders also have an important role to play in encouraging this buy-in from governments. Where government participation is absent, advocacy is needed to insert CD in political agendas.

In each of the countries involved, the members responsible for implementing the activities of the consortium either are an executing part of the local health ministries (INLASA-Bolivia, Fiocruz-Brazil, INS-Colombia and SENEPA-Paraguay). This guarantees the adhesion and involvement of the main national and local stakeholders, with the guarantee of jointly building a program to strengthen national agendas. In addition, PAHO's own regional involvement, which in addition to providing technical and scientific support to countries, shows interest and motivation for the project as an opportunity to strengthen the EMTCT-plus initiative agenda.

WHO’s interest and motivation for the project’s actions are related to the agenda 2030 of the Sustainable Development Goals (SDGs), in particular Goal 3 to ensure health and well-being for all, including reproductive, maternal, and child health. Three relevant targets of Goal 3 bring intersection with the objectives of this project: 1) ending epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases (including CD) and combating hepatitis, water-borne diseases, and other communicable diseases by 2030; 2) ensuring universal access to sexual and reproductive health care services, including services related to family planning, information, and education, and integrating reproductive health into national strategies and programs by 2030; and 3) reducing the global maternal mortality ratio.

Through CCSE, civil society will be involved in the planning and design of policies, programs, and strategies. This will contribute to the sustainability of the interventions and to ensure CS buy-in and participation in the project. Considering that building institutional relationships takes time and that hallmarks of good relationships – trust, mutual respect, and understanding – evolve over time based

on individual and collective experiences and interactions, project teams in Bolivia, Brazil, Colombia and Paraguay will engage with stakeholders from the early stages of project development.

Early engagement with stakeholders will provide a valuable opportunity to influence public perception and set a positive tone from the start. Local stakeholders can help to generate ideas and alternative solutions guided by the specificities of each territory. Early interactions may be used as a predictor of potential issues and risks.

Table 10 summarizes the expected involvement (which can be adjusted, expanded over time) of stakeholders at different levels. This table will be further completed through the stakeholder mapping exercise that is planned in the project's inception phase, which will also include a description of the way Fiocruz plans to engage with each stakeholder.

Table 10. Stakeholders, interests/motivation and anticipated roles

Stakeholder	Interests and motivation	Anticipated role / engagement in the project
National governments of Bolivia, Brazil, Colombia and Paraguay	New, evidence-based knowledge will serve as a catalyst tool to the national CD programs to move towards the fulfillment of the goals at the national level (elimination of congenital transmission) as well as international/global commitments. The availability of a set of strategies for implementing access to diagnosis and treatment of CD will have a great interest considering the implementation on local contexts of the countries. This include tools already available as well as the new ones generated by the project, particularly the use of rapid tests to support the expansion of access to diagnosis in their realities of primary health care. In addition, to make available the use of new and effective antiparasitic treatment schemes that are more feasible, ensuring adherence and use in real settings.	To incorporate and implement recommendations generated through this project in the national health systems prioritizing primary health policies on female, reproductive, maternal and infant health. In addition, they will scale-up a number of the interventions that were initiated through this project to other endemic areas in their respective countries thereby ensuring sustainability of our efforts. Considering that the 4 countries are in different stages of CD control, there is an interest in expanding the exchange of experiences and strategies reached for success in controlling mother-to-child transmission. Integrated actions within the project between national, state and local teams of CD control programs with those involved in maternal and child health programs.
Instituto Nacional de Laboratorios de Salud (INLASA)	As a decentralized public institution in Bolivia, with technical and managerial autonomy, it expects laboratory diagnostics for CD as well as quality control. It opens up the possibility of strengthening its role in supporting the epidemiological surveillance of the disease, within	To incorporate and implement recommendations generated through this project in the national health systems for CD diagnosis in laboratories prioritizing reproductive, maternal and infant health. INLASA will have a strategic role in supporting the validation process (including

	the protocols already established within the local realities for other diseases (HIV, syphilis, viral hepatitis). INLASA also plays an important role in the development of research and technical documentation of results and consensus with a view to strengthening and proposing policies for the Health System. It is an institution with authority and leadership over public and private laboratories, contributing to the fulfillment of objectives of improving the quality of life of the Bolivian population.	quality control), as well as in the regulation of new diagnostic tools for CD, with an emphasis on controlling mother-to-child transmission.
Instituto Nacional de Salud de Colombia (INS)	As a technical-scientific institute with legal personality, administrative autonomy and its own assets, the INS, being linked to the Ministry of Health and Social Protection, brings national perspectives to reach the project in Colombia. With a focus on public health and national action, it aims to protect health, being an important institutional actor for integrating the project's evidence into national guidelines, strengthening M&E actions for CD. It is part of the General Regime of Social Security in Health and the National System of Science, Technology and Innovation, which expands the potential of incorporating innovations and protocols validated by the project.	To incorporate and implement recommendations generated through this project in the Colombian national health system prioritizing primary health policies on female, reproductive, maternal and infant health. In addition, they will scale-up a number of the interventions that were initiated through this project to other endemic areas thereby ensuring sustainability of our efforts.
Servicio Nacional de Erradicación del Paludismo (SENEPA)	As responsible for the development of CD control actions in Paraguay SENEPA's participation in the project brings the possibility to validate, through evidence, new diagnostic tools, new therapeutic schemes as well as strategies for implementing access to health in CD. New, evidence-based knowledge will serve as a catalyst tool to the Paraguayan CD programs.	To incorporate and implement recommendations generated through this project in the Paraguayan national health system prioritizing primary health policies on female, reproductive, maternal and infant health. In addition, they will scale-up a number of the interventions that were initiated through this project to other endemic areas thereby ensuring sustainability of our efforts.
State/provincial and local governments – including health managers	Programs and the local health system (departmental, municipal, state) are generally directly	In addition to managers and health professionals, policy makers must be involved in order

	responsible for the health care and operational actions from health supplies to management of health providers at different levels (from primary health centers to referral hospitals). Have scientific evidence on the process of implementing a set of effective interventions to control congenital CD, as well as information on the cost-effectiveness of these interventions. Inclusion as a public policy will be facilitated by evidence of the project's external validity given the possibility of being replicated in other territories.	to have access to and disseminate evidence, and especially, to incorporate recommendations generated through this project in health policies on female, reproductive, maternal and infant health into government plans at different levels of management. The project will engage these stakeholders through continuous dialogue, meetings and participation in activities.
State/provincial and local health managers and professionals	Access to new diagnostic tools and more suitable treatment schemes. To qualify the health work carried out in endemic areas for the control of CD, aiming at protocols more adjusted to local realities and capacities. Health professionals will need to develop technical competence and have infrastructure to act in the prevention, diagnosis, treatment and follow-up of congenital CD. For that, there is the possibility of professional training in health through IEC actions, including more technical courses and the possibility of conducting training with specialization, master's or doctorate. The involvement of these professionals is essential to operationalize the set of strategic actions proposed for the pilot project.	In the states and municipalities, managers and health professionals will be mobilized for implementation research as key implementers (including doctors, nurses, community health agents or agents for CD control, among other possible strategic actors). Health professionals will be the main implementers within the project, considering the need for effective and sustainable actions at the local level, with a strong base in primary health care. The level of incorporation of protocols in health systems is directly related to the institutional culture and the level of involvement of health professionals in the proposed interventions. In this sense, a training plan, together with M&E, will involve these actors from the beginning of the project, with maintenance throughout the intervention.
Educational sector - professionals and social mobilizers	The education sector has the possibility of expanding the inclusion of the CD theme in education in endemic areas. In addition, there is an opportunity for insertion in community campaigns aimed mainly at adolescents and women of childbearing age, as well as pregnant women for testing for the disease. To develop integrated	Insertion in support of community-based activities, in addition to specific actions to be developed in schools and universities. The school community working in the health education and training process directed towards CD transmission, prevention, and health care. Support for the development of diagnostic campaigns in target

	actions with the health sector with a view to preventing CD among adolescents, including mother-to-child transmission, with an emphasis on health promotion and secondary prevention actions. Considering the possible barriers to health care for adolescents in health units (especially in primary care), it is opportune to also recognize and approach this population in other spaces where they have a greater insertion, such as in schools.	populations of the study, constituting one of the strategies for counseling and testing.
Women of childbearing potential and pregnant women at risk of *T. cruzi* infection	Women must have their health needs, as well as that of their children and other members of their family, attended to in terms of prevention, diagnosis and timely treatment of CD with a view to eliminating congenital disease. The achievement of the project's objectives necessarily depends on the reach of this population as well as adherence to the proposed actions.	Women of childbearing age and pregnant women diagnosed with CD should participate actively not only in their comprehensive care, but also in the process of monitoring the infection status of their children and other family members at increased risk for CD. Adherence to self-care and follow-up of the newborn depends on processes of reception, mobilization and co-responsibility of these actors to achieve the project's objectives. The project will reach this population through primary health care, health campaigns and maternity wards.
Community leadership at the local level	Having access to evidence-based information for translating knowledge, making them even more capable of mobilizing the entire community (including the private target population of the study) to seek health services in search of diagnosis and treatment for CD. In addition, having health education processes for endemic communities in order to develop Lobby & Advocacy actions at the local level, contributing to the sustainability of the project's actions and the expansion of its scope within the country.	The pilot implementation project considers local leaders of the community as implementers as well, since they should be involved in local mobilization actions. Having the support of leaders, who understand CD as a health problem to be overcome, will be essential for the increased demand for diagnostic and treatment actions, indirectly strengthening epidemiological surveillance actions. In addition, local leaders will be trained in recognizing CD signs and symptoms, as well as possible adverse effects of treatment so that they can refer community members to primary health centers.

International Federation of Associations of People Affected by CD (FINDECHAGAS): **COLOMBIA** - ASOCHAGAS – International Foundation: Casanare, Yopal **BOLIVIA** - Asociacion de Chuquisaca, Dep. de Chuquisaca, Monteagudo - Personas con mal de Chagas, Latidos Sucre, Ciudad de Sucre - ACHABEN - Beni, Trinidad - Asociación de afectados, amigos y médicos unidos por el Chagas (ASAAMUCH) - Santa Cruz - Corazones Unidos por el Chagas, Depto. de Cochabamba, Aiquile - Corazones Unidos por el Chagas - Ciudad de Cochabamba **BRAZIL** - Associação dos portadores de doença Chagas de Campinas Campinas (ACCAMP) - Associação dos Chagásicos da Grande São Paulo (ACHAGRASP) - Associação dos portadores de doença de Chagas do Rio de Janeiro (Rio Chagas) - Associação dos Portadores de doença de Chagas, Insuficiência Cardíaca e Miocardiopatia de Pernambuco (Associação Chagas)	These organizations represent the voice of the people affected by the CD. To expand the health access to diagnosis and treatment for all people in need. These movements fight for the defense of human and social rights to the health of people and communities affected and / or living with neglected and infectious diseases, especially CD through common and democratic spaces of representation, support, empowerment and articulation. They act through collective and articulated actions of people, and movements that compose it, seeking to be recognized as a legitimate space and national reference of struggle for the visibility of the needs of affected people and communities and/or living with neglected diseases and for their social rights. and humans. Among its common objectives are: defending the Right to Health; promote the unity and expansion of its representation spaces; and to promote the visibility of themes related to CD. With more visibility, diagnostic tools and options for therapeutic schemes, the possibility opens up to strengthen the fight against the stigma and social impacts of CD. A relevant role as essential actors to be actively mobilized to strengthen Lobby & Advocacy actions for policies aimed at eliminating congenital CD.	To ensure the voice of people affected by CD is incorporated in policies and activities, keep governments accountable to their commitments. The possibility of interface through joint actions and exchange of experiences opens an important and strategic space. Countries like Paraguay do not yet formally have organizations dedicated to the fight against CD. The project will open space to recognize legitimate movements in these countries and to connect FINDECHAGAS with a view to supporting their legitimation and formalization. It also includes participation in the process of discussion on the proposal under development to adapt to local realities, as well as insertion with recommendations for M&E activities.
HIV/Aids, hepatitis and syphilis NGOs	To expand the health access to HIV/Aids, hepatitis and syphilis diagnosis and treatment for all people in need. The experience of these social movements will also be important to strengthen social movements in CD, recognizing specificities, and building agendas with common actions.	To ensure the voice of people affected by other diseases with mother-to-child transmission integrating control actions in policies and activities, keep governments accountable to their commitments. All countries included in the project have organizations that work with specific agendas to fight these diseases. The identification of those most active with guidelines on mother-child transmission will

		be carried out in stages with a greater interface in loco.
Latin American Universities / academia / scientific societies (specially for tropical diseases) of Bolivia, Brazil, Colombia and Paraguay	These institutions will be able to expand the development of lines of research focusing on CD, including congenital transmission. To expand the integration of themes related to CD in teaching and research actions at universities (health professions, in particular). There is the prospect of greater knowledge about the development of strategic clinical research in CD, as well as implementation research. The involvement of professors, researchers and students is an important action to strengthen their capacities and vocations to respond to the CD.	To contribute with the academic expertise, context knowledge, and installed capacity of innovation processes. The possibility of expanding training processes for undergraduate and graduate students with this theme also expands.
Fiocruz	Fiocruz has a historic commitment, in addition to technical-operational and scientific legitimacy, for the development of innovation in all dimensions for the control of CD globally. There is great interest in the possibility of advancing research to develop new diagnostic tools and treatment schemes for CD. In particular, we emphasize the possibility of implementing strategic actions in local health systems to control the disease, contributing to local, national and global policies. Fiocruz has the potential to support the production of strategic inputs (diagnosis and treatment), the training of high-level health personnel to control, monitor and evaluate the disease, as well as partnerships to enable policies for CD. Fiocruz also expects to expand the exchange of experiences with countries in order to enhance future large-scale actions to control CD in other endemic areas.	Through the activities of its various research units, Fiocruz will coordinate the project (Fiotec and Evandro Chagas National Institute of Infectious Diseases – INI) and develop all project materials together with the consortium partners. In addition, Fiocruz's Centro de Relações Internacionais em Saúde (CRIS), will assist in the coordination of the international activities.
PAHO	Focus on global elimination of mother-to-child transmission of CD, particularly in endemic countries. PAHO has the concrete	To include the newly validated tools in the Strategic Fund and take up recommendations on implementation so that other

	possibility of compiling, through consistent evidence in different realities in Latin America, a set of actions based on protocols and models for implementing CD control. In particular, strengthen the EMTCT-plus initiative, a Framework for the Elimination of Mother-to-Child Transmission of HIV, Syphilis, Hepatitis B, and CD. Expansion of the coverage of *T. cruzi* screening among pregnant women, testing of neonates with *T. cruzi* seropositive mothers and carrying out antiparasitic treatment after the delivery of *T. cruzi* seropositive mothers. Includes the possibility to support the generation of scientific evidence on implementation models capable of being used in other endemic realities in Latin America, as well as the adoption of new tools for diagnosis (adult and newborn) and treatment of CD.	countries may follow the examples of Bolivia, Brazil, Colombia and Paraguay.
WHO	Focus on global elimination of mother-to-child transmission of CD, particularly in endemic countries. The evidence generated by the project may strengthen control actions in both endemic and non-endemic contexts. To strengthen the 2030 agenda for sustainable development goals. It also inserts the possibility of supporting the generation and availability of scientific evidence on implementation models capable of being used in other local realities, as well as new tools for diagnosis (adults and newborns) and treatment of CD, enhancing the model implementation of the ETMCT-plus initiative.	To incorporate recommendations and best practices in international guidelines on the global control of CD.
UNITAID	Focus on new interventions aimed at accelerating the availability, adoption and expansion of improved tools to diagnose and treat CD. Includes the pilot implementation of "test, treat and care" approaches in endemic	As a financing institution, to contribute as a mediator and evaluator of the proposal elaboration and development process through specific Committee. This includes project supervision, acting as a link

	countries, with a focus on active and systematic screening of girls and women at risk of infection, and their newborns.	between the management team and the project leader; providing general guidance and maintaining project quality and priority.
Laboratório Farmacêutico do Estado de Pernambuco Governador Miguel Arraes (LAFEPE)	LAFEPE focuses on researching, developing, producing and distributing medicines, products and services to meet public health policies aimed for CD, with guaranteed safety, quality and sustainability at affordable prices.	To support the production of benznidazole to be used in research sites in the 4 countries within the project to implement access to diagnosis and treatment of CD.
Foundation for Innovative New Diagnostics (FIND)	With a focus on diagnosis as a guiding action for the health of all people, it is inserted as a partner in this project in the search for solutions that are more adjusted to the local realities of the national health systems of endemic countries for CD, with scope for the realization of access in the primary health care.	To provide technical input and collaboration in the project. FIND will be involved in the protocols related to the enhanced access to diagnosis of CD.
World Heart Federation (WHF)	The WHF is the principal representative body for the global cardiovascular community, representing more than 200 heart foundations, scientific societies, civil society and patient organizations from over 100 countries, including the project countries. WHF has developed a roadmap for CD to contribute to the elimination of the disease.	To be included in advocacy efforts.
NHR Brasil	NHR Brasil is an NGO based in Brazil that seeks to institutionally support and strengthen organized civil society, foster public policies and support the realization of projects that contribute to inclusive development and health, working on agendas on leprosy, disabilities and NTDs.	To provide technical input and collaboration in the project. NHR Brasil will be involved in the local implementation protocols, articulation of implementers, strengthening of local associations to fight against CD, as well as recognition and strengthening of leaders. It also includes recognizing and addressing stigma locally, as well as supporting IEC actions.
DND*i*	Focus on the development of new treatments for the control of neglected diseases and other infectious diseases.	To provide technical input and collaboration in the project based on their experience.
Global Chagas Disease Coalition: a collaborative alliance of stakeholders working on CD which promote cohesion to individual actors' advocacy efforts and is also	As essential actors to be mobilized to support the development of Lobby & Advocacy actions for policies aimed at eliminating congenital CD.	To raise awareness and conduct advocacy activities on CD through an alliance of institutions involving DND*i*, Fundación Mundo Sano, FINDECHAGAS, Instituto Carlos

a valuable vehicle for pooling knowledge and technical expertise on CD		Slim de la Salud, Sabin Vaccine Institute, FIND, CEADES and ISGlobal. To contribute in the proposal's discussion process to adapt to local realities.
CD diagnostics and therapeutics manufacturers	Essential actors in the provision of the tools needed to diagnose and treat CD.	Through the market landscaping and market strategy development, the project will identify the key players to engage with and develop further interventions.
International and national donors	Essential actors to finance the scale-up of project interventions and activities	Will be included in advocacy efforts and targeted separately, from the start of the project. Concrete plans to be developed

7. SCALABILITY AND TRANSITION

The project will assess the validate new diagnostic algorithms, treatments and 'test, treat and care' strategies for contributing to the elimination of congenital CD, with a view on country adoption and scale-up at national level. The evidence generated will also be disseminated to other endemic countries for replication. In particular, the project will deliver:

1. Evidence on new technologies to improve access via primary healthcare: molecular diagnostic tools for congenital cases, a new PoC diagnostic algorithm based on rapid tests, and a shortened treatment regimen. This evidence can facilitate adoption and/or inform further research, with potential to greatly simplify testing and treatment and minimize costs and delays for patients and the health system, paving the way for scale-up.
2. Access models which are piloted in different countries and contexts. Because the 'test, treat and care' models are implemented with the collaboration of the health system, their transference to other in-country settings is facilitated. Models can be adjusted and adapted based on lessons learned through the project. Evidence on implementation, assured through a rigorous data collection system, will be shared broadly.
3. A competitive market for diagnostic tools and drugs: current diagnostic tools are suboptimal and the market for BZN is small and fragmented. The consortium, with the support of PAHO and WHO, will work to increase the market size for BZN by creating demand for the product and stimulate price decrease through market shaping strategies. On the diagnostic side, the project will work on improving pricing of diagnostic solutions and increasing supply security by consolidating the supply base and helping suppliers improve their market penetration.
4. Government ownership and integration into health systems: the project will be developed in partnership with, and led by, partner governments from its inception, creating a pathway towards sustainable transition and increasing government investment, both financially as well as in-kind. The models of implementation will be developed with a long-term view in mind and the project will aim to work through and empower existing government structures, to ensure continuity after project ends.
5. Enabling global and country policy environment: The consortium will work with PAHO/WHO, national regulatory agencies, and other key global stakeholders to create a conducive global policy environment for scale-up. It will work with the manufacturers of promising products to generate the evidence needed to enable PAHO to purchase and distribute the products through its Strategic Fund. It will also support guideline and policy changes at national level to promote adoption of the more effective treatment regimens and diagnostic algorithms and tools.
6. Domestic funding from national governments: In the countries where the project is implemented, government funding for CD is insufficient. The national agencies within this project are committed to directly rolling out the more cost-effective implementation models demonstrated through this project, which would ultimately free up fiscal space for more patients diagnosed and treated. Also, the project will be undertaking advocacy campaigns at both regional and national level, targeted directly at policy makers and key decisions makers in relevant agencies (like Health, Education and Finance).
7. Mitigation of risks and challenges: As a response to the COVID-19 pandemic, the project will involve additional training to health systems on Chagas disease testing and treatment during the pandemic, and inclusion of a detailed contingency plan for the clinical trial.

Figures 6 and 7 and Table 11 describe scalability models and provide detailed information on global/regional and country scalability. Stakeholder engagement is described in chapter 6 and the risk assessment is described in chapter 10 and Annex 1.13.

Figure 6. Regional/global scalability: anticipated progress for Chagas disease diagnosis and treatment

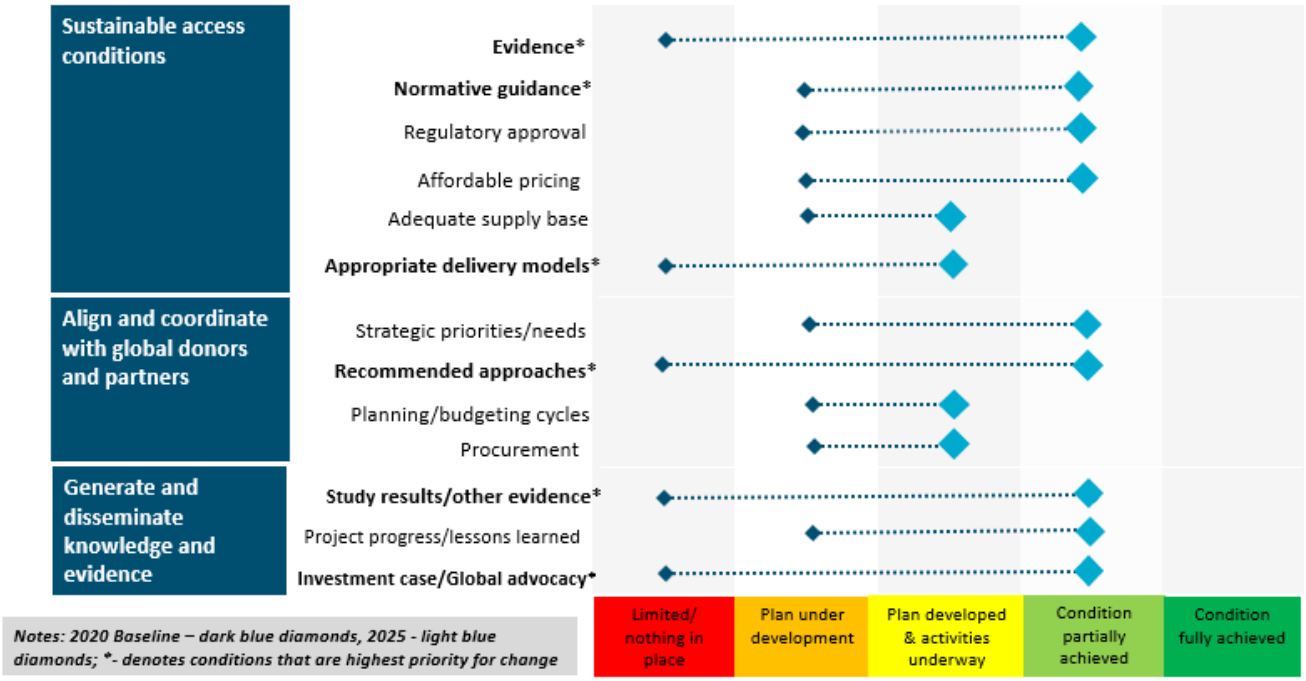


Figure 7. Country readiness for scale-up: anticipated progress for Chagas disease diagnosis and treatment in project countries

		Bolivia		Brazil		Colombia		Paraguay	
	Conditions	2020	2025	2020	2025	2020	2025	2020	2025
Secure political and financial support	Political engagement & buy-in	2	4	2	4	3	4	2	4
	Donor funding	1	3	1	3	1	3	1	3
	Domestic funding	2	4	3	4	2	4	2	4
	National advocacy	2	4	3	4	2	4	2	4
Ensure programmatic and operational readiness	Supportive policies	3	4	3	4	2	4	2	4
	Integration into national programs	2	4	2	4	2	4	2	4
	Effective supply chain systems	2	3	2	3	2	3	2	3
	Adequate health systems capacity	1	3	1	3	1	3	1	3
	Timely registration of products	3	4	3	4	3	4	2	4
Create community-driven demand	Civil society engagement	2	4	1	4	2	4	1	4
	Grassroots advocacy	1	4	1	4	1	4	1	4

Table 11. Summary of activities and key partners to facilitate country level readiness for scale-up of Chagas disease diagnosis and treatment approaches

Condition	Illustrative activities and key partners
Secure political and financial support	
Political engagement & buy-in	Activities: engagement of MoH in external advisory board (central level), meetings with the MoH and PAHO, invite to important events (e.g. kick-off or other events), peer exchanges, advocacy activities. Key Partners: MoH at different administrative levels, other government departments, PAHO
Donor funding	Activities: advocacy activities based on project evidence, develop clear communication materials, build relationships with donors and invite them, where possible, to participate in activities. Key partners: PAHO, WHO, Bill & Melinda Gates Foundation, NIH, BID, UNDP, European Commission, DFID, USAID.
Domestic funding	Activities: advocacy activities based on project evidence, develop clear communication materials, conduct regular meetings, understand the local/national power structures and the decision makers (formative research - actor mapping) Key partners: MoH, Ministry of Finance, local and regional PAHO offices
National advocacy	Activities: advocacy activities based on the evidence gathered through the studies, develop clear communication materials, conduct regular meetings with key stakeholders Key partners: MoH at different administrative levels, PAHO, WHO, CSO networks
Supportive policies	Activities: produce strong scientific evidence, best practices and recommendations that can be taken up in regional and national policies; strengthen CSO networks and build capacity for advocacy Key Partners: MoH, PAHO, WHO, CSO networks, local leaders
Ensure programmatic and operational readiness	
Integration into national programs	Activities: generate strong scientific evidence, best practices and recommendations that can be taken up in regional and national policies; build support and capacity among health workers and to increase demand for service integration Key Partners: MoH, PAHO, WHO, CSO networks, community leaders
Effective supply chain systems	Activities: develop multi-year need and demand forecasts, implement market interventions, provide business planning support Key Actors: MoH, PAHO, local and international manufacturers.
Adequate health systems capacity	Activities: develop and test a package of training modules that can be easily contextualized, provide online training modules through the Fiocruz platform, develop multi-year needs and demand forecasts, work with manufacturers to identify opportunities for cost-structure optimization, through the clinical trial and RDT validation, provide newly validated tools and drugs that make the diagnosis and treatment of CD more efficient. Key partners: MoH, PAHO, local and international manufacturers, CSOs
Timely registration of products	Activities: provide business planning support, facilitate interactions with regulators and provide backstop support on all matters relating to regulatory affairs Key partners: MoH, regulatory agencies, PAHO, WHO
Create community demand	
Civil society engagement	Activities: create a community advisory board (central level), contract community mobilizers, conduct a CS mapping, train local leaders on signs and symptoms of CD, potential adverse reactions of treatment and the need to refer patients to primary health posts, conduct a leadership training with CSO and local leaders, include CS in the information and education campaigns, CS networking consolidation and facilitate CS advocacy campaigns. Key Partners: local, national, regional and international CS actors (to be identified), local leaders
Grassroots advocacy	Activities: create a community advisory board (central level), contract community mobilizers, conduct a CS mapping, train local leaders on signs and symptoms of CD, potential adverse reactions of treatment and the need to refer patients to primary health posts, conduct a leadership training with CSO and local leaders, include communities in the different information and education campaigns. Key partners: local leaders, communities affected by CD

8. COMMUNITY AND CIVIL SOCIETY ENGAGEMENT

Community and Civil Society Engagement (CCSE) is central in any public health intervention, but potentially even more so in settings where there is evidence of inequalities in health. Due to the nature of Chagas disease and it being classified as an NTD, the focus on CCSE becomes even more important. However, the inclusion of communities and civil society (CS) in the combat against Chagas disease is relatively new and represents a somewhat unchartered territory. For instance, there are not that many civil society organizations (CSOs) dedicated to the cause, which is different from diseases like HIV, which have vibrant and vocal CSs on many different levels (global, regional, national, local).

For Chagas disease, one of the most well-known initiatives is the federation Findechagas, which comprises more than 20 associations worldwide. FINDECHAGAS was involved in the preparation of the project proposal and the project will continue to seek inclusion of the federation and individual members in the project activities and potentially the CAB. Table 12 demonstrates the organizations per project country.

Table 12. Organizations per project country

Country	Organizations
Bolivia	· Asociación de Chuquisaca, Dep. de Chuquisaca, Monteagudo · Personas con mal de Chagas Latidos Sucre, Ciudad de Sucre, ACHABEN - Beni, Trinidad · Asociación de afectados, amigos y médicos unidos por el Chagas (ASAAMUCH) - Santa Cruz · Corazones Unidos por el Chagas, Depto. de Cochabamba, · Aiquile and Corazones Unidos por el Chagas - Ciudad de Cochabamba.
Brazil	· Associação dos Portadores de doença de Chagas, Insuficiência Cardíaca e Miocardiopatia de Pernambuco (APDCIM/PE) · Associação dos portadores de doença Chagas de Campinas · Associação dos Chagásicos da Grande São Paulo (ACHAGRASP) · Associação dos portadores de doença de Chagas do Rio de Janeiro Brasil (Rio Chagas)
Colombia	· ASOCHAGAS – International Foundation
Paraguay	n.a.

Additional international initiatives include the Chagas platform and the global Chagas disease Coalition, of which Fiocruz is a member/contributor, and the World Heart Federation, a federation that is focused on cardiovascular diseases, but places special focus on CD.

To obtain a better understanding of CCSE in each target country, the project foresees a mapping exercise as part of the formative research that is planned for this project. This exercise will allow the project to understand the types of initiatives and organizations that exist on local and national levels, either directly linked to Chagas disease, or linked to platforms or programs that have a strong relation to (congenital) Chagas disease, such as maternal and child health, women's rights, or patient associations (amongst others). This mapping will feed into the additional activities that are being planned around CCSE. In addition, the project will identify local traditional, religious, women and youth leaders that will be targeted by the project and included in information and communication campaigns and capacity building initiatives.

CCSE activities and initiatives that are foreseen in the project are:

- Set-up of a community advisory board;
- Contract community mobilizers;
- Mapping of CS, knowledge and research institutes and local leaders;
- IEC campaigns;
- Leadership training of traditional and CS leaders;
- Setting up of selfcare/self-help groups for persons affected by Chagas disease, thereby providing safe spaces where they can meet their peers;
- Training of local leaders to recognize signs and symptoms of CD as well as potential adverse effects of treatments and refer people to the nearest primary health facility;
- Mobilize local leaders involved in maternal and child health (midwives, primary care health professionals, local and national managers) so that the topic of Chagas' disease is discussed in prenatal care and in the care of children and newborns;
- Local, national, and regional advocacy campaigns;
- Facilitate networking between CSOs.

The expected outcomes of the project's work on CCSE are to contribute to a visible and vibrant CS for persons affected by CD, a better representation of persons affected by CD in initiatives that concern them, and increased effectiveness of the different information and communication campaigns. In addition, the proper representation of communities and CS will contribute to the sustainability of the interventions. The old health paradigm of curative medical care focused on treatment of disease and public health measures in which people were merely passive beneficiaries. The REA will define the importance of the social, economic, cultural, and environmental determinants of health, and communities and civil society will be involved not only in execution of measures, but also in the planning and design of policies, programs, and strategies.

One of civil society's basic functions is to give a voice to vulnerable populations and communities for policy-making purposes. Since scientific knowledge about a health problem or its determinants can never substitute the experience of the people living with the problem, it is essential that policies and decisions be genuinely inclusive to ensure holistic solutions that respond to the needs to the persons affected.

Due to the complex nature of CD, the particular set of challenges that accompany the disease, and the fact that it often affects the poorest regions of the countries targeted in the project, potential risks and challenges are significant. As this project will be implemented in four different countries, the diversity among the target groups will be significant. The direct beneficiaries of the project will belong to different cultural groups, such as indigenous peoples, and will experience different levels of vulnerability. The areas where this project will enter, have often been neglected which means that attitudes towards strangers coming in to implement something new could be be somewhat negative. This reaffirms the necessity to create and maintain direct relations with local authorities, but also to work with local project staff who understand the local context and the communities. In addition, cultural and linguistic differences will be taken into account through the design of inclusive IEC materials that incorporate local languages and local cultural contexts, thereby facilitating the inclusion of people belonging to vulnerable and forgotten groups in society. In addition to being culturally sensitive, the project will produce IEC materials in various formats (audio and visual) in order to be broadly inclusive, also taking into account people with disabilities.

As congenital CD transmission currently represents one of the main sources of infection, this project will develop approaches to reach women of childbearing age, including during pregnancy. However, the project will have to be mindful of producing appropriate messaging that is sensitive to specific cultural contexts, including gender dynamics.

CD is a disease that suffers from a high burden of stigma, discrimination, anxiety and other psychosocial afflictions, which are currently not always well understood but may present significant barriers for persons affected to participate in activities. The project will address these issues by using the results from the formative research to inform healthcare delivery (through capacity building) and design culturally appropriate IEC materials and activities which address patients' perspectives and concerns about CD.

The mapping exercise may find that local CS presence is limited, fragmented or informal, which may present a challenge for inclusion in project activities. Equally, the mapping may find that there are organizations present in the country, though not in the target locations of the project.

The project will compensate the travel of community and CS partners should they participate in activities that require travel, such as the leadership training. In addition, they will be offered lunch and refreshments, if their participation is requested for a longer period of time. The project will however not pay them a fee for their time as this is not customary in Latin America. The formative research will inform the specific activities that community and CS partners will be part of.

The following graphic demonstrates the importance and reach of this project. The project will serve several important and underserved populations while addressing various complex aspects of CD.

Global/**Governance** level CCSE	National **level** CCSE	**Key populations and groups**
• Raise awareness and conduct advocacy activities on CD through an alliance of institutions involving important national and international stakeholders. •Generating evidence on test, treat and care approaches to share with partners including WHO and PAHO to contribute to global guidance. •Developing a project Community Advisory Board (CAB) and ensure CS represetation in other project committees and technical advisory groups. • Across the project, raise awareness, develop and distribute materials and provide counselling and aftercare in local languages using both visual and audio. •Strengthen regional collaboration	• Advocacy for MoH/countries, for policy adoption and scale up and demand creation. • Community mobilization and eduction • Mapping of CS, knowledge and research institutes and local leaders. • Campaigns at health centres,in schools, wiith local leaders, on radio, and social media. • Developing selfcare groups •Leveraging other programmes, like maternal and child health (midwives, primary care health professionals, local and national managers) to discusss and train on CD • Developing CSO networks.	• Women and children. • Vulernable and underserved populations such as indiginous people populations. • Migrant populations. • Gender sensitivies. • People living with disability. • High burden of stigma, discrimination, anxiety and other psychosocial afflictions in CD.

9. EXTERNAL COMMUNICATION APPROACH

The project's main knowledge management, advocacy and communication goal is to disseminate research findings, recommendations and best practices generated through this project to key local, national, regional and global stakeholders, such as health managers, governments, research and academic institutions, civil society and regional and global health organizations. In addition to this main goal, a number of specific objectives have been identified:

1. Create a detailed project communication plan, including a visual identity and key communication messages
2. Inform and educate the project's target populations on Chagas disease in general (forms of transmission, including congenital, clinical manifestations, available health services and available care) and the project's initiatives in particular
3. Inform and educate the general population on Chagas disease
4. Advocate for the inclusion of the project's research findings, recommendations and best practices in regional and national policies on maternal and child health
5. Ensure effective internal communication to promote the integration and engagement of the various teams and organizations involved in the project
6. Build relationships between the project's consortium and key local, national, regional and global stakeholders.

In order to achieve the goal and the objectives, the project will undertake the following activities:

- Design a project specific communication plan;
- Design general project communication messages and materials;
- Set-up of a project website;
- Set-up and active use of project specific social media accounts;
- Organize a project kick off in each country on national and local levels;
- Organize regular meetings with key stakeholders;
- Peer learning exchanges between national level MoH Chagas disease program managers, MRNCH stakeholders and technical working groups in order to promote cross-fertilization;
- Participate in (inter)national and regional events that are relevant to the subject of this project and organize side events to ensure sufficient attention for Chagas disease;
- Organize campaigns and events to increase the visibility of the project, including campaigns on the world Chagas disease day on the 14th of April;
- Specific IEC campaigns targeted at different populations (e.g. school, primary health centre, social media).

The buy-in of the different target populations is key to the success of this project and will be achieved through a number of interventions and activities. For governments and key health organizations, the project plans to ensure buy-in in two ways. First, each Ministry of Health of the participating countries has designated a local institution to be a member of the consortium, directly implementing activities foreseen under this project, thereby strengthening the local buy-in. Second, the project will set up an external advisory board consisting of representatives of the ministries of health of each participating country and representatives of PAHO and WHO. This advisory board will meet virtually twice a year, and provide political and technical input into the project.

For the direct beneficiaries, the project plans to ensure buy-in through a number of initiatives and activities. The formative research that is planned at the start of the project will greatly assist in developing a better understanding of the local contexts, providing valuable information on all of the

different target locations and populations, as well as a better understanding of the local realities of Chagas disease. The data that is collected through this formative research will feed into the IEC activities and campaigns. The materials that are to be developed will take geographical, cultural, ethnic, gender and linguistic specificities into account and will be made as inclusive as possible. Community mobilizers, that are based in the region and are themselves part of local communities, will be contracted to assist in the formative research, improve our understanding of each local context and facilitate relations with local communities.

Civil society and project partner buy-in is also foreseen in two ways. First, the project will set up a community advisory board (CAB) which will be composed of community members who share a common identity, history, symbols, language, and culture. As the CAB members come from the same communities as the project target populations, they can serve as a liaison between study participants and researchers and may assist in the development of IEC materials as well as represent participants' concerns to the consortium members. In addition, the project plans to organize specific capacity building sessions for civil society leadership as well as assist them in their advocacy and networking efforts.

The impact of the communication strategy will be monitored in different ways. For the website and the social media accounts, the project will use google analytics to monitor the number of unique views, time spent on each page, the number of button clicks, amongst others. This will allow the project to monitor the traffic on each site, as well as evaluate whether it is achieving the goals it had set out when creating the different platforms. To monitor the impact of the IEC campaigns, the project will include a few items on the intake forms at the primary health clinics that will try to filter out the reasons why people have come to seek medical attention and if this can somehow be related to the project's activities. In addition, anecdotal evidence will be gathered through the local coordinators and community mobilizers in each territory.

Unitaid will be invited with reasonable notice in advance to participate in all major communications activities relating to the Project being organized by the consortium and/or any third party recipients of Project Funding. This invitation will be done through email. Fiotec will facilitate access for Unitaid to images, data, spokespeople, audio visual assets and information on the Project, as well as site visits (where relevant to the Project) on Unitaid's request and as far as is logistically possible. Unitaid may also require Fiotec to provide samples of communications materials. To ensure Unitaid's validation joint materials prior to release, the project will develop a proper planning at the start of each major communication activity or event and ensure adequate time to send the materials to Unitaid for their review. Plans, changes and new events will be reported to Unitaid in advance, in writing.

Unitaid will be clearly acknowledged as the funder of the Project in all external communications. The reference will be positioned prominently in the item of communication. Unitaid's logo will appear alongside the logo of the consortium and will be displayed in the same size and with equal prominence as that of the consortium. Fiotec will seek permission from Unitaid to ensure that Unitaid's logo can be included alongside the consortium's logo on any external communications materials for the project. "External communications" include all written or formal verbal communications (including speeches or statements to the media) directly referring to the Project which are addressed to third parties outside Fiotec's own organization or those of its Consortium Members. A link to the Unitaid website will be included in all electronic references to the project.

Table 13 describes the objectives and the deliverables of the external communication approach for the first year of the project.

Table 13. External communication approach – objectives and deliverables year 1

Objectives	Audience	Type of deliverable	Deliverable	Timeline
Create a detailed project communication plan, including a visual identity and key communication messages	Consortium members, project direct target populations, PAHO, WHO, policy makers, MRNCH programs, other key stakeholders, and general public	A communication plan for the project Key communication messages Create a visual identity for the project Design communication materials and a website	Communication plan Website Communication materials	Q1 of the first year Q2 of the first year
Inform and educate the project's target populations on Chagas disease in general (forms of transmission, including congenital, clinical manifestations, available health services and available care) and the project's initiatives in particular	Women of childbearing age, their household contacts, and their communities	Health center campaign School campaign Social media campaign	Social Media Communication campaign	From Q4 of the first year
Inform and educate the general population on Chagas disease	General population, stakeholders, policy makers, press	Radio campaigns Social media campaigns Health center campaigns Website	Social media Website Communication campaigns	Q4 of the first year
Ensure effective internal communication to promote the integration and	Consortium members and partners	Communication plan Online communication platform	Communication plan Online platform	From Q1 of the project

Objectives	Audience	Type of deliverable	Deliverable	Timeline
engagement of the various teams and organizations involved in the project				
Build relationships between the project's consortium and key local, national, regional and global stakeholders	MoH of participating countries, PAHO, WHO, CSOs, community leaders	Project kick-off in each country on national and local levels Regular meetings with stakeholders Events Technical working groups	Project kick-off Minutes of meetings	From Q2 of the project

10. RISK MANAGEMENT

There are quite a few risks that have been identified in the Unitaid Risk Tool. The most critical risks, those with a likelihood and impact of 3 or 4, thereby rated medium-high or high, are:

Implementation risks:

1. Reduced access to people and territories included in this study; The COVID-19 pandemic has depleted the national resources on health (financial, human, material); High turnover of health professionals; Natural disasters that impede project implementation.
2. Lack of experience in managing multi-country projects that includes a consortium and sub-grantees & Inability of FIOTEC to manage certain consortium members which form part of national governments independently (leading to lack of accountability for such consortium members).
3. COVID-19 restrictions remain in place well beyond the start of the project.
4. Health professionals lack time to participate in the capacity building sessions.

Mitigation plan:

1. Through the work with local partners in each countries, access to territories will be facilitated. In addition, the implementation research will adopt a strategy that will allow the project to gain access to the target population, building trust and relationships that will facilitate access; All essential products for the execution of the project have been included in the budget. As the project will aim to find a connection to existing health services, the additional burden on health staff will be minimal; Unfortunately, high staff turnovers is something the project has no control over. What we can do is ensure that training materials are easily available so that crucial training elements may be facilitated. In addition, the project will try to build institutional memory at the health centers which should facilitate in building the capacity of new staff coming in; A natural disaster preparedness plan will be developed that will indicate what happens with the project should one of the target areas be hit by a natural disaster.
2. Sub-grantee management manual created to address and optimize programatic, finance and implementation controls and oversight amongst the consortium. Controls to be built in Annex 4 and SC to ensure that the direct payment to the grantees does not undermine FIOTEC's leverage to oversee the sub-grantees. Dedicated Project Management team with a strong Project Director, Project Manager and additional finance support staff to strengthen financial and programmatic oversight structures and ensure reporting and programmatic management of all consortium members and sub-contractors. Regular updates on consortium's financial management to be provided during quarterly touch points.
3. The project has been designed in such a way that a number of in-person activities can also be done online. In addition, the budget includes PPE materials.
4. The project will try to be as efficient as possible in the capacity building activities, making use of distance techniques, on the job learning and trying to keep in-person sessions as concise as possible, while at the same time maintaining high quality standards.

Scalability risks:

1. National governments lack the financial resources for scale-up and no other donors are willing to facilitate scale-up in countries
2. Delays in the uptake of project recommendations and best practices in global health organizations' guidelines

Mitigation plan:

1. A lack of financial resources often goes hand in hand with a lack of a sense of urgency / a lack of priority. The different advocacy activities will contribute to making CD more visible at national levels, and the gathered evidence will provide countries with a ready made roadmap and scalable solutions.
2. The project will work very closely with global health organizations in each stage of the project (design, implementation, analysis and reporting). PAHO and WHO will be part of the external advisory board, which will increase their buy-in in the project, and ensure that their input is included throughout. In addition, PAHO will support the project through an 'enabler grant', under Unitaid's direct oversight. Their role will be to participate in research protocol consultations in order to ensure that the planned research addresses key evidence gaps, accelerate policy development and access to new products, technologies and approaches emerging from the project and other on-going research under the same scope, and amplify public health impact within project countries and beyond through evidence dissemination & guideline development.

11. PROCUREMENT AND SUPPLY MANAGEMENT (PSM) APPROACH

During the inception phase of the project Fiotec will initiate negotiations with the PAHO Strategic Fund to make use of this mechanism for the procurement of all diagnostic tests and drugs. For this, Fiotec will make use of the existing fast-tracked process for Unitaid projects under the special agreement that currently exists between Unitaid and PAHO. However, it is currently unclear how long this process will take, which is why Fiotec will initially procure the diagnostic tests and drugs directly with manufacturers and have them shipped to each individual country, where the consortium partners (or their administrative agents) will receive the products, clear them, and distribute them to each municipality. Should an agreement with PAHO be reached during the inception phase, then the project will work through the strategic fund from year 1, procuring the tests and drugs directly through this mechanism. Important to note is that the procurement strategy and commodities will not change, the only thing that will change is the mechanism that is used for procurement.

The following core products will be procured for this project:

- Rapid Diagnostic Tests
    - Implementation Research: in Bolivia, Colombia and Paraguay we will use the StatPak test that is produced by Chembio Diagnostics and is registered with local regulatory agencies. Because this test is not registered with the Brazilian regulatory agency ANVISA, we will most likely use the RT-Biomanguinhos test, produced by Biomanguinhos in Brazil. However, the final selection of the test will be dependent on the results of a preliminary study that was executed in 2020, which included a lab-based evaluation of a number of Chagas disease rapid tests, registered in Brazil. Preliminary results indicate that RT-Biomanguinhos produces the best results.

    - Algorithm Validation Research: the selection of the RDTs may differ per country. FIND will execute similar studies to the one in Brazil in Colombia and Bolivia in order to make a selection of tests that will be used in the first phase of the validation study. The tests for the validation research may be bought in bulk.

- Serology – Enzyme-Linked Immunosorbent Assays (ELISAs)
    - Each country uses different types of ELISAs, depending on locally registered products. Fiotec is currently in the process of identifying which tests are used per country so that they may also be procured in bulk.

- Molecular Biology
    - Molecular biology will be used in the clinical trial and for the diagnosis of congenital CD in newborns. The main items to be procured are thermocyclers and PCR kits. The latter are not available commercially for CD, and countries are currently using in-house methodologies. As the project needs a standardized method across the three countries included in the clinical trial, in order to adhere to the quality levels necessary to ensure adoption of the results later on, Fiotec has requested Bio-Manguinhos to provide the services related to PCR in each country. These services include the procurement and installing of the thermocyclers, provision of the necessary kits and consumables, provision of training on the use of both and the provision of quality control. As the use of PCR is an important element in our efforts to produce a new algorithm for the diagnosis of newborns as well, the project has requested Bio-Manguinhos to replicate the same services in Paraguay, to ensure that all countries have a similar starting point. The costs for indirect sourcing through Bio-Manguinhos

are similar to direct sourcing, but the project will gain significantly in terms of quality assurance.

Treatment:

- Benznidazole: there are currently two producers in Latin America that provide Benznidazol, Elea-Phoenix and Lafepe. The Elea-Phoenix product is registered in Bolivia, Colombia and Paraguay and will therefore be procured for the use in these countries. However, the Elea-Phoenix product is not registered for use in Brazil, which means that the project will procure the Lafepe product. There are currently no expected issues with active pharmaceutical agents (API) for Benznidazole.

The commodity targets for the implementation research are as follows:

Full project period - 4 years - diagnostics, number of tests			
	RDT	Serology	Molecular Biology
Bolivia	86,000	31,000	3,250
Brazil	50,000	2,200	150
Colombia	52,000	20,800	500
Paraguay	46,000	3,000	220

Full project period, number of people treated			
	Adult	Child	Newborn
Bolivia	5,300	1,000	150
Brazil	400	75	10
Colombia	1,050	200	25
Paraguay	500	90	10

Full project period - 4 years - treatment - in tablets*				
	Benznidazol - adult - 100mg	Benznidazol - child up to 30kg - 100mg	Benznidazol - child up to 30kg - 12.5mg	Benznidazol - newborn - 12.5mg
Bolivia	954,000	120,000	120,000	27,000
Brazil	72,000	10,125		195
Colombia	189,000	24,000	24,000	4,500
Paraguay	90,000	10,800	10,800	1,800

*Estimates based on the following information:
LAFEPE only produces 100mg tablets
Elea-Phoenix produces tablets of 12.5mg, 50mg and 100 mg - prices 12.5mg = 0.087, 50mg = 0.281, 100mg = 0.457. For planning purposes the 12.5mg and 100mg options are used
The child dosage is 5mg up to 10mg per kilo. For planning purposes we will use 7.5mg per kilo
Children up to 30kg will use 2 100mg tablets and 2 12.5mg tablets per day.

The annual commodity targets for the implementation research are:

Diagnostics

1st year (20%)	RDT	Serology	Molecular Biology
Bolivia	17,200	6,200	650
Brazil	10,000	440	30
Colombia	10,400	16,160	100
Paraguay	9,200	600	44
2nd year (35%)	RDT	Serology	Molecular Biology
Bolivia	30,100	10,850	1,138
Brazil	17,500	770	53
Colombia	18,200	2,030	175
Paraguay	16,100	1,050	77
3rd year (35%)	RDT	Serology	Molecular Biology
Bolivia	30,100	10,850	1,138
Brazil	17,500	770	53
Colombia	18,200	2,030	175
Paraguay	16,100	1,050	77
4th year (10%)	RDT	Serology	Molecular Biology
Bolivia	8,600	3,100	325
Brazil	5,000	220	15
Colombia	5,200	580	50
Paraguay	4,600	300	22

Treatment

1st year (20%)	Benznidazol - adult - 100mg	Benznidazol - child up to 30kg - 100mg	Benznidazol - child up to 30kg - 12.5mg	Benznidazol - newborn - 12.5mg
Bolivia	190,800	24,000	24,000	5,400
Brazil	14,400	2,025	-	39
Colombia	37,800	4,800	4,800	900
Paraguay	18,000	2,160	2,160	360

2nd year (35%)	Benznidazol - adult - 100mg	Benznidazol - child up to 30kg - 100mg	Benznidazol - child up to 30kg - 12.5mg	Benznidazol - newborn - 12.5mg
Bolivia	333,900	42,000	42,000	9,450
Brazil	25,200	3,544	-	68
Colombia	66,150	8,400	8,400	1,575
Paraguay	31,500	3,780	3,780	630

3rd year (35%)	Benznidazol - adult - 100mg	Benznidazol - child up to 30kg - 100mg	Benznidazol - child up to 30kg - 12.5mg	Benznidazol - newborn - 12.5mg
Bolivia	333,900	42,000	42,000	9,450
Brazil	25,200	3,544	-	68
Colombia	66,150	8,400	8,400	1,575
Paraguay	31,500	3,780	3,780	630

4th year (10%)	Benznidazol - adult - 100mg	Benznidazol - child up to 30kg - 100mg	Benznidazol - child up to 30kg - 12.5mg	Benznidazol - newborn - 12.5mg
Bolivia	95,400	12,000	12,000	2,700
Brazil	7,200	1,013	-	20
Colombia	18,900	2,400	2,400	450
Paraguay	9,000	1,080	1,080	180

For the RDT based diagnostic algorithm validation, the following product will be procured:

Country	Diagnostic test	*Y1*	*Y2*	*Y3*	*Y4*
Bolivia	*ELISAs (confirmation)*	*1500 (750 x 2 ELISAs)*	*2000 (1000 x 2 ELISAs)*	*2000 (1000 x 2 ELISAs)*	*NA*
	RDTs (RDT-algo evaluation Y1 and validation Y2-3)	*2250 (750 x 3 RDTs)*	*2000 (1000 x 2 RDTs)*	*2000 (1000 x 2 RDTs)*	*NA*
	Molecular tests (follow-up CT)	*1224 (306 x 4 PCRs)*	*612 (306 x 2 PCRs)*	*306 PCRs*	*NA*
Brazil	*ELISAs (confirmation)*	*1500 (750 x 2 ELISAs)*	*2000 (1000 x 2 ELISAs)*	*2000 (1000 x 2 ELISAs)*	*NA*
	RDTs (RDT-algo evaluation Y1 and validation Y2-3)	*2250 (750 x 3 RDTs)*	*2000 (1000 x 2 RDTs)*	*2000 (1000 x 2 RDTs)*	*NA*
	Molecular tests (follow-up CT)	*1224 (306 x 4 PCRs)*	*612 (306 x 2 PCRs)*	*306 PCRs*	*NA*
Colombia	*ELISAs (confirmation)*	*1500 (750 x 2 ELISAs)*	*2000 (1000 x 2 ELISAs)*	*2000 (1000 x 2 ELISAs)*	*NA*
	RDTs (RDT-algo evaluation Y1 and validation Y2-3)	*2250 (750 x 3 RDTs)*	*2000 (1000 x 2 RDTs)*	*2000 (1000 x 2 RDTs)*	*NA*
	Molecular tests (follow-up CT)	*1224 (306 x 4 PCRs)*	*612 (306 x 2 PCRs)*	*306 PCRs*	*NA*

For the clinical trial, we will procure a total of 118,125 100mg tablets of BZN produced by Elea-Phoenix (300mg per day, for 60 days, for 525 patients plus 300mg a day, for 15 days, for 525 patients).

During the inception phase of the project Fiotec will initiate negotiations with the PAHO Strategic Fund to make use of this mechanism for the procurement of diagnostic tests and drugs. However, it is currently unclear how long this process will take, which is why Fiotec has developed a plan to procure the tests and drugs directly with the manufacturers as a back-up. This means that the PSM strategy for the first year will most likely be different from the one for the subsequent years.

The project's objective for the market shaping component is to develop a healthy, competitive and transparent market for diagnosis and treatment of CD, with affordable prices for quality diagnostic tools and treatment options, increased market volumes, increased numbers of registered manufacturers and sustainable procurement strategies. The key objective for the procurement strategy is to make it more efficient, sustainable, and reflective of actual needs.

Each country has their own PSM operations, but as they are managed centrally, it will be very complex for the project to tap into these mechanisms. This is why the project will initially centralize procurement through Fiotec, while negotiations are initiated with the PAHO Strategic Fund in order to establish pooled procurement. Under output 5, the project will work with individual countries to improve forecasting and planning and find sustainable ways of continuing procurement.

12. HUMAN SUBJECT RESEARCH

The following studies will be executed under this project:

	Protocols			
Countries	**Implementation**	**RDT Validation**	**Clinical Trial**	**Country PI**
Bolivia	Dr. Jorge Aruni Dr. Justo Chungara	Bioq. Enzo Gamarra Alfaro	Dr. Justo Chungara	**Dr. Jorge Aruni**
Brazil	Dr. Eliana Amorim	Dr. Alejandro Luquetti	Dr. Israel Molina	**Dr. Fernanda Sardinha**
Colombia	Dr. Gabriel Parra Dr. Magdalena Wiessner	Dr. Astrid Carolina Florez	Dr. Mario Olivera Dr. Marcela Mercado	**Dr. Gabriel Parra**
Paraguay	Dr. Vidalia Lesmo			**Dr. Hernan Rodriguez**
Protocol PI	**Dr. Andréa Silvestre**	**Dr. Albert Picado de Puig**	**Dr. Israel Molina**	**Dr. Andréa Silvestre**

The research questions that will be addressed by this project are:

For the implementation research: 'To what extent can an integrated model of implementation strategies increase the access of women of childbearing age, their infants, children and household contacts to Chagas disease diagnosis, treatment and comprehensive care through primary health care in endemic areas in Bolivia, Brazil, Colombia and Paraguay, in order to control the congenital transmission of Chagas disease?'

For the clinical trial: 'Is a reduced benznidazole treatment scheme with a fixed oral dose of 300mg / day for 15 days as effective as the standard treatment of 300mg / day for 60 days in the treatment of chronic Chagas' disease, in its indeterminate or mild cardiac form?'

For the RDT validation: 'Can RDT-based algorithms can be implemented to diagnose chronic CD (chronic *T. cruzi* infection) in endemic countries as an alternative to the current (laboratory-based) diagnostic algorithms?'

The research questions were designed by the consortium partners and discussed with WHO and PAHO. The research questions correspond to critical action points in key documents of the two global health organizations. The draft protocols will be validated with stakeholders and template protocols shared with countries in the region and beyond for researchers seeking to replicate the studies in their own context.

The organization responsible for HSR in the Consortium is Fiocruz, represented by Principal Investigator Dr. Andrea Silvestre de Sousa.

Fiocruz is a public health research institution located in the state of Rio de Janeiro, Brazil, considered to be one of the world's leading public health research institutions. The complete organizational chart may be accesses through the link https://portal.fiocruz.br/organograma. Fiocruz was founded by Dr. Oswaldo Cruz, a notable epidemiologist, in 1900. It is the birthplace of great names in the history of

Brazilian research, including Carlos Chagas, a researcher who discovered and gives name to Chagas disease. His professor Oswaldo Cruz, besides composing the name of the institution (Fundação Oswaldo Cruz), is also present in the denomination of the etiological agent of Chagas disease: the parasite *Trypanosoma cruzi* receives Cruz in his honor. Today, the institute houses 21 technical-scientific units, 11 of which are located in Rio de Janeiro, 10 are located in other Brazilian states and one is located in Maputo, capital of Mozambique. It is the technical arm of the Ministry of Health of Brazil, with the capacity to produce biological inputs - from diagnostic kits to medicines and vaccines (from its Bio-Manguinhos and Farmanguinhos units), in addition to providing health care (in its hospital units in Rio de Janeiro – INI/Fiocruz and National Institute of Health of Women, Children and Adolescents Fernandes Figueira – IFF/Fiocruz), with great insertion in public health education through its numerous postgraduate courses in biological sciences, epidemiology, humanities and social sciences.

A list of HSR studies conducted over the last 5 years with resulting publications is presented in the separate HSR Assessment.

The Fiocruz Clinical Research Network (RFPC) is an initiative that brings together research groups from Fiocruz in order to strengthen the strategic role of this activity in the institution. The RFPC was created in 2012 and, since then, promotes interaction between more than 60 clinical research groups from Fiocruz, in addition to representing them with the National Clinical Research Network (RNPC). The activities developed by RFPC are focused on establishing a forum for analyzing the situation and priorities, participating in the Management of National Policy on Health Technology, in partnership with the Brazilian Health Technology Network and the National Clinical Research Network; Strengthen and expand the technological, regulatory and professional competence of clinical research at Fiocruz; Intensify and formalize internal and external, national and international partnerships; Expand multidisciplinary professional training and technical-scientific training in clinical research and encourage debate and increase Fiocruz's participation in the definition of national guidelines related to bioethics and research involving human beings.

All relevant on-site staff will be trained according to the methodology that will be designed. All the staff involved in the Clinical trial and diagnostic studies will receive a GCP (Good Clinical Practice) training. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In addition to GCP, mandatory topics are human subject research, specific procedures and protocols. Other specific training will be provided according to the needs that will be identified in the field.

The investigator will be responsible for ensuring that the subjects fully understand the nature and purpose of the study. Informed consent will be obtained in person from proposed trial subjects or, if the person is not able to give informed consent by his or her legal representative, who will have been given the opportunity, in a prior interview with the investigator or a member of the investigating team, to be informed of the objectives, possible risks, harms and inconveniences related to conduct of the trial as well as all the conditions under which it will be conducted, the purpose of the collection and storage of data/biological material, the methods and techniques used, the measures taken to protect confidentiality, to whom access to the data will be given and for how long it will be stored. The subject will be also informed of his right to withdraw from the trial at any time. Indeed, the information will

make clear that refusal to participate in or withdrawal from the study at any stage of the trial will not prejudice in any way the subject's subsequent care. Lastly, subjects will be allowed sufficient time to decide whether or not they wish to participate. Only after this entire process, will the subject or, when the person is not able to give informed consent, his legal representative, be asked to provide written informed consent.

The subjects will give their written informed consent before participating in the clinical protocols. The signed Informed Consents will be retained by the investigator and made available (for review only) to the study monitor, auditor and inspector. All information related to the proposed clinical protocols (the objectives, possible risks, harm and inconvenience related to the conduct of the research as well as all the conditions under which it will be conducted, the purpose of collection and the storage of data/biological material, the methods and techniques used, the measures taken to protect confidentiality, the names of those who will be allowed, how long the information will be stored) will be provided to the subjects before their decision to participate or abstain from participation.

No personal information will be included on clinical research forms or kept with biological samples. All documents that include this type of information (for example, patient charts) will be available only to the study team. We will not include patients that have not explicitly given their consent through specific consent forms that have been approved by the ethical review committee. During the consent process the patient will receive all available information on the study and will have the opportunity to ask questions. Patients will also receive a signed copy of the information to take with them.
The language of the consent form will be accessible and appropriate for each study site, according to the general characteristics of the investigated population.

Reference documents for the conduct of HSR will be applied such as:
- Guideline for good clinical practice E6 (R2). International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH). 2016.
- *International ethical guidelines for health-related research involving humans.* Council for International Organizations of Medical Sciences (CIOMS). 2016.
- *Belmont Report.* Ethical *Principles* and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979
- Nurenberg Code, 1947. Trials of war criminal before the Nuremberg Military Tribunals Control Council Law 1949; 10 (2): 181-182: (http://www.ufrgs.br/bioetica/nuremcod..htm)
- Declaration of Helsinki. Ethical principles involving human beings in medical research. Adopted at the 18th World Medical Assembly in Helsinki, Filnância in June 1964, amended in 1975,1983,1989,1996,2000. (http://www.datasus.gov.br/conselho/RESOL97/res24697.htm)
- International Harmonization Conference (ICH). Manual for Good Clinical Practice. January / 1997. (http://www.ich.org/cache/compo/276-254-1.htm)
- NATIONAL HEALTH COUNCIL. 466. Guidelines and regulatory standards for research involving human beings. . 12 Dec. 2012.
- PAHO / WHO - Document of the Americas - Good Clinical Practice. IV PAN AMERICAN CONFERENCE TO HARMONIZE PHARMACEUTICAL REGULATION Dominican Republic, 2005. Available at: http://bvsms.saude.gov.br/bvs/publicacoes/boas_praticas_clinicas_opas.pdf

Data will be collected through case report form (CRF) specially designed for study protocols. Each country will have monitoring team supervised by the local PI, in charge of CRF monitoring all study sites in the country. The monitors are trained in the protocol procedures, filling, data quality control,

good clinical practices, and local regulations about human beings enrolled in clinical research. The monitoring plan includes:
-On-line monitoring of questionnaire answers, by weekly checking of electronic data system. This procedure allows verification of data consistency and completed CRF, and is applicable for 100% of study forms.
-Monitoring visits to each study site, the first one after the enrollment of 50 participants and each 6 months after that. During these visits the monitor verifies signed Inform Consent Forms (100%), regulatory research files (100%), eligibility (20%), stored biological samples (100%), and participants' chart (20%). Reports summarizing the on-line monitoring findings are generated every week and sent to the central coordination of the project (all reports) and sites' PIs (site specific reports). Reports summarizing the monitoring visits procedures and findings are generated after each site visit, sent to the central coordination of the project (all reports) and sites' PIs (site specific reports). Specific SOPs will be designed to contain the necessary information.

The samples that will be obtained in the study will be stored at central laboratories in each country. The chain of custody will be documented and traceable throughout. Quality control measures will be put in to place to ensure the quality of the samples.
The study will comply with the Data Protection Legislation which requires data to be anonymized as soon as it is mandatory to do so. All samples which requires storage will be labeled with anonymized participant ID numbers.

The project staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on the CRF and any electronic database. Data will be stored at servers at the study's technical lead (INI/Fiocruz). All necessary safety measures will be put in to place to assure that data is kept, and that confidentiality is assured.
Periodic reports will be produced by the technical lead and will be sent to the regulatory and ethical committees. The final report will be revised by all the researchers involved in the study, sent to the ethical committee and published.

Fiocruz, through its Open Data Plan (PDA-Fiocruz), establishes actions for the implementation and promotion of data opening under its responsibility. https://www.arca.fiocruz.br/bitstream/icict/42561/2/plano_de_dados_abertos_fiocruz_2018.pdf.
The consortium team ensures that all data generated by the project will be made available to WHO / UNITAID as needed for the development of guidelines and policies. All data generated by the consortium will be made available to the public health community, in terms of appropriate open access.

At the end of the study, a final report detailing the clinical trial and its results will be sent to all national regulatory agencies and Ethics' Committees. Information on the content, start and termination of the studies will be widely available. If necessary, the beneficiary may grant WHO / UNITAID a sublicensable, royalty-free license to use the data for non-commercial, public health and educational purposes. It should be noted that the confidentiality of any data generated by the project will be respected and maintained.

PROJECT PLAN APPENDICES

APPENDIX 1: KEY PERSONNEL

	Name	Position	Organization	Country	LoE	Description
1	Dr. Andréa Silvestre de Sousa	Grant PI	Fiocruz	Brazil	80%	Overall responsible for all grant related activities
2	to be recruited	PI Implementation Research	Fiocruz	Brazil	100%	Oversees and guides the execution of implementation research activities in all project countries
3	Dr. Israel Molina	PI Clinical Trial	Fiocruz	Brazil	40%	Oversees and guides the execution of clinical trial activities in all project countries
4	Dr. Albert Picado de Puig	Senior Scientific Officer / PI Validation Study	FIND	Switzerland	40%	Oversees and guides the execution of validation studies activities in all project countries
5	Dr. Eloan Pinheiro	Market and Procurement Coordinator	Fiocruz	Brazil	60%	Responsible for development and coordination of market and procurement strategies for CD
6	Ms. Debbie Vermeij	Project Director	Fiocruz	Brazil	100%	Strategic management of grant activities; conducts stakeholders engagement including liaising with donor and country counterparts, and streamlines project components integration.
7	To be recruited	Project Manager	Fiocruz	Brazil	100%	Responsible for timely execution of project activities; supports project director and Grant PI; and coordinates financial and administrative activities for smooth implementation (Fiotec and sub-grantees)
8	To be recruited	M&E Manager	Fiocruz	Brazil	100%	Oversees M&E activities, data systems, data collection and data analysis throughout all project related activities
9	To be recruited	Communication and Community Engagement Manager	Fiocruz	Brazil	100%	Develop project's communication and community engagement strategy; Responsible for the development of communication materials and community engagement/demand creation approaches in Brazil.
10	To be recruited	Communication Assistant	Fiocruz	Brazil	100%	Responsible for regular updating project communication channels such as social media, and newsletter
11	Dr. Tiago Nery	Political Advisor	Fiocruz	Brazil	20%	Supports project integration in project country governments and regional agencies

12	Ms. Renata Rabello	HSR Officer	Fiocruz	Brazil	80%	Ensures compliance with human subject research and good clinical practices in all studies, all countries
13	To be recruited	IT and Systems Officer	Fiocruz	Brazil	100%	Development, training and maintenance of project data collection systems
14	Luiz Abiel Rabelo Martins	Project Analyst - Senior	Fiotec	Brazil	100%	Responsible for financial monitoring activities related to the project implementation in all countries
15	To be identified	Financial analyst	Fiotec	Brazil	100%	Responsible for activities related to the financial control and project´s audit.
16	To be identified	Lawyer	Fiotec	Brazil	40%	Responsible for analysis of agreements and legal assistance.
17	To be identified	Buyer	Fiotec	Brazil	100%	Responsible for activities related to the purchase process
18	To be identified	Project Analyst - Junior	Fiotec	Brazil	100%	Responsible for financial monitoring activities related to the project implementation in all countries
19	Dr. Fernanda Sardinha	Country PI	Fiocruz	Brazil	40%	Overall responsible for all studies conducted in the country
20	Dr. Israel Molina	Clinical Trial Manager	Fiocruz	Brazil	50%	Responsible for the execution and daily operations of clinical trial study in the country
21	Dr. Alejandro Luquetti	RDT Validation Manager	Fiocruz	Brazil	40%	Responsible for the execution and daily operations of validation studies in the country
22	Dr. Eliana Amorim	Implementation Manager	Fiocruz	Brazil	60%	Responsible for the implementation research and respective daily operations in country
23	To be recruited	Data Officer	Fiocruz	Brazil	100%	Responsible to ensure timely data collection in all sites and real time data quality control
24	Ms. Larissa de Paula	Project Assistant	Fiocruz	Brazil	100%	Supports the grant PI, project Director and Project Manager on daily activities in Brazil
25	Dr. Jorge Aruni	Country PI	INLASA	Bolivia	40%	Overall responsible for all studies conducted in the country
26	Dr. Justo Chungara	Clinical Trial Manager	INLASA	Bolivia	50%	Responsible for the execution and daily operations of clinical trial study in the country
27	Bioq. Enzo Gamarra	RDT Validation Manager	INLASA	Bolivia	50%	Responsible for the execution and daily operations of validation studies in the country
28	Dr. Jorge Aruni / Dr. Justo Chungara	Implementation Manager	INLASA	Bolivia	60%	Responsible for the implementation research and respective daily operations in country

29	To be recruited	M&E Officer	INLASA	Bolivia	100%	Oversees data systems, data collection and data analysis throughout all project related activities in the country
30	To be recruited	Data Officer	INLASA	Bolivia	100%	Coordinates data collection and data quality control in country
31	To be recruited	Communication and Community Engagement Officer	INLASA	Bolivia	100%	Responsible for the development of communication materials and community engagement/demand creation approaches
32	To be recruited	Logistics and Admin Officer	INLASA / UNDP	Bolivia	100%	Responsible for timely supply of products to sites and general project administration
33	To be recruited	UNDP Project Manager	UNDP	Bolivia	100%	Responsible for the monitoring of the project execution
34	Dr. Gabriel Parra	Country PI	INS	Colombia	40%	Overall responsible for all studies conducted in the country
35	Dr. Mario Olivera / Dr. Marcela Mercado	Clinical Trial Manager	INS	Colombia	50%	Responsible for the execution and daily operations of clinical trial study in the country
36	Dr. Astrid Carolina Florez	RDT Validation Manager	INS	Colombia	50%	Responsible for the execution and daily operations of validation studies in the country
37	Dr. Gabriel Parra / Dr. Magdalena Wiessner	Implementation Manager	INS	Colombia	60%	Responsible for the implementation research and respective daily operations in country
38	To be recruited	M&E Officer	INS	Colombia	100%	Oversees data systems, data collection and data analysis throughout all project related activities in the country
39	To be recruited	Data Officer	INS	Colombia	100%	Coordinates data collection and data quality control in country
40	To be recruited	Communication and Community Engagement Officer	INS	Colombia	100%	Responsible for the development of communication materials and community engagement/demand creation approaches
41	To be recruited	Logistics and Admin Officer	INS	Colombia	100%	Responsible for timely supply of products to sites and general project administration
42	Dr. Hernan Rodriguez	Country PI	SENEPA	Paraguay	40%	Overall responsible for all studies conducted in the country
43	Dr. Vidalia Lesmo	Implementation Manager	SENEPA	Paraguay	60%	Responsible for the implementation research and respective daily operations in country
44	To be recruited	M&E Officer	SENEPA	Paraguay	100%	Oversees data systems, data collection and data analysis throughout all project related activities in the country
45	To be recruited	Data Officer	SENEPA	Paraguay	100%	Coordinates data collection and data quality control in country

46	To be recruited	Communication and Community Engagement Officer	SENEPA	Paraguay	100%	Responsible for the development of communication materials and community engagement/demand creation approaches
47	To be recruited	Logistics and Admin Officer	SENEPA / CIRD	Paraguay	100%	Responsible for timely supply of products to sites and general project administration
48	To be identified	Senior Scientific Officer	FIND	Switzerland	3%	Senior Scientific Officer to support market analysis activities
49	To be identified	CTU Manager	FIND	Switzerland	10%	CTU staff to support preparation and development RDT evaluation studies
50	To be identified	Data Manager	FIND	Switzerland	5%	Data management staff to support analysis RDT evaluation studies
51	To be identified	Sourcing and Supply Chain Manager	FIND	Switzerland	6%	To support market strategy activities
52	To be identified	Market Analyst	FIND	Switzerland	5%	To support market strategy activities

APPENDIX 2: PROJECT MILESTONES

Project Management Milestones

Project Management		
Milestone	**Description**	**Target date**
PM.1	Project staff contracted and capacitated to take up roles	Q1 – Year 1
PM.2	Local offices equipped for project execution	Q1 – Year 2
PM.3	External advisory board and community advisory board established and functioning	Inception phase
PM.4	Project kick-offs organized	Inception phase
PM.5	Consortium meetings organized	Q4 each year

Inception phase (IP) Critical Milestones			
Milestone	**Description**	**Deliverables**	**Target date**
IP.1	Co-funding contract with Brazilian MoH for US$ 4 million signed.	Confirmation of signed contract and key terms around reprogramming and disbursements	Inception phase
IP.2	Contract between Fiotec and Fiocruz renewed	Confirmation of signed contract	Inception phase
IP.3	Contracts signed between Fiotec and each individual consortium member	Confirmation of signed contracts	Inception phase
IP.4	MoUs for each project country in place	Confirmation of MoU signed	Inception phase
IP.5	Development of a terms of reference (ToR), including membership criteria, to guide the selection of participants of the external advisory board (EAB) and the community advisory board (CAB) and outline roles and responsibilities in order to avoid potential conflicts of interest Selection of members and set-up of the EAB and CAB	All charters, ToRs and proposed members submitted to Unitaid	Inception phase
IP.6	Develop HSR SOPs	HSR SOPs submitted to Unitaid	Inception phase
IP.7	Ethical approval obtained for each study (outputs 1, 3 and 4)	WHO ERC and national final approvals submitted to Unitaid	Inception phase
IP. 8	National, regional and country stakeholder and civil society mappings completed (output 1-4)	Stakeholder mappings submitted to Unitaid	Inception phase
IP.9	Desk review of SBCC and CCSE tools and approaches completed (output 2)	SBCC and CCSE tools & approaches submitted to Unitaid	Inception phase
IP.10	Key project director, finance, procurement, market access, SBCC and M&E staff hired	Confirmation submitted to Unitaid	Inception phase

IP.11	Procurement and supply management (PSM) country plans and budgets finalized and approved by Unitaid for all project countries, based on assessments and discussions with national and regional stakeholders.	PSM plan and strategy approved by Unitaid	Inception phase
IP.12	PAHO Strategic Fund MoUs signed	Confirmation of signed MoU	Inception phase
IP.13	Product landscape and equitable access strategy finalized and approved by Unitaid (output 5).	Equitable access strategy (including measurement approach) approved by Unitaid.	Inception phase
IP.14	Finalization of project management manual, policies on conflict of interest/ compliance manual, wrongdoing guidelines	Final project management manual conflict of interest/ compliance manual, wrongdoing guidelines submitted to Unitaid	Inception phase
IP.15	Assessment of the Covid-19 situation in all project countries and confirmation that project activities can start and be fully implemented as planned or reprogramming submitted.	Final COVID-19 assessment and plans submitted to Unitaid	Inception phase

Output Milestones

Output 1: Evidence generated on effective test, treat and care approaches through implementation research		
Milestone	**Description**	**Target date**
1.1	Study protocol approved at all ERB levels	Inception phase
1.2	Sites equipped and supplied	Inception phase
1.3	Formative research completed	Q2 – Year 1
1.4	Training of health professionals completed	Q2 – Year 2
1.5	Patient enrollment initiated	Q2 – Year 1
1.6	Data on implementation strategies collected and analyzed	Every 6 months
1.7	Mid-term analysis	Q4 – Year 2
1.8	Final study report completed	Q2 – Year 4
1.9	Completion of cost-effectiveness study report	Q1 – Year 4
1.10	Project results disseminated	Q2 – Year 4

Output 2: Community and civil society engaged at local, national and regional levels to increase demand for services and advocate for integration of recommended approaches for Chagas disease in policies, strategies and plans		
Milestone	**Description**	**Target date**
2.1	SBCC strategies developed	Q1 – Year 1
2.2	IEC strategy and campaigns developed and deployed	Q2 – Year 1
2.3	CS advocacy campaigns launched	Q3 – Year 2, 3, 4
2.4	Local leaders capacitated in CD	Q2 – Year 1
2.5	CSOs strengthened and capacitated	Q3 – Year 4

Output 3: Diagnostic algorithms validated for chronic and congenital CD		
Milestone	**Description**	**Target date**
3.1	Study protocol approved at all ERB levels	Inception phase
3.2	Patient enrollment initiated	Q1 – Year 1
3.3	Recruitment of 25%, 50%, 75% and 100% of the target sample size	Q1-Q3 – Year 1
3.4	Completion of data collection	Q2 – Year 3
3.5	Completion of data analysis	Q2 – Year 3
3.6	Completion of final study report	Q3 – Year 3
3.7	Completion of cost-effectiveness study report	Q3 – Year 3
3.8	Dissemination of results	Q3 – Year 3

Output 4: Evidence generated on improved treatment options		
Milestone	**Description**	**Target date**
4.1	Study protocol approved at all ERB levels	Inception phase
4.2	Patient enrollment initiated	Q1 – Year 1
4.3	Recruitment of 25%, 50%, 75% and 100% of the target sample size	Year 1-Year 2
4.4	Completion of data collection	Q2 – Year 4
4.5	Completion of data analysis	Q3 – Year 4
4.6	Completion of final study report and manuscript submission	Q4 – Year 4
4.7	Completion of cost-effectiveness study report	Q1 – Year 4
4.8	Dissemination of results	Q4 – Year 4

Output 5: Market shaping and supply chain interventions to ensure equitable access to innovative products		
Milestone	**Description**	**Target date**
5.1	Diagnostic and therapeutic landscape reports developed	Inception phase
5.2	Market strategy developed	Inception phase
	Other milestones will be included after approval of strategy	Inception phase

APPENDIX 3: PROCUREMENT STRATEGY DEVELOPMENT

During the inception phase of the project Fiotec will initiate negotiations with the PAHO Strategic Fund to make use of this mechanism for the procurement of all diagnostic tests and drugs. For this, Fiotec will make use of the existing fast-tracked process for Unitaid projects under the special agreement that currently exists between Unitaid and PAHO. However, it is currently unclear how long this process will take, which is why Fiotec will initially procure the diagnostic tests and drugs directly with manufacturers and have them shipped to each individual country, where the consortium partners (or their administrative agents) will receive the products, clear them, and distribute them to each municipality. Should an agreement with PAHO be reached during the inception phase, then the project will work through the strategic fund from year 1, procuring the tests and drugs directly through this mechanism. Important to note is that the procurement strategy and commodities will not change, the only thing that will change is the mechanism that is used for procurement.

The following core products will be procured for this project:

- Rapid Diagnostic Tests
    - Implementation Research: in Bolivia, Colombia and Paraguay we will use the StatPak test that is produced by Chembio Diagnostics and is registered with local regulatory agencies. Because this test is not registered with the Brazilian regulatory agency ANVISA, we will most likely use the RT-Biomanguinhos test, produced by Biomanguinhos in Brazil. However, the final selection of the test will be dependent on the results of a preliminary study that was executed in 2020, which included a lab-based evaluation of a number of Chagas disease rapid tests, registered in Brazil. Preliminary results indicate that RT-Biomanguinhos produces the best results.

    - Validation Research: the selection of the RDTs may differ per country. Similar studies to the one in Brazil will be executed in Colombia and Bolivia in order to make a selection of tests that will be used in the first phase of the validation study. The tests for the validation research may be bought in bulk.

- Serology – ELISAs
    - Each country uses different types of ELISAs, depending on locally registered products. Fiotec is currently in the process of identifying which tests are used per country so that they may also be procured in bulk.

- Molecular Biology
    - Molecular biology will be used in the clinical trial and for the diagnosis of congenital CD in newborns. The main items to be procured are thermocyclers and PCR kits. The latter are not available commercially for CD, and countries are currently using in-house methodologies. As the project needs a standardized method across the three countries included in the clinical trial, in order to adhere to the quality levels necessary to ensure adoption of the results later on, Fiotec has requested Bio-Manguinhos to provide the services related to PCR in each country. These services include the procurement and installing of the thermocyclers, provision of the necessary kits and consumables, provision of training on the use of both and the provision of quality control. As the use of PCR is an important element in our efforts to produce a new algorithm for the diagnosis of newborns as well, the project has requested Bio-Manguinhos to replicate the same services in Paraguay, to ensure that all countries have a similar starting point. The costs involved with including Bio-Manguinhos are

slightly higher when compared with direct sourcing, mainly due to the capacity building and monitoring services, however, the quality of PCRs will be equal across the board.

Treatment:

- Benznidazole: there are currently two producers in Latin America that provide Benznidazol, Elea-Phoenix and Lafepe. The Elea-Phoenix product is registered in Bolivia, Colombia and Paraguay and will therefore be procured for the use in these countries. However, the Elea-Phoenix product is not registered for use in Brazil, which means that the project will procure the Lafepe product.

The market situation and key market shortcomings that can be identified are different for both treatment and diagnostics. These are:

Diagnostics

Different diagnostic tools are used to diagnose *T. cruzi* infection, depending on the stage of the disease. In general, direct methods (e.g. microscopy, molecular tests) are used to diagnose acute *T. cruzi* infections (e.g. oral and congenital transmission) and serological tests (e.g. Enzyme-Linked Immunosorbent Essay - ELISA, indirect immunofluorescence - IFI, RDTs) are used to screen and diagnose patients suffering from chronic *T. cruzi* infection. The complexity of the diagnostic market for Chagas disease is further increased by the fact that there are multiple producers, the registration and (market) availability in endemic countries varies significantly, and the use of diagnostic tests differs among countries. All these factors make the procurement and supply management of diagnostic tools very challenging.

Treatment

There are only two drugs available for the treatment of CD, namely benznidazole and nifurtimox. Both drugs have proven to be effective in treating patients for acute CD, reactivation in immunosuppressed hosts, congenital disease, and most chronic cases. Despite the fact that the majority of Latin American countries have large pharmaceutical industries, only Brazil and Argentina produce BZN tablets and API. This impacts the pharmaceutical production chain because it creates an external dependence upon the production of the finished formulation. The current API production is sufficient for approximately 220 thousand patients per year, much less than the estimated number of people in need of treatment, according to the data of WHO. Nifurtimox is produced by Bayer in Central America, and is donated to countries through a WHO agreement.

Over the past three years, the supply of BZN and NFX has been provided through the bidding mechanism adopted by PAHO. However, repressed demand makes for insuffient procurement, which is demonstrated in the recent number of treatments that were reported by PAHO last year: BZN 100 mg, 16,727.21 treatments and NFX 120mg, 2,024.42 treatments. BZN was provided by the Elea-Phoenix laboratory, as it is the only producer with FDA approval and is therefore able to participate in the mechanism. NFX was donated by Bayer.

The project's objective for the market shaping component is to develop a healthy, competitive and transparent market for diagnosis and treatment of CD, with affordable prices for quality diagnostic tools and treatment options, increased market volumes, increased numbers of registered manufacturers and sustainable procurement strategies. The key objective for the procurement strategy is to make it more efficient, sustainable, and reflective of actual needs.

The procurement levers to shape the market will be identified in the inception period of the project, where a market landscape and strategy will be defined. The procurement strategy should be defined in such a way that it feeds into this market strategy to ensure the maximum results.

The four countries included in this project currently procure diagnostic tests and drugs, but as mentioned before, this process is flawed. This is why the project will invest in diagnostics tests and drugs, not only for the innovation studies, but also for the implementation research, in order to ensure that the planned activities can and will take place. Other donors that are currently funding access research include the Brazilian Ministry of Health, co-funder of this project as well.

PSM Operations

The forecasting for this project was done through the impact calculation and statistical calculations of patients to be included in the innovation studies, thereby determining the number of diagnostic tools and drugs that are necessary. The broader forecasting, on country level, will be part of the activities under output 5, which will be further defined during the project's inception period. The transactional procurement (including insurance, shipping and clearing) for four countries will be made through a global negotiation so that we can require a discount on the values of the products and the shipments will be carried out through the Incoterm CIP to the International Airport of each country. Regarding the acquisition procedure, Fiotec will start negotiations with suppliers so that products are shipped at the same time to each country, and check the customs procedures in both countries of origin and destination. The shipments will be carried out by the exporters through INCOTERM CIP, the cargo arriving at the destination airport will be cleared and distributed by each participating institution, as customs legislations do not allow a third party to clear the goods on their behalf. Payment to suppliers will be made globally after delivery of the goods. Fiotec will require periodic reports for inventory and data management purposes.

All the products that are earmarked for procurement under the implementation research are registered in the countries. For the innovation studies, the situation is slightly different. For the clinical trial the project will solely procure BZN that is produced by Elea-Phoenix in order to ensure uniformity, thereby adhering to necessary quality standards. For the validation of the diagnostic algorithm, the project may decide to use RDTs that are not currently registered in each country. They will however have a registration in at least one of the participating countries, ensuring adherence to quality standards. The use of non-registered products will be allowed as they will be used within specific, limited research settings.

Fiotec as the lead grantee will provide the necessary support and oversight of overall Project Safety Management procedures, including ensuring that the consortium partners follow the norms and regulations pre-established by UNITAID. Fiotec has a bilingual staff graduated in International Relations and Administration working in the international procurement department and in the international projects department, with a lot of expertise with international organizations and other donors.

The actual flow of procurement procedures for project implementation at Fiotec is: the PI or a pre-designated technical staff downloads the specific form from the Fiotec form website, and includes the information according to the process described in Fiotec manual (http://www.fiotec.fiocruz.br/pdfs/manuais/manual-fiotec-execucao.pdf). The project analyst registers the Purchase Request in the system, sends it to the logistics department, and assigns it to an analyst responsible for negotiation and approvals. The purchase requisition, sent by the project coordinator from Fiocruz, must include the address to deliver the product/service and the person responsible for receiving it. When purchases are delivered at Fiotec, the stockroom is responsible for

receiving it and direct the product its buyer. Fiotec´s policies and procedures consider such matters as quality, cost and delivery. The project coordinator signs the documents necessary to initiate purchasing of consumables, equipment and services.

The Purchase Analyst is responsible for checking all invoices. The Purchase Analyst is responsible for reviewing Duty fees and Value Added Taxes. Fiotec and Fiocruz do not have a tax exempt status on duty fees and VAT. The Purchase Analyst also reviews the Freight charges or allowances.

There is a written policy and procedure for emergency acquisitions that requires the PIs signature. Vouchers/invoices, supporting documents and expenses or other distributions are reviewed and initiated by a designated employee before payment is authorized. In case purchased goods are returned to the vendor the follow-up department is notified.

There is a system for the recording and checking of partial deliveries. The follow-up department is responsible for recording the deliveries, and any partial delivery is managed through e-mail. If an obligation was established for the grant account and only a partial order is received, the grant account is credited for the undelivered portion of the order. Ensuring high product quality is an indispensable element of Fiotec's approach to procurement. Fiotec's central goal is to provide the best quality product for the best price. Fiotec insists that all manufacturers/vendors follow stringent professional product production, sampling, independent laboratory testing and provide quality certification documentation, as well as follow Fiotec's own technical procurement and logistics guidelines.

Each country has their own PSM operations, but as they are managed centrally, it will be very complex for the project to tap into these mechanisms. This is why the project will initially centralize procurement through Fiotec, while negotiations are initiated with the PAHO Strategic Fund in order to establish pooled procurement. Under output 5, the project will work with individual countries to improve forecasting and planning and find sustainable ways of continuing procurement.

Fiotec is currently verifying customs issues of each country so that the import process may be carried out with total security. All International Chamber of Commerce laws will be followed, as well as international packaging procedures and cold chain regulations.

A global requirement strategy will be developed, including separate shipments for each country. This strategy will include a bulk negotiation to guarantee the lowest price for the total quantity for the project. Fiotec is already in contact with some suppliers and has requested some quotations to start the negotiations of prices and better logistics. In addition, Fiotec is currently researching the customs procedures of each country for accurate logistics. The negotiations with suppliers, shipment of goods, clearance from origin/destination and delivery at final destination will be monitored by Fiotec's Import Department.

Compliance with Quality Standards

The products that are to be procured under the implementation research have all been registered in the countries where they will be used. This means that local regulatory bodies have assessed and approved the products before including them in their registries. The drugs that will be procured for the clinical trial are FDA registered. For validation of the RDT based diagnostic algorithm, the tests that are to be used will either have direct local registration or registration in one of the participating countries.

Fiotec will assure that all products procured under this project will meet the UNITAID Quality Assurance Guidelines for this category of health commodities. To assure compliance with national regulatory and importation requirements, Fiotec has specialized and dedicated staff.
Fiotec has purchasing policies and procedures regulations, and follows the Decree 8,241 / 2014, which regulates Article 3 of Law in 8958, which provides for the acquisition of goods and contracting of works and services by supporting foundations in educational projects, research, extension, institutional, scientific and technological and stimulating innovation, including the administrative and financial management needed to implement such projects.

http://www.planalto.gov.br/ccivil_03/_Ato2011-2014/2014/Decreto/D8241.htm

The procedures governed by this Decree shall comply with the principles of impersonality, morality, probity, publicity, transparency, efficiency, competitiveness, permanent quest for quality and durability, and linkage to the convening instrument. Fiotec uses a pre-qualification procedure, prior to selection, aimed at identifying suppliers and goods that qualify or meet the technical and quality requirements of the support foundation.

Green Procurement
Fiotec has been creating an internal Green Procurement Policy, and also will analyze the "Informal Interagency Task Team on Sustainable Procurement in the Health Sector" website: http://iiattsphs.org instructions in order to cooperate for a green planet.
Based on Unitaid's Green procurement policies, Fiotec will seek to procure goods and services that lessen the burden on the environment in their production, use, and final disposal, whenever possible and economical. To effect green procurement, Fiotec will support the 4 R's strategy to (i) re-think the requirements to reduce environmental impact, (ii) reduce material consumption, (iii) recycle materials/waste, and (iv) reduce energy consumption. Before finalizing the procurement of goods and/or services, Fiotec will consider environmental concerns, including energy consumption, toxicity, ozone depletion, and radiation. The applicable eco-label ratings, including Energy Star, EU Eco-label, etc., will be evaluated to determine how environmentally friendly the goods and/or services are. The aim is to identify green goods and services, which have fewer harmful effects on human health and the environment than competing goods and services serving the same purpose. Fiotec will have to carefully consider the environmental impact of their work, especially on transportation and disposal of cartridges, machines, wastes, etc.

Avoidance of Fraud, Waste and Diversion
Fiotec and the Consortium Partners will have adequate procedures, systems, and measures in place, in accordance with the provisions of the grant agreement to ensure the quality and security of supplied items and avoid any fraud, diversion, and/or waste (e.g., drug expiries, product damage, improper storage) throughout the supply chain.

Fiotec records all its expenditures in SAP, which is used to verify any financial inconsistency within the use of resources. The purchase orders for supplies and/or equipment are generated within SAP and are project specific, therefore the same item cannot be charged to different grants / paid from different sources. Fiotec has a tracking system, within its SAP, in which the CPF (Brazilian personnel EIN) is monitored to check if the salaries for the same person are according to the established standard level. All approved Fiocruz projects are submitted to Fiotec and set up within its SAP system, which does not allow more than one project to be opened with the same specifications.

FIOTEC may conduct or commission financial audits, reviews, and operational or programmatic evaluations of any or all of a Consortium Partners' procurement activities, documents, and/or records relating to this UNITAID- funded project.

Procurement Plan

The Applicant will submit an up to date Procurement Plan in line with the agreed template. The Procurement Plan is separate to the Procurement Strategy and will be required with each periodic report and disbursement request. The Procurement Plan will be submitted in support of any Disbursement Request containing commodity funds request. The same Procurement Plan template makes provision for reporting on procurement executed in the preceding period.

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