Call: HORIZON-JU-GH-EDCTP3-2023-02-two-stage

(Research and Innovation actions supporting the global health EDCTP3 Joint Undertaking)

Topic: HORIZON-JU-GH-EDCTP3-2023-02-02-two-stage

Type of Action: HORIZON-JU-RIA

(HORIZON JU Research and Innovation Actions)

Proposal number: 101159438-2

Proposal acronym: CryptoTT

Type of Model Grant Agreement: HORIZON Action Grant Budget-Based

Table of contents

Proposal ID **101159438-2**

Acronym **CryptoTT**

1 - General information

Fields marked * are mandatory to fill.

Topic	HORIZON-JU-GH-EDCTP3-2023-02-02-two-st	Type of Action	HORIZON-JU-RIA
Call	HORIZON-JU-GH-EDCTP3-2023-02-two-stage	Type of Model Grant Agreement	HORIZON-AG

Acronym: CryptoTT

Proposal title: A CRYPTOSPORIDIOSIS POINT-OF-CARE TEST-AND-TREAT STRATEGY IN CHILDREN WITH DIARRHOEA

Note that for technical reasons, the following characters are not accepted in the Proposal Title and will be removed: < > " &

Duration in months: 48

Fixed keyword 1: Diagnostics

Fixed keyword 2: Infectious diseases

Free keywords: *LED-microscopy, Cryptosporidium, diarrhoea, children, treatment*

Abstract *

Cryptosporidium is an intestinal parasite causing cryptosporidiosis, a prevalent diarrheal disease among young children in low- and middle-income countries. This infection causes approximately 48,000 deaths and the loss of 7.9 million disability-adjusted life-years annually. Despite the existence of a low-cost drug, access to treatment is hindered by the limited availability of affordable, straightforward, point-of-care (POC) diagnostic tests. LED microscopy of auramine-phenol (AP) stained fecal smears has demonstrated promising diagnostic accuracy in detecting cryptosporidiosis.
In this project, we will implement a test-and-treat strategy in a stepped-wedge cluster randomized trial. The aim is to assess the clinical effectiveness of LED-AP testing, in conjunction with access to targeted drug treatment, in reducing the duration of cryptosporidiosis-induced diarrhea. We will evaluate diagnostic accuracy, operational issues, cost-effectiveness, and test turnaround times in realistic setting in two Sub-Saharan African (SSA) countries. Additionally, we will investigate whether rectal swab samples can expedite test turnaround times compared to bulk stool samples.
This project aligns with the UN Sustainable Development Goal 3 and WHO initiatives to reduce the burden of diarrheal diseases. Effective POC diagnostics and treatment are expected to alleviate diarrhea and reduce long-term complications. The findings will be instrumental in updating current diarrheal treatment guidelines, which primarily advocate for syndromic treatment.

The outcomes will be of significant interest to health facility staff, ministries of health in SSA, WHO, and the scientific community. This study will provide crucial data on optimizing LED-AP testing to guide clinical decision-making and targeted treatment, thereby preventing the overuse of antibiotics. The introduction of cryptosporidiosis testing can enhance surveillance of this critical pathogen.

Remaining characters 44

Has this proposal (or a very similar one) been submitted in the past 2 years in response to a call for proposals under any EU programme, including the current call? ○ Yes ◉ No

Please give the proposal reference or contract number.
Previously submitted proposals should be with either 6 or 9 digits.

Administrative forms

Proposal ID **101159438-2**

Acronym **CryptoTT**

Declarations

Field(s) marked * are mandatory to fill.

1) We declare to have the explicit consent of all applicants on their participation and on the content of this proposal. *	☒
2) We confirm that the information contained in this proposal is correct and complete and that none of the project activities have started before the proposal was submitted (unless explicitly authorised in the call conditions). *	☒
3) We declare: - to be fully compliant with the eligibility criteria set out in the call - not to be subject to any exclusion grounds under the EU Financial Regulation 2018/1046 - to have the financial and operational capacity to carry out the proposed project. *	☒
4) We acknowledge that all communication will be made through the Funding & Tenders Portal electronic exchange system and that access and use of this system is subject to the Funding & Tenders Portal Terms and Conditions. *	☒
5) We have read, understood and accepted the Funding & Tenders Portal Terms & Conditions and Privacy Statement that set out the conditions of use of the Portal and the scope, purposes, retention periods, etc. for the processing of personal data of all data subjects whose data we communicate for the purpose of the application, evaluation, award and subsequent management of our grant, prizes and contracts (including financial transactions and audits). *	☒
6) We declare that the proposal complies with ethical principles (including the highest standards of research integrity as set out in the ALLEA European Code of Conduct for Research Integrity, as well as applicable international and national law, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Rights and its Supplementary Protocols. Appropriate procedures, policies and structures are in place to foster responsible research practices, to prevent questionable research practices and research misconduct, and to handle allegations of breaches of the principles and standards in the Code of Conduct. *	☒
7) We declare that the proposal has an exclusive focus on civil applications (activities intended to be used in military application or aiming to serve military purposes cannot be funded). If the project involves dual-use items in the sense of Regulation 2021/821, or other items for which authorisation is required, we confirm that we will comply with the applicable regulatory framework (e.g. obtain export/import licences before these items are used). *	☒
8) We confirm that the activities proposed do not - aim at human cloning for reproductive purposes; - intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or - intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer. - lead to the destruction of human embryos (for example, for obtaining stem cells) These activities are excluded from funding. *	☒
9) We confirm that for activities carried out outside the Union, the same activities would have been allowed in at least one EU Member State. *	☒

The coordinator is only responsible for the information relating to their own organisation. Each applicant remains responsible for the information declared for their organisation. If the proposal is retained for EU funding, they will all be required to sign a declaration of honour.

False statements or incorrect information may lead to administrative sanctions under the EU Financial Regulation.

2 - Participants

List of participating organisations

#	Participating Organisation Legal Name	Country	Role	Action
1	UNIVERSITETET I BERGEN	Norway	Coordinator	
2	ARMAUER HANSEN RESEARCH INSTITUTE	ET	Partner	
3	FUNDACAO MANHICA	Mozambique	Partner	
4	Addis Center for Ethics and Priority Setting	ET	Partner	
5	Simbona Africa Engineering solution	ET	Partner	

Organisation data

PIC	Legal name
999974456	*UNIVERSITETET I BERGEN*

Short name: UiB

Address

Street	MUSEPLASSEN 1
Town	BERGEN
Postcode	5020
Country	Norway
Webpage	www.uib.no

Specific Legal Statuses

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/12/2022	- no
SME self-assessment	31/12/2022	- no
SME validation	unknown	

Departments carrying out the proposed work

Department 1

Department name	Department of Clinical Science	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Jonas Lies vei 87	
Town	Bergen	
Postcode	5021	
Country	Norway	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Prof.

Gender: ○ Woman ◉ Man ○ Non Binary

First name*: **Kurt**

Last name*: **HANEVIK**

E-Mail*: **kurt.hanevik@med.uib.no**

Position in org.: Professor

Department: Deartment of Clinical Science

☐ Same as organisation name

☐ Same as proposing organisation's address

Street: Jonas Lies vei 87

Town: Bergen

Post code: 5021

Country: Norway

Website: https://www.uib.no/en/persons/Kurt.Hanevik

Phone: +47 55974624

Phone 2: *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Susanna	Pakkasma	susanna.pakkasmaa@uib.no	+xxx xxxxxxxxx
Liv-Grethe	Gudmundsen	post@fa.uib.no	+4755584965
Stein	Gulliksen	stein.gulliksen@uib.no	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier	
Prof	Kurt	Hanevik	Man	Norway	kurt.hanevik@med.uib.no	Category A Top grade re	Leading	0000-0002-1466-2326	Orcid ID	
Prof	Halvor	Sommerfelt	Man	Norway	halvor.sommerfelt@uib.no	Category A Top grade re	Team member	7003541706	Other ID	Scopus author identifier
Dr	Christina	Saghaug	Woman	Norway	christina.saghaug@uib.no	Category C Recognised	Team member	0000-0003-0836-7889	Orcid ID	
Dr	Janne	Mannseth	Woman	Norway	janne.mannseth@uib.no	Category B Senior resea	Team member	0000-0003-1386-5073	Orcid ID	
Dr	Øystein	Johansen	Man	Norway	haarklau@gmail.com	Category B Senior resea	Team member	0000-0001-6020-7802	Orcid ID	

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☒
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Johansen ØH, Abdissa A, Zangenberg M, Mekonnen Z, Eshetu B, Bjørang O, Alemu Y, Sharew B, Langeland N, Robertson LJ, Hanevik K. Performance and operational feasibility of two diagnostic tests for cryptosporidiosis in children (CRYPTO-POC): a clinical, prospective, diagnostic accuracy study. Lancet Infect Dis. 2021 May;21(5):722-730. doi: 10.1016/ S1473-3099(20)30556-9. Epub 2020 Dec 3. PMID: 33278916*
Publication	*Johansen ØH, Abdissa A, Bjørang O, Zangenberg M, Sharew B, Alemu Y, Moyo S, Mekonnen Z, Langeland N, Robertson LJ, Hanevik K. Oocyst Shedding Dynamics in Children with Cryptosporidiosis: a Prospective Clinical Case Series in Ethiopia. Microbiol Spectr. 2022 Aug 31;10(4):e0274121. doi: 10.1128/spectrum.02741-21. Epub 2022 Jun 14. PMID: 35699433; PMCID: PMC9430463.*
Publication	*Tellevik MG, Moyo SJ, Blomberg B, Hjøllo T, Maselle SY, Langeland N, Hanevik K. Prevalence of Cryptosporidium parvum/hominis, Entamoeba histolytica and Giardia lamblia among Young Children with and without Diarrhea in Dar es Salaam, Tanzania. PLoS Negl Trop Dis. 2015 Oct 9;9(10):e0004125. doi: 10.1371/journal.pntd.0004125. PMID: 26452235*
Publication	*Sakkestad ST, Steinsland H, Skrede S, ..., Sommerfelt H, Hanevik K. A new human challenge model for testing heat-stable toxin-based vaccine candidates for enterotoxigenic Escherichia coli diarrhea - dose optimization, clinical outcomes, and CD4+ T cell responses. PLoS Negl Trop Dis. 2019 Oct 30;13(10):e0007823. doi: 10.1371/journal.pntd.0007823. PMID: 31665141*
Publication	*Nasrin D, Blackwelder WC, Sommerfelt H, ..., Mandomando I, Nhampossa T, Bassat Q, Roose A, O'Reilly CE, Mintz ED, Ramakrishnan U, Powell H, Liang Y, Nataro JP, Levine MM, Kotloff KL. Pathogens Associated With Linear Growth Faltering in Children With Diarrhea and Impact of Antibiotic Treatment: The Global Enteric Multicenter Study. J Infect Dis. 2021 Dec 20;224(12 Suppl 2):S848-S855. doi: 10.1093/infdis/jiab434. PMID: 34528677*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
CryptoPOC	*The CRYPTO-POC study was a evaluation of LED-microscopy and a rapid test as diagnostic methods for cryptosporidiosis. This was a field study in an Ethiopian hospital and a rural health centre including 912 children with diarrhoea and 706 controls. LED-AP had a sensitivity for cryptosporidiosis of 88% (95% CI 79–94) and a specificity of 99% (98–99).*
TaDiGe	*This is a study examining the effects of introduction of PCR method for Cryptospordidium and Giardia detection at six microbiology laboratories across Norway from 2014 to 2021. Samples positive for Giardia and Cryptosporidium are genotyped to examine mini-outbreaks and potential transmission patterns, as well as discerning differences between infections obtained domestically or abroad.*
CISMAC	*The Centre for Intervention Science in Maternal and Child Health (CISMAC) is a Centre of Excellence funded by the Norwegian Research Council, located at the University of Bergen. Since its start in 2013 it has fostered XX publications in well reputed journals like xxxx*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Infectious disease laboratory	*A well equipped laboratory facility. Can be used by visiting CryptoTT PhD students to learn and perform DNA extraction and qPCR to quantify Cryptosporidium DNA for specific studies in samples collected in the CryptoTT study.*

SAFE	*SAFE (secure access to research data and e-infrastructure) is a solution for secure processing of sensitive personal data in research, developed by the IT division at UiB*
BIOS	*The core facility for biostatistics and data analysis works to enhance the methodological quality of research and research proposals at the Faculty of Medicine and Dentistry (MOF).*
CISMAC	*CISMAC is a consortium of Centre for International Health at the University of Bergen, and research institutions in Bangladesh, Ethiopia, India, Nepal, Pakistan, Palestine, South Africa, Uganda and Zambia. The consortium also includes Chr. Michelsens Institute, Innlandet Hospital Trust, the Norwegia*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
889740358	*ARMAUER HANSEN RESEARCH INSTITUTE*

Short name: ARMAUER HANSEN RESEARCH INSTITUTE

Address

Street	JIMMA ROAD ALERT COMPOUND
Town	ADDIS ABABA
Postcode	1005
Country	Ethiopia
Webpage	https://ahri.gov.et/

Specific Legal Statuses

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	11/02/2022 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name: Clinical Trials Directorate ☐ not applicable

☒ Same as proposing organisation's address

Street: JIMMA ROAD ALERT COMPOUND

Town: ADDIS ABABA

Postcode: 1005

Country: Ethiopia

Department 2

Department name: Communicable and Non-Communicable Diseases Directorate ☐ not applicable

☐ Same as proposing organisation's address

Street: Jimma Road ALERT compound

Town: Addis Ababa

Postcode: 1005

Country: Ethiopia

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Dr

Gender ○ Woman ◉ Man ○ Non Binary

First name* **Abel**

Last name* **Abera**

E-Mail* **abel.abera@ahri.gov.et**

Position in org. Resercher

Department Communicable and Non-communicable Diseases Research Directorate

☐ Same as organisation name

☒ Same as proposing organisation's address

Street JIMMA ROAD ALERT COMPOUND

Town ADDIS ABABA

Post code 1005

Country Ethiopia

Website https://ahri.gov.et/

Phone +251909791028

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Alemseged	Abdissa	alemseged.abdissa@ahri.gov.et	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Abel Abera	Negash	Man	Ethiopia	abel.abera@ahri.gov.et	Category B Senior resea	Leading	0000-0003-1015-9704	Orcid ID
Dr	Hawult Taye	Adane	Man	Ethiopia	hawult.taye@ahri.gov.et	Category B Senior resea	Team member	0000-0002-5604-9706	Orcid ID
Dr	Fregenet	Tesfaye	Woman	Ethiopia	fregenettesfaye90@gmail.com	Category B Senior resea	Team member	0000-0001-6331-8137	Orcid ID
Dr	Adamu Bayissa	Kilytu	Man	Ethiopia	adamu.bayissa@ahri.gov.et	Category C Recognised	Team member	0000-0001-8658-9298	Orcid ID
Dr	Alemseged	Abdissa		Ethiopia	alemseged.abdissa@ahri.gov.et	Category A Top grade re	Team member	0000-0003-3798-5037	Orcid ID
Dr	Rawleigh	Howe	Man	United States	rawleigh.howe@ahri.gov.et	Category A Top grade re	Team member		

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☒
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Johansen ØH, Abdissa A, Zangenberg M, Mekonnen Z, Eshetu B, Sharew B, Moyo S, Sommerfelt H, Langeland N, Robertson LJ, Hanevik K. A comparison of risk factors for cryptosporidiosis and non-cryptosporidiosis diarrhoea: A case-case-control study in Ethiopian children. PLoS Negl Trop Dis. 2022 Jun 6;16(6):e0010508. doi: 10.1371/journal.pntd.0010508*
Publication	*Zangenberg M, Johansen ØH, Abdissa A, Eshetu B, Kurtzhals JAL, Friis H, Sommerfelt H, Langeland N, Hanevik K. Prolonged and persistent diarrhoea is not restricted to children with acute malnutrition: an observational study in Ethiopia. Trop Med Int Health. 2019 Sep;24(9):1088-1097. doi: 10.1111/tmi.13291*
Publication	*Desai SN, Akalu Z, Teshome S, Teferi M, Yamuah L, Kim DR, Yang JS, Hussein J, Park JY, Jang MS, Mesganaw C, Taye H, Beyene D, Bedru A, Singh AP, Wierzba TF, Aseffa A. A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. Am J Trop Med Hyg. 2015 Sep;93(3):527-533. doi: 10.4269/ajtmh.14-0683*
Publication	*Goodall RL, Meredith SK, Nunn AJ, Bayissa A, Bhatnagar AK, Bronson G, Chiang CY, Conradie F, Gurumurthy M, Kirenga B, Kiria N, Meressa D, Moodliar R, Narendran G, Ngubane N, Rassool M, Sanders K, Solanki R, Squire SB, Torrea G, Tsogt B, Tudor E, Van Deun A, Rusen ID; STREAM study collaborators: Evaluation of two short standardized regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. Lancet.2022 Nov 26;400*
Publication	*Walles JK, Tesfaye F, Jansson M, Balcha TT, Winqvist N, Kefeni M, Garoma S, Belachew F, Sturegård E, Björkman P. 2018. Performance of QuantiFERON-TB gold plus for detection of latent tuberculosis infection in pregnant women living in a tuberculosis- and HIV-endemic setting. PloS One 2018;13.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
CRYPTO-POC	*The primary objective of this study was to estimate the accuracy and operational performance of simple microscopy of auramine stained stool samples for diagnosis of Cryptosporidium infection. Secondary aims are to evaluate risk factors for Cryptosporidium infection and shedding over time. 1500 Ethiopian children below 5 years presenting to a Teaching Hospital or Health center with diarrhea over a 12-month enrollment period will be included. Additionally, 750 healthy controls from health centers*
Ethiopia Cholera Control and Prevention (ECCP)	*Cholera Vaccine Trail: Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. ECCP will evaluate the effectiveness and impact of OCV after vaccination and collect epidemiological data of cholera and other diarrhea diseases by conducting follow-up monitoring for several years*
ECD	*Baseline survey aiming to assess a comprehensive implementation strategy and establish baseline value used to evaluate the impact of early childhood development (ECD) program in Oromia region and Dire Dawa city administration. Funder: Big Win Philanthropy*
EFEd	*Enteric Fever Surveillance in Ethiopia, aiming to estimate the sero-incidence of S. typhi and S. paratyphi A infection in presumed high risk districts in Ethiopia.*
STREAM II	*A multi-center and multi-arm parallel randomized control trial used for Evaluation of Standardized Treatment Regimen of Anti-TB drugs for patients with MDR TB*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Research Electronic Data Capture (REDCap)	*REDCap provides user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and the ability to set up a calendar to schedule and track critical study events such as blood-draws, participant visits, etc.*
Cloud-Based Web Server	*This Cloud-hosting enables our institute (AHRI) to make applications and websites available on the internet using the cloud. It pools computing resources from a network of virtual and physical servers, allowing for greater scalability and flexibility to quickly make changes.*
State-of-the-art microbiology laboratory	*AHRI has equipments including BACTEC, NEXTSeq 500, thermal cyclers and other equipments required for phenotypic and molecular charcaterization of pathogens.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
954910390	*FUNDACAO MANHICA*

Short name: FM

Address

Street	RUA 12 BAIRRO CAMBEVE DISTRITO DA MANHIC
Town	VILA DA MANHICA MAPUTO
Postcode	1929
Country	Mozambique
Webpage	www.cismmanhica.org

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is unknown (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Centro de Investigação em Saúde de Manhica (CISM)	☐ not applicable
	☒ Same as proposing organisation's address	
Street	RUA 12 BAIRRO CAMBEVE DISTRITO DA MANHIC	
Town	VILA DA MANHICA MAPUTO	
Postcode	1929	
Country	Mozambique	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Dr

Gender ◯ Woman ◉ Man ◯ Non Binary

First name* **Delfino**

Last name* **Vubil**

E-Mail* **delfino.vubil@manhica.net**

Position in org. Researcher

Department Centro de Investigação em Saúde de Manhica (CISM)

☐ Same as organisation name

☒ Same as proposing organisation's address

Street RUA 12 BAIRRO CAMBEVE DISTRITO DA MANHICA

Town VILA DA MANHICA MAPUTO

Post code 1929

Country Mozambique

Website *Please enter website*

Phone +258845827040

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Godifre	Capinga	godifre.capinga@manhica.net	+xxx xxxxxxxxx
Meritxell	Molinos	meritxell.molinos@manhica.net	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Delfino	Vubil	Man	Mozambique	Delfino.vubil@manhica.net	Category B Senior resea	Leading	0000-0001-9139-5594	Orcid ID
Dr	Inacio	Mandomando	Man	Mozambique	Inacio.mandomando@manhica.net	Category A Top grade re	Team member	0000-0002-1078-2187	Orcid ID
Dr	Auria	Jesus	Woman	Mozambique	Auria.jesus@manhica.net	Category D First stage r	Team member	0000-0001-9845-0250	Orcid ID
Mr	Augusto	Messa jr.	Man	Mozambique	Augusto.junior@manhica.net	Category A Top grade re	Team member	0000-0002-1794-2462	Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☒
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Diarrheal Disease in Rural Mozambique: Burden, Risk Factors and Etiology of Diarrheal Disease among Children Aged 0-59 Months Seeking Care at Health Facilities. Nhampossa T, Mandomando I, Acacio S, Quintó L, Vubil D, Ruiz J, Nhalungo D, Sacoor C, Nhabanga A, Nhacolo A, Aide P, Machevo S, Sigaúque B, Nhama A, Kotloff K, Farag T, Nasrin D, Bassat Q, Macete E, Levine MM, Alonso P.PLoS One. 2015 May 14;10(5):e0119824. doi: 10.1371/journal.pone.0119824. eCollection 2015.PMID: 25973880*
Publication	*Impact of rotavirus vaccination on diarrheal hospitalizations in children younger than 5 years of age in a rural southern Mozambique. Manjate F, Quintó L, Chirinda P, Acácio S, Garrine M, Vubil D, Nhampossa T, João ED, Nhacolo A, Cossa A, Massora S, Bambo G, Bassat Q, Kotloff K, Levine M, Alonso PL, Tate JE, Parashar U, Mwenda JM, Mandomando I.Vaccine. 2022 Oct 19;40(44):6422-6430. doi: 0.1016/j.vaccine.2022.09.050. Epub 2022 Oct 1.PMID: 36192272*
Publication	*First identification of genotypes of Enterocytozoon bieneusi (Microsporidia) among symptomatic and asymptomatic children in Mozambique. Muadica AS, Messa AE Jr, Dashti A, Balasegaram S, Santin M, Manjate F, Chirinda P, Garrine M, Vubil D, Acácio S, Köster PC, Bailo B, Nhampossa T, Calero-Bernal R, Mwenda JM, Mandomando I, Carmena D.PLoS Negl Trop Dis. 2020 Jun 30;14(6):e0008419. doi: 10.1371/journal.pntd.0008419. eCollection 2020 Jun.PMID: 32603325*
Publication	*Molecular Characterisation of Cryptosporidium spp. in Mozambican Children Younger than 5 Years Enrolled in a Matched CaAntibiotic resistance and molecular characterization of shigella isolates recovered from children aged less than 5 years in Manhiça, Southern Mozambique. Vubil D, Balleste-Delpierre C, Mabunda R, Acácio S, Garrine M, Nhampossa T, Alonso P, Mandomando I, Vila J.Int J Antimicrob Agents. 2018 Jun;51(6):881-887. doi: 10.1016/j.ijantimicag.2018.02.005. Epub 2018 Feb 12.PMID: 29448013*
Publication	*Clinical features, risk factors, and impact of antibiotic treatment of diarrhea caused by Shigella in children less than 5 years in Manhiça District, rural Mozambique. Vubil D, Acácio S, Quintò L, Ballesté-Delpierre C, Nhampossa T, Kotloff K, Levine MM, Alonso P, Nataro JP, Farag TH, Vila J, Mandomando I.Infect Drug Resist. 2018 Oct 31;11:2095-2106. doi: 10.2147/IDR.S177579. eCollection 2018.PMID: 30464552*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Diarrheal diseases in children under 5 years old	*This was a multi country case-control study to determine the microbiologic etiology of diarreha in children aged less than 5 years residing the sub-Saharan Africa and south Asia, conducted from 2007-2012. The aim was to define the true pathogens (bacterial, virus and parasites) causing diarrhoea in these age groups. We demonstrated that Rotavirus, Shigella and Cryptosporidium were the most important causes of diarrhoea*
Impact of rotavirus vaccine in children under 5	*This study is integrated within the surveillance of diarrheal diseases in our study setting. The main object is to assess the impact of the introduction of Rotavirus vaccine into the country immunization program in Mozambique*
Effectiveness of PCV-10 and PCV-13	*This study is integrated within the surveillance of invasive bacterial infections in our study setting. The main object is to assess the impact of the introduction of pneumococcal conjugate vaccine into the country immunization program in Mozambique*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

Laboratory	*The laboratory is organized into five areas: clinical analyses (hematic parasitology and hematology/biochemistry); microbiology (general bacteriology and mycobacteriology); immunology; molecular biology; and quality assurance & biosafety. Samples are stored in 4ºC fridges and -20ºC /-80ºC freezers.*
Health and demographic Surveillance	*CISM has a morbidity surveillance system, through which demographic data, signs, symptoms and diagnoses of all outpatients and inpatients under the age of 15 are routinely collected. There is also a demographic surveillance system (DSS) conducted within the Manhiça district.*
Date Centre	*The management and storage of huge databases generated by all the studies are guaranteed by computer servers meeting the highest standards of quality control. This department is responsible for data management, database creation, data entry, query management and questionnaire storage.*
Social Science Research Unit	*The CISM has a Social Sciences Unit which gives support to the projects with important socio-behavioral components, through community engagement and the adaptation of the information given to the participants and the development of social and behavioral data collection tools.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
878181256	*Addis Center for Ethics and Priority Setting*

Short name: Addis Center for Ethics and Priority Setting, Addis Ababa University

Address

Street	Zambia St., CHS campus
Town	Addis Ababa
Postcode	1000
Country	Ethiopia
Webpage	

Specific Legal Statuses

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	02/03/2024 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Addis Center for Ethics and Priority Setting	☐ not applicable
	☒ Same as proposing organisation's address	
Street	Zambia St., CHS campus	
Town	Addis Ababa	
Postcode	1000	
Country	Ethiopia	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Dr

Gender: ○ Woman ◉ Man ○ Non Binary

First name*: **Solomon Tessema**

Last name*: **Memirie**

E-Mail*: **tess_soul@yahoo.com**

Position in org.: Director

Department: Addis Center for Ethics and Priority Setting

☐ Same as organisation name

☒ Same as proposing organisation's address

Street: Zambia St., CHS campus

Town: Addis Ababa

Post code: 1000

Country: Ethiopia

Website: *Please enter website*

Phone: +251911403936

Phone 2: *+xxx xxxxxxxxx*

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Solomon Tessema	Memirie	Man	Ethiopia	tess_soul@yahoo.com	Category A Top grade re	Leading	0000-0003-3806-2453	Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Memirie ST, Tolla MT, Rumpler E, Sato R, Bolongaita S, Tefera YL, et al. (2023) Out-of-pocket expenditures and financial risks associated with treatment of vaccine-preventable diseases in Ethiopia: A cross-sectional costing analysis. PLoS Med 20(3): e1004198. https:// doi.org/10.1371/ journal.pmed.1004198.*
Publication	*Memirie ST, Tolla MT, Desalegn D, Hailemariam M, Norheim OF, Verguet S, Johansson KA. A cost effectiveness analysis of maternal and neonatal health interventions in Ethiopia. Health Policy and Planning 2019; 1-9. PubMed PMID:31106346.*
Publication	*Memirie ST, Desalegn H, Naizgi M, et al. Introduction of birth dose of hepatitis B virus vaccine to the immunization program in Ethiopia: an economic evaluation. Cost Eff Resour Alloc 2020;18:23. https://doi.org/10.1186/s12962-020-00219-7.*
Publication	*Memirie ST, Yigezu A, Zewdie SA, et al. Hospitalization costs for COVID-19 in Ethiopia: empirical data and analysis from Addis Ababa's largest dedicated treatment center. PLoS ONE 2022;17(1): e0260930. https://doi.org/10.1371/journal.pone.0260930*
Publication	*Memirie ST, Metaferia ZS, Norheim OF, Levin CE, Verguet S, Johansson KA. Household expenditures on pneumonia and diarrhea treatment in Ethiopia: a facility-based study. BMJ Global Health 2017;1:e000166. PubMed PMID:28589003.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Disease Control Priorities-Ethiopia project	*The aim of the project was to strengthen the health economic capacity within the Federal Ministry of health (FMoH) and establish a health economics unit. Nine members of the FMoH were trained in health economics at a master's level (seven) and Ph.D. level (two).*
From Priorities to Plans:	*Developing Recommendations to Support the Integrated Delivery of NCD Care, The aim of the project is identifying NCD care delivery approaches at different levels of health care system in Ethiopia and evaluate the quality of care and cost (using time-driven activity based costing) of delivering priority NCD services by NCD service delivery models at different levels of care.*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
880847689	*Simbona Africa Engineering solution*

Short name: Simbona Africa Engineering solution

Address

Street	Addis Ababa,Ethiopia
Town	AddisAbaba
Postcode	1165
Country	Ethiopia
Webpage	www.simbona.net

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	03/09/2023 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name: Product Design Team ☐ not applicable

☐ Same as proposing organisation's address

Street: Alem Bank Road

Town: ADDIS ABABA

Postcode: 1165

Country: Ethiopia

Department 2

Department name: End Users and Biomedical Engineers/Technicians Training ☐ not applicable

☐ Same as proposing organisation's address

Street: Alem Bank Road

Town: Addis Ababa

Postcode: 1165

Country: Ethiopia

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Mr

Gender ○ Woman ◉ Man ○ Non Binary

First name* **Habtamu**

Last name* **Abafoge**

E-Mail* **habtamufoge@gmail.com**

Position in org. General Manager

Department Product Design Team

☐ Same as organisation name

☐ Same as proposing organisation's address

Street Alem Bank Road

Town Addis Abeba

Post code 1165

Country Ethiopia

Website www.simbona.net

Phone 0911339892

Phone 2 0913377121

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier

Administrative forms

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☐
Technology developer	☒
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Other achievement	*Simbona has worked on 5 medical devices re-engineering.3 of them developed successfully based international standards. Product designing, developing, manufacturing, assembling, installing and medical devices training provision are some of our achievements.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Healthcare technology innovation	*Simbona has worked on different medical devices re-engineering works*
Embedded system development	*Simbona has worked on different medical devices re-engineering works*
Training	*We have trained more than 300 hundred health professionals*
Installation	*Simbona has experience at devices installation and management*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Expertise	*Experience in medical devices training materials development and giving training. Skilled and experienced biomedical engineers in both designing and training program.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

Proposal ID **101159438-2**

Acronym **CryptoTT**

3 - Budget

No.	Name of beneficiary	Country	Role	Personnel costs/€	Subcontracting costs/€	Purchase costs - Travel and substistence/€	Purchase costs - Equipment/€	Purchase costs - Other goods, works and services/€	Internally invoiced goods and services/€ (Unit costs-usual accounting practices)	Indirect costs/€	Total eligible costs	Funding rate	Maximum EU contribution to eligible costs	Requested EU contribution to eligible costs/€	Max grant amount	Income generated by the action	Financial contributions	Own resources	Total estimated income
1	Universitetet I Bergen	NO	Coordinator	468 000	0	510 000	0	0	0	244 500.00	1 222 500.00	100	1 222 500.00	1 222 500.00	1 222 500.00	0.00	0.00	80 577.00	1 303 077.00
2	Armauer Hansen Research	ET	Partner	964 000	0	316 000	0	0	0	320 000.00	1 600 000.00	100	1 600 000.00	1 600 000.00	1 600 000.00	0.00	0.00	0.00	1 600 000.00
3	Fundacao Manhica	MZ	Partner	951 000	0	409 000	0	0	0	340 000.00	1 700 000.00	100	1 700 000.00	1 700 000.00	1 700 000.00	0.00	0.00	0.00	1 700 000.00
4	Addis Center For Ethics And Priority Setting	ET	Partner	90 000	0	17 360	0	0	0	26 840.00	134 200.00	100	134 200.00	134 200.00	134 200.00	0.00	0.00	0.00	134 200.00
5	Simbona Africa Engineering	ET	Partner	21 200	0	13 440	0	0	0	8 660.00	43 300.00	100	43 300.00	43 300.00	43 300.00	0.00	0.00	0.00	43 300.00
			TOTAL	2 494 200	0	1 265 800	0	0	0	940 000.00	4 700 000.00		4 700 000.00	4 700 000.00	4 700 000.00	0.00	0.00	80 577.00	4 780 577.00

4 - Ethics & security

Ethics Issues Table

1. Human Embryonic Stem Cells and Human Embryos			Page
Does this activity involve Human Embryonic Stem Cells (hESCs)?	○ Yes	◉ No	
Does this activity involve the use of human embryos?	○ Yes	◉ No	
2. Humans			**Page**
Does this activity involve human participants?	◉ Yes	○ No	8
Are they volunteers for non medical studies (e.g. social or human sciences research)?	○ Yes	◉ No	
Are they healthy volunteers for medical studies?	○ Yes	◉ No	
Are they patients for medical studies?	◉ Yes	○ No	8
Are they potentially vulnerable individuals or groups?	◉ Yes	○ No	9
Are they children/minors?	◉ Yes	○ No	8
Are they other persons unable to give informed consent?	○ Yes	◉ No	
Does this activity involve interventions (physical also including imaging technology, behavioural treatments, etc.) on the study participants?	◉ Yes	○ No	10
Does it involve invasive techniques?	○ Yes	◉ No	
Does it involve collection of biological samples?	◉ Yes	○ No	12
Does this activity involve conducting a clinical study as defined by the Clinical Trial Regulation (EU 536/2014)? (using pharmaceuticals, biologicals, radiopharmaceuticals, or advanced therapy medicinal products)	◉ Yes	○ No	11
Is it a clinical trial?	◉ Yes	○ No	11
Is it a low-intervention clinical trial?	○ Yes	◉ No	
3. Human Cells / Tissues (not covered by section 1)			**Page**
Does this activity involve the use of human cells or tissues?	○ Yes	◉ No	
4. Personal Data			**Page**
Does this activity involve processing of personal data?	◉ Yes	○ No	12
Does it involve the processing of special categories of personal data (e.g.: genetic, biometric and health data, sexual lifestyle, ethnicity, political opinion, religious or philosophical beliefs)?	◉ Yes	○ No	12
Does it involve processing of genetic, biometric or health data?	◉ Yes	○ No	12
Does it involve profiling, systematic monitoring of individuals, or processing of large scale of special categories of data or intrusive methods of data processing (such as, surveillance, geolocation tracking etc.)?	○ Yes	◉ No	
Does this activity involve further processing of previously collected personal data (including use of preexisting data sets or sources, merging existing data sets)?	○ Yes	◉ No	
Is it planned to export personal data from the EU to non-EU countries?	○ Yes	◉ No	
Is it planned to import personal data from non-EU countries into the EU or from a non-EU country to another non-EU country?	◉ Yes	○ No	20

Need to specify here

Does this activity involve the processing of personal data related to criminal convictions or offences?	○ Yes	◉ No	

5. Animals			Page
Does this activity involve animals?	○ Yes	◉ No	

6. Non-EU Countries			Page
Will some of the activities be carried out in non-EU countries?	◉ Yes	○ No	9

Ethiopia and Mozambique

In case non-EU countries are involved, do the activities undertaken in these countries raise potential ethics issues?	◉ Yes	○ No	19

Ethiopia and Mozambique

It is planned to use local resources (e.g. animal and/or human tissue samples, genetic material, live animals, human remains, materials of historical value, endangered fauna or flora samples, etc.)?	○ Yes	◉ No	
Is it planned to import any material (other than data) from non-EU countries into the EU or from a non-EU country to another non-EU country? For data imports, see section 4.	◉ Yes	○ No	17

This may become relevant

Is it planned to export any material (other than data) from the EU to non-EU countries? For data exports, see section 4.	○ Yes	◉ No	
Does this activity involve low and/or lower middle income countries, (if yes, detail the benefit-sharing actions planned in the self-assessment)	◉ Yes	○ No	9
Could the situation in the country put the individuals taking part in the activity at risk?	○ Yes	◉ No	

7. Environment, Health and Safety			Page
Does this activity involve the use of substances or processes that may cause harm to the environment, to animals or plants.(during the implementation of the activity or further to the use of the results, as a possible impact) ?	○ Yes	◉ No	
Does this activity deal with endangered fauna and/or flora / protected areas?	○ Yes	◉ No	

Proposal ID **101159438-2**

Acronym **CryptoTT**

Does this activity involve the use of substances or processes that may cause harm to humans, including those performing the activity.(during the implementation of the activity or further to the use of the results, as a possible impact) ?	○ Yes	◉ No	

8. Artificial Intelligence			Page
Does this activity involve the development, deployment and/or use of Artificial Intelligence-based systems?	○ Yes	◉ No	

9. Other Ethics Issues			Page
Are there any other ethics issues that should be taken into consideration?	○ Yes	◉ No	

I confirm that I have taken into account all ethics issues above and that, if any ethics issues apply, I will complete the ethics self-assessment as described in the guidelines How to Complete your Ethics Self-Assessment ☒

Ethics Self-Assessment

Ethical dimension of the objectives, methodology and likely impact

We will develop a detailed protocol for the trial, including sub-studies, which will be reviewed and approved by ethical committees of participating countries.

Ethical issues related to the objectives of the study
The overall morbidity and mortality related to diarrhoeal diseases in young children, at a global level, highlights the health vulnerability of this population and is an underlying motivation for conducting this study. The study will be conducted in populations that are considered representative for larger-scale roll-out of cryptosporidiosis testing-and-treatment. A major limitation is our inability to include children in the age range 3-12 months, as we know that the cryptosporidiosis burden is high in 6-12-month-olds. We are unfortunately restricted by the lack of regulatory approval for the use of nitazoxanide in children younger than 12 months.

We will not enforce population-level selection criteria to specifically target underprivileged populations/areas. However, we expect that the included facilities (and surrounding catchment areas) will be overrepresented by impoverished populations and geographical areas and areas that lack of access to clean water and sanitation (e.g., facilities who serve areas with overall low socioeconomic status), as children in these areas are likely to be at higher risk for diarrhoea and cryptosporidiosis (REF Johansen 2022) (https://doi.org/10.1371/journal.pntd.0010508)

Guidelines for the dissemination of project outputs, including authorship in manuscripts, conference participation, and workshop involvement, will be developed by month 3 (WP2, task2.5). Requirements for co-authorship of publications will be in line with the Vancouver criteria. These guidelines will be reviewed by all consortium members and approved by the steering committee.

Remaining characters 3179

Compliance with ethical principles and relevant legislations

The diagnostic procedures in this project carries a very small risk for the study subjects. Stool sampling for all enrolled children will follow regular routine procedures. Rectal swab sampling will be performed only after separate consent has been obtained, will use anatomically designed swabs, and will either be performed by personnel trained in the technique, or by caregivers having received careful instruction, and under observation by, such trained study personnel. Patients in the public health care system (including both our study sites) are covered by the standard Ethiopian Ministry of Health patient insurance system.
Children in healthcare facilities observed under intervention conditions will be offered nitazoxanide, which is otherwise not available. Possible side-effects and contraindications to nitazoxanide are few, but will be explained both prior to obtaining consent for participation, and again before treatment is prescribed, as the effort involved in collecting stool samples and rectal swabs may deter some caregivers from participation.

Children in healthcare facilities observed under control conditions will submit stool samples without obtaining a result, and can therefore not be offered cryptosporidiosis treatment. This will be explained carefully to participants and caregivers before they consent to participation. The randomized and “stepped” roll-out of treatment will need to be explained to caregivers, e.g., that treatment will be offered at the facility in the future, and the crucial value of participation as a control group, will also be emphasized. LED-AP results for control participants will be performed (blinded, independent) within 30 days after enrolment, and results of testing will be unscrambled and made available to clinical and study staff after the 60-day follow-up period is over. Study staff will contact these children in the case of a positive result, and offer testing-and-treatment, or direct nitazoxanide treatment, depending on whether the facility has since moved to the testing-and-treatment stage.

Data collected during the study and results of laboratory tests will be kept confidential. Patients with positive test results will get appropriate treatment and children with positive HIV test during enrolment will be considered for antiretroviral treatment and counselling as per standard guidelines [34, 35], with free provision offered in the routine health care system. We will apply for the necessary permissions to establish a biobank of nucleic acid extracts for later PCR tests. Costs related to allow the participants to travel to return to healthcare facilities for follow-up visits or to submit follow-up stool samples will be compensated by to each participant.
Ethical issues related to the likely impact of the study.

Because of ocular and cutaneous toxicity, work with auramine-phenol should be performed using personal safety equipment (eye

protection, gloves, clothing) in rooms with good ventilation (REF), and this will be carefully incorporated in the standard operating procedures, and in the supervision protocols. If local procedures and systems for healthcare waste and laboratory waste is not in place, or is insufficiently implemented on the ground, the study staff will implement local systems to ensure safe disposal. Unlike halogen bulbs, LEDs do not release potentially toxic products into the environment if broken. Battery power packs, if used, or other electrical waste, will be disposed of as special waste by study staff if this service is not offered as part of the local public waste management.
Compliance with ethical principles and relevant legislations.

Ethical clearance will be obtained from the Research Ethics Review Board of any University-affiliated healthcare facilities included in the study, with National Research Ethics Review Committees in Ethiopia and Mozambique, and also the Regional Committee for Medical and Health Research Ethics of Western Norway. Letters of permission to conduct the study will be obtained from the health facility management and clinical directors. Permission from the community catchment area surrounding health centres will be sought before initiating the study by official letters from the local research institutions (e.g., Universities) to the responsible district administrative offices. Written informed consent will be obtained from the caregiver(s) before recruiting children or healthy controls to the study. The purpose of the study will be clearly described to the study participants and caretaker(s) including benefits and risks. We will follow the standards for human research in Ethiopia as detailed in the Ethiopian National Research Ethics Review Guideline (5th 6th edition, 20142022) and the study will be conducted in accordance with the Helsinki Declaration.

Remaining characters 163

Administrative forms

Proposal ID **101159438-2**

Acronym **CryptoTT**

Security issues table

1. EU Classified Information (EUCI)[2]			Page
Does this activity involve information and/or materials requiring protection against unauthorised disclosure (EUCI)?	○ Yes	◉ No	
Does this activity involve non-EU countries which need to have access to EUCI?	○ Yes	◉ No	
2. Misuse			**Page**
Does this activity have the potential for misuse of results?	○ Yes	◉ No	
3. Other Security Issues			**Page**
Does this activity involve information and/or materials subject to national security restrictions? If yes, please specify: (Maximum number of characters allowed: 1000)	○ Yes	◉ No	
Are there any other security issues that should be taken into consideration? If yes, please specify: (Maximum number of characters allowed: 1000)	○ Yes	◉ No	

Security self-assessment

Please specify: (Maximum number of characters allowed: 5000)

Remaining characters 5000

[2]According to the Commission Decision (EU, Euratom) 2015/444 of 13 March 2015 on the security rules for protecting EU classified information, "European Union classified information (EUCI) means any information or material designated by an EU security classification, the unauthorised disclosure of which could cause varying degrees of prejudice to the interests of the European Union or of one or more of the Member States".

[3]Classified background information is information that is already classified by a country and/or international organisation and/or the EU and is going to be used by the project. In this case, the project must have in advance the authorisation from the originator of the classified information, which is the entity (EU institution, EU Member State, third state or international organisation) under whose authority the classified information has been generated.

[4]EU classified foreground information is information (documents/deliverables/materials) planned to be generated by the project and that needs to be protected from unauthorised disclosure. The originator of the EUCI generated by the project is the European Commission.

5 - Other questions

Essential information to be provided for proposals including clinical Trials / studies / investigations

Clinical study means, for the purpose of this document, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by Regulation 536/2014 (on medicinal products), clinical investigation and clinical evaluation as defined by Regulation 2017/745 (on medical devices), performance study and performance evaluation as defined by Regulation 2017/746 (on in vitro diagnostic medical devices).

Are clinical studies / trials / investigations included in the work plan of this project? (●) Yes ( ) No

Please upload the dedicated annex 'Essential information for clinical studies / trials / investigations' (a Word template is provided under 'download templates' in the up-load section for Part B and Annexes).

This document should include the relevant information of each clinical study / trial / investigation included in the work plan of this project.

Please give a short title, an acronym or a unique identifier to each clinical study / trial / investigation, to be used as a reference/ identifier in the other parts of the proposal.
CryptoTT

Impact of a cryptosporidiosis point-of-care test-and-treat strategy in children with diarrhoea (Crypto-TT)

List of participants *[e.g. 1 page]*

Participant No. *	Participant organisation name	Country
1 (Coordinator)	Universitetet i Bergen	Norway
2	Armauer Hansen Research Institute	Ethiopia
3	Fundacao Manhica	Mozambique
4	Addis Ababa University	Ethiopia
5	Simbona	Ethiopia

Contents

1 Excellence

1.1 Objectives and ambition

1.1.1 Background

1.1.1.1 Diarrhoea burden

According to UNICEF diarrhoeal disease is the second leading cause of death in children younger than five years and causes almost 450,000 deaths in children per year. The majority of deaths are in South Asia and sub-Saharan Africa. The Global Enteric Multicenter Study (GEMS), involving 22,568 children with and without diarrhoea across multiple sites in Africa and Asia, estimated that the odds of dying 50-90 days after a diarrhoeal episode was 8.5-fold higher in children with moderate-to-severe diarrhoea [1].

In Ethiopia, childhood diarrhoea is the second most important cause of life years lost, after lower respiratory tract infections [2]. On average, each Ethiopian child suffers 3-5 episodes of diarrhoea per year [3] and diarrhoea contributed to 13.2% of deaths among children under five years in 2019 [4]. In Mozambique, paediatric diarrhoeal disease was estimated to account for over 4,000 deaths [2]. Over the last decade it has become increasingly clear that the burden of diarrhoeal disease is considerably higher when also accounting for long-term morbidity, including recurrent or prolonged diarrhoea, loss of weight, and linear growth faltering [5] .

1.1.1.2 Cryptosporidium - an important cause of childhood diarrhoea and growth retardation

Several species of the protozoan parasite *Cryptosporidium* can cause intestinal infection. When infection leads to disease it is referred to as **cryptosporidiosis**, usually characterised by watery diarrhoea which is often accompanied by dehydration, fever, and lethargy in children. Cryptosporidiosis is usually self-limiting in immunocompetent individuals, but a significant proportion develop prolonged or persistent diarrhoea. *Cryptosporidium* oocysts are shed in the stool for a median duration of one month after infection [6] enabling further transmission.

The majority of diarrhoeal diseases are caused by 15 viral, bacterial, and parasitic pathogens, and all are spread by faecal-oral transmission. The GEMS study found that *Cryptosporidium* is the third most common cause of diarrhoea. *Cryptosporidium* was also one of three pathogens associated with significantly increased risk of death in toddlers aged 12-23 months [1]. The study estimated a *Cryptosporidium* burden of approximately 202,000 deaths per year in sub-Saharan Africa and the India/Pakistan/Bangladesh/Afghanistan/Nepal region combined. The annual number of *Cryptosporidium*-attributable diarrhoea episodes was 2.9 million in children younger than 2 years in

sub-Saharan Africa [7].

Several studies have highlighted important long-term consequences. *Cryptosporidium* is **associated with raised levels of inflammatory markers and growth faltering, particularly stunting, following infection** [8-11]. *Cryptosporidium* infection among toddlers (12–23 months) was found to be significantly associated with a decline in linear growth during a 60-day-follow-up-period [12]. *Cryptosporidium* infection in 3-6-month-old infants was negatively correlated with rate of change in height-for-age Z-score during the first and second year of life [10]. One study also reported long-term cognitive impairment after *Cryptosporidium* infection [13].

Khalil et al (2018) estimated that acute cryptosporidiosis causes a loss of more than 4.2 million disability-adjusted life-years (DALYs) per year showing that the **impact of cryptosporidiosis had been significantly underestimated** previously. Each episode of cryptosporidiosis was associated with subsequent reduction in growth [5]. After taking into account both the acute and long-term effects of cryptosporidiosis the health burden estimates were raised to 133 422 deaths and 8.2 million DALYs per year by the Institute for Health Metrics and Evaluation in 2019. This is higher than what has been estimated for other diarrhoeal diseases such as cholera (117 000 deaths, 7.1 million DALYs) and is comparable with the impact of shigellosis (148 000 deaths, 10 million DALYs). In fact, the impact of cryptosporidiosis, when measured in deaths and DALYs lost, is much higher than what has been found for the WHO recognized list of "neglected tropical diseases" (figure 1).

A meta-analysis of 13 studies from Ethiopia reported a prevalence of cryptosporidiosis of 11% (ranging from 1% to 34%) (Tarekegn 2021). However, it pooled findings from a heterogenous mix of studies done in adults, children and HIV positive patients, using a wide range of diagnostic methods. A more recent study of children with

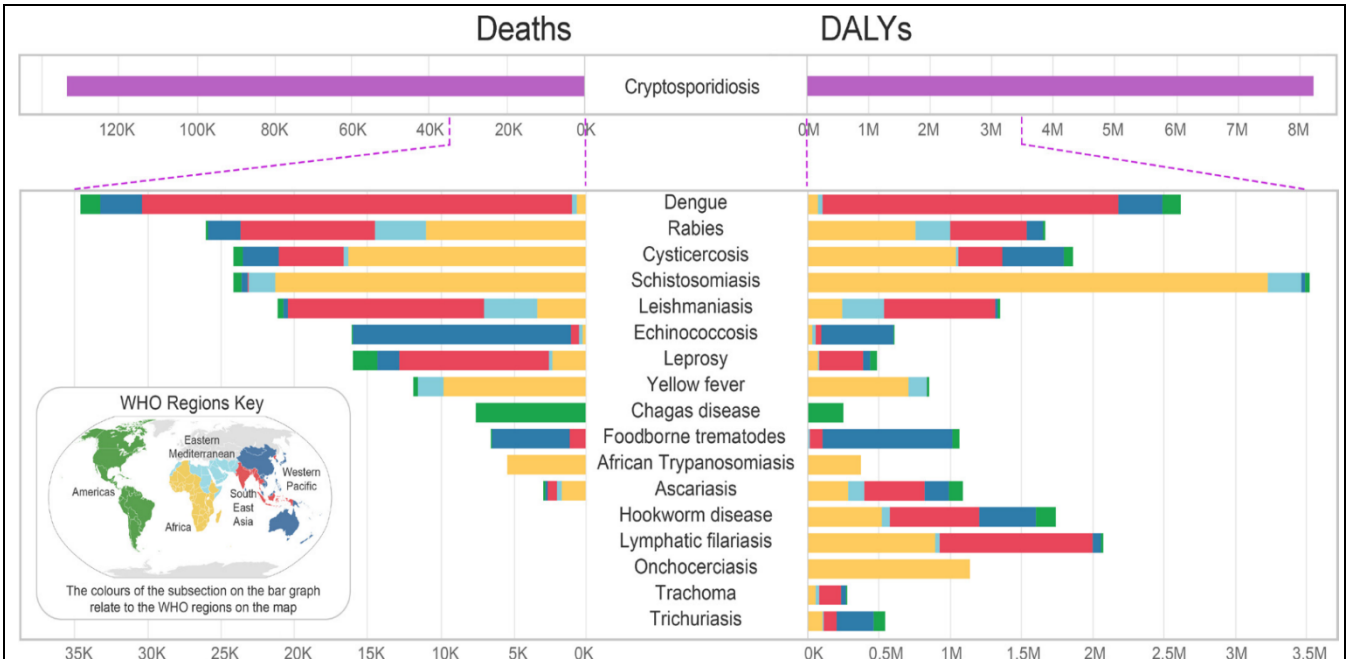


Figure 1. (NB: note the difference in scales in the figure). There are estimated to be 133 000 deaths and 8.2 million disability-adjusted life-years (DALYs) lost per year due to cryptosporidiosis (purple). This greatly exceeds the similar metrics for all of the WHO neglected tropical diseases. Figure from Gilbert IH, et al. BMJ Glob Health 2023

healthcare-presenting diarrhoea in Jimma, Ethiopia, reported a cryptosporidiosis prevalence of 9%, using light-emitting diode fluorescence microscopy with auramine-phenol staining (LED-AP) as a diagnostic method, and a similar prevalence was found by qPCR with adjusted cut-offs for non-diarrhoea controls [14].

National surveillance of intestinal parasites in Mozambique from 2014-2019 found a prevalence for diarrhoea attributed to *Cryptosporidium* of 8% in 1424 children, using modified acid-fast microscopy [15].

Some groups of children are extra vulnerable to cryptosporidiosis. Severe acute malnutrition was found in 9% of children who presented for healthcare with diarrhoea in Ethiopia [14] and both moderate- and severe acute malnutrition was found to be strongly associated with cryptosporidiosis in under-2-year-old children [16]. Prolonged and persistent diarrhoea represent a large healthcare burden [17], and cryptosporidiosis is particularly associated with prolonged diarrhoeal duration [16].

The above studies highlight the enormous health burden attributable to *Cryptosporidium* in Africa and Asia. Interventions designed to prevent and effectively treat *Cryptosporidium* infection in children younger than 5 years have been estimated to have large potential to impact public health and on social development in children [5]. Strikingly, the above findings have not been translated into interventions in the healthcare setting. Notably, **no studies have assessed the impact of targeted treatment of cryptosporidiosis in children by using a combined strategy for diagnosing and treatment**. It remains an open question whether this kind of clinical intervention can significantly reduce diarrhoeal duration or limit sequelae [18]. The cost-effectiveness of targeted treatment of cryptosporidiosis has not been assessed. **A major obstacle for such studies has been the limited availability of a reliable point-of-care diagnostic test for cryptosporidiosis.**

1.1.1.3 Access to cryptosporidiosis treatment is limited by lack of a diagnostic test

The standard treatment of diarrhoea in most of Africa is syndromic, with oral rehydration and zinc supplementation as the key recommended interventions. Antimicrobial treatment is only indicated when there is bloody diarrhoea or fever (i.e., empirical treatment for *Shigella* dysentery). The only drug approved to treat cryptosporidiosis is nitazoxanide. The recommended dose in 12-23-month-olds is 100 mg oral suspension 2 times daily for 3 days. Nitazoxanide is approved by the US Food and Drug Administration in children from 12 months of age. Side effects are rare. The clinical efficacy has been demonstrated in immunocompetent patients but has been found to be ineffective in immunocompromised HIV-positive patients [19]. The available data on clinical efficacy in children with acute malnutrition are conflicting; some studies found reduced parasitological clearance and reduced clinical efficacy, although one clinical trial reported reduced case fatality in children with severe acute malnutrition and cryptosporidiosis who received nitazoxanide [20].

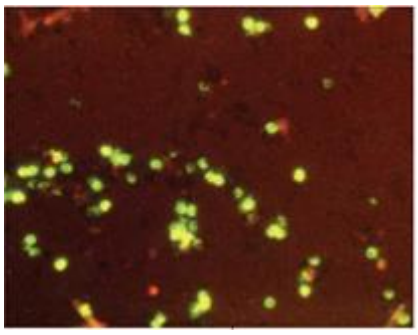
Nitazoxanide can be made accessible in sub-Saharan Africa as several well-reputed generic drug companies produce the drug as a low-cost formulation. The Ethiopian Food and Drug Authority has registered Nitazoxanide under the list of medicines for community pharmacies (EFDA, LMCP, 2021). In Mozambique the drug is not part of the Ministry of Health drug formulary but has previously been approved for use in a clinical study (antiCOV, not yet published).

Unfortunately, nitazoxanide is rarely available to children in Africa. An important reason is that most healthcare facilities lack access to affordable and reliable diagnostic point-of-care (POC) tests.

There are several candidate antiparasitic drugs in the pipeline for treatment of cryptosporidiosis, and some of these may reach the clinical trial stage over the coming years [21]. However, unless access to an affordable and reliable diagnostic test is also provided and integrated with roll-out of treatment provision, new drugs will likely be out of reach for children in Sub-Saharan Africa.

1.1.1.4 A point-of-care test for cryptosporidiosis

For many years detection of *Cryptosporidium* relied on acid-fast staining (usually the "modified Ziehl-Neelsen" method) followed by conventional light microscopy, with sensitivity ranging from 30% to 70% [22]. An important development was immunofluorescent antibody staining on stool smears, followed by fluorescence microscopy (IFAT), with significant gain in both sensitivity and specificity. These stains are expensive. In the last two decades nucleic acid-based methods such as PCR are increasingly being used in high income countries to diagnose infectious causes of diarrhoea. However, these assays are too costly and difficult to maintain for health care systems in low- or middle-income countries (LMIC). Immunochromatographic rapid tests (e.g., strips, cassettes) and ELISA antigen test kits are now available but are expensive and require refrigeration. A rapid test strip that does not require refrigeration was developed by TechLab, but is expensive, and the company has discontinued its commercial development as it was not considered commercially viable (September 2023, personal communication). Healthcare workers in SSA therefore lack effective tools to diagnose cryptosporidiosis.



However, exploiting the feature of acid-fast oocyst staining, light-emitting diode (LED) fluorescence microscopy has presented itself as an inexpensive and feasible cryptosporidiosis test. *Cryptosporidium* oocysts can be easily visualised in stool smears by auramine phenol (AP) staining followed by LED microscopy (figure 2). The LED-AP technique is already recommended by the WHO as a primary test for detection of acid-fast tuberculosis bacilli due to its improved diagnostic sensitivity when compared with traditional Ziehl-Neelsen microscopy (WHO 2011).

Figure 2. Fluorescent green Cryptosporidium oocysts as seen with a LED-microscope after AP-staining (Johansen 2020)

In the CRYPTO-POC study, a large phase-3 diagnostic accuracy study in south-west Ethiopia, we found that LED-microscopy of AP-stained stool smears had high sensitivity (88%) and specificity (99%) for the diagnosis of cryptosporidiosis in children. This was the first adequately powered, prospective, diagnostic accuracy study for cryptosporidiosis in children who present for health care with diarrhoea in a low-resource setting [14]. The diagnostic accuracy estimates were consistent with estimates from a previous study conducted in a high-income country [23], and a small study in HIV-positive adults in India [24]. LED-AP can detect all species of *Cryptosporidium*. A major advantage of LED-AP is that the use of fluorescence creates a clear distinction between the oocysts and the non-fluorescent background, simplifying interpretation. Faecal concentration techniques are therefore not necessary, and this simplifies interpretation and reduces the testing time. Minimal prior training and experience is needed for health care staff to acquire reliable skills in LED-AP microscopy [25].

LED microscopes have already been distributed to many healthcare facilities in Ethiopia and Mozambique, as part of the STOP TB campaign. This represents an opportunity for realistic scale up of the LED-AP technique.

The total test turn-around time (TAT) is crucial for timely decision support for clinicians [26]. The analytical time of LED-AP if a single slide is processed, is approximately 30 minutes in hot and dry conditions, or if a regular lab incubator is used to speed up air-drying the faecal sample on a glass slide. Pre-analytical time (transport of specimen) and post-analytical time (result communication) need to be added to the analytical time, meaning that a best-case estimate of total TAT is around 60 minutes, still sufficient to provide an actionable result while the patient is still in the healthcare facility.

We consider LED-AP as a "dual-use technology" that can be easily integrated with existing laboratory infrastructures in low-resource settings [14]. LED-AP can be set up and used by primary care health workers in any health facility that has access to electricity for the microscope. As LED-microscopes run on low power, battery packs, rechargeable by solar panels, can be used to mitigate power outages if a backup generator is not available. However, power adaptors are vulnerable to voltage fluctuations which are common in LMIC, and this is a common cause for repair.

As LED-AP is the currently best validated method for diagnosing cryptosporidiosis in LMIC settings [14], we propose that the next logical step is to evaluate its effect in LMICs as a point-of-care diagnostic to guide treatment of cryptosporidiosis.

Important data are missing before large-scale roll-out of LED-AP can be endorsed. There is not yet a WHO target product profile for cryptosporidiosis diagnostic tests. The operational value of LED-AP for cryptosporidiosis and its impact on disease outcomes has not yet been demonstrated in a clinical trial. Also, its accuracy in scaled-up routine testing, its cost-effectiveness, and its potential impact on treatment decisions and thereby short- and long-term health outcomes, needs to be investigated. The LED-AP method for diagnosis of cryptosporidiosis is therefore at a technology readiness level around 7. LED-AP is currently the only near-patient test that has been evaluated in a phase-3 diagnostic accuracy study in low-income settings. The next recommended step for POC test evaluation is usually a diagnostic randomised controlled trial (D-RCT), or what has been referred to as "phase-4" diagnostic study. The purpose is to evaluate the "testing-and-treatment"-intervention as a combined package, better approximating clinical reality.

The CRYPTO-POC study identified total test turn-around-times (TAT) as a possible bottleneck for implementation. We therefore suggest investigating alternative methods to speed up TAT, by using rectal swab specimens instead of bulk stool samples. Importantly, we will determine if rectal swabs attain similar, or at least acceptable, levels of diagnostic accuracy as with the conventional use of bulk stool specimens.

1.1.1.5 Hypothesis

A testing-and-treatment package combining LED-AP POC testing for cryptosporidiosis in 12-23-month-old children who present to healthcare with diarrhoea, followed by targeted treatment with nitazoxanide, will reduce the mean diarrhoeal duration with at least two days.

1.1.1.6 Primary objective

Estimate the effectiveness of a low-cost point-of-care test followed by targeted cryptosporidiosis treatment with nitazoxanide on diarrheal duration in children presenting to health care facilities with diarrhoea

1.1.1.7 Secondary objectives

1. To **validate the sensitivity, specificity, positive and negative predictive values (PPV and NPV),** of LED-AP cryptosporidiosis POC-testing scaled-up real-life clinical settings, compared with quantitative PCR as a reference test
2. To assess sensitivity, specificity, PPV and NPV, and reduction in total test TAT of using **rectal swab specimens** instead of bulk stool samples
3. To assess the **cost-effectiveness** of an LED-AP based test-and-treat strategy against cryptosporidiosis
4. To explore differences in **mortality and growth parameters** 60 days after enrolment in children in the intervention arm with LED-AP based testing-and-treatment compared with children in the control arm
5. To explore the effectiveness of an LED-AP-based test-and-treat strategy in **vulnerable groups** such as children with acute malnutrition or prolonged or persistent diarrhoea

1.2 Methods

1.2.1 Experimental set-up

We will examine several questions related to targeted cryptosporidiosis treatment in children. Our main objective is to study whether a combined testing-and-treatment intervention can reduce the duration and severity of diarrhoea in children who present for healthcare. Cases diagnosed with cryptosporidiosis will be offered antiparasitic treatment with oral nitazoxanide. Although it is well established that nitazoxanide can reduce diarrhoeal duration and mortality in children with cryptosporidiosis, the drug has not been evaluated as part of a combined testing-and-treatment intervention, and its actual implementation in routine care, or longer-term outcomes after treatment, have not yet been studied.

Instead of an individual-level diagnostic RCT, we will use the stepped wedge cluster randomized trial (SW-CRT) study design. As nitazoxanide is already an approved treatment for cryptosporidiosis, it would be ethically problematic, and a risk of introducing bias, if we withhold treatment or provide placebo, after reporting a positive cryptosporidiosis test result. Furthermore, the phased roll-out ensures that all participating facilities eventually receive the intervention, which will enhance buy-in from local healthcare staff and communities.
Lastly, due to the inclusion in the trial of a high number of diverse real-life healthcare facilities, an SW-CRT provides an evidence base for larger-scale implementation. A randomisation procedure will determine which facilities will receive the packaged test-and-treat intervention, or standard of care, but as the trial progresses, all facilities will gradually switch from providing standard of care, to receiving the intervention, following a randomly allocated sequence.
Although randomisation happens at the facility level (i.e., the clusters), the study design permits the comparison of clinical outcomes between individual participants. The primary outcome is difference in duration of the diarrhoeal episode, after presentation for healthcare, between children who are offered testing-and-treatment, compared with children who receive standard-of-care treatment. Secondary outcomes are turnaround times of testing, 60-day mortality, linear and ponderal growth during a 60-day follow-up period, and overall cost-effectiveness of cryptosporidiosis testing-and-treatment provision. The diagnostic accuracy of LED-AP microscopy will be estimated by blinded comparison to a qPCR reference standard.
We will also investigate whether collection of rectal swabs instead of conventional “bulk stool” samples can reduce turnaround-time, i.e., the total time from healthcare presentation until an actionable test result is available. As the diagnostic accuracy of LED-AP from rectal swabs has not been evaluated previously, we will embed a complete diagnostic accuracy study within the SW-CRT. This will entail collecting both rectal swabs and bulk stool samples from all participants, followed by a comparison of LED-AP testing, performed on both sample types, in a blinded fashion. By comparing findings from both sample types with a quantitative PCR reference standard we will be able to estimate sensitivity, specificity, and positive and negative predictive values, of both swabs and bulk stool testing. A paired analysis will enable us to estimate if there is a difference in diagnostic accuracy between the sample types.

1.2.2 Stepped wedge cluster randomized trial of cryptosporidiosis

testing-and-treatment

1.2.2.1 Trial design

A stepped wedge cluster randomized trial (SW-CRT) [27] will be conducted at hospitals and health centers in Ethiopia and Mozambique. The main scientific, ethical, and practical reasons for choosing the SW-CRT design will be outlined here.

1.2.2.1.1 Ethics of and risk of bias from withholding treatment

A SW-CRT design is in some respects similar to large-scale implementation programmes for roll-out of a new diagnostic test (in our case, a repurposed test). Due to the randomised sequence determining the time point for the intervention at a given site, we are able to gather important implementational evidence, with a formal evaluation of the clinical efficacy and cost-effectiveness of the whole test-and-treat package.

Alternative study designs would be a traditional diagnostic RCT (D-RCT), where individual participants are randomised to receive either the test, the treatment, or both, or a conventional cluster randomised trial, where whole facilities are randomized to either receive the intervention or to continue with standard-of-care. However, as there is already an approved drug available for cryptosporidiosis it seems ethically problematic to offer placebo or to withhold treatment. We also anticipate a risk of bias due to lower participation and buy-in from local healthcare staff involved in the study unless they are able to offer both the test and the treatment. The SW-CRT design allows us to address these concerns: although the timing will vary between facilities, all clusters will receive the testing-and-treatment package.

1.2.2.1.2 Phased roll-out provides an evidence base for larger-scale implementation

The SW-CRT design allows for a phased rollout of cryptosporidiosis testing-and-treatment. Larger-scale rollout will be considered as a next step, based on the findings from the study. Resource allocation should be based on data-driven insights from the early stages of a programme with an aim to ensure equitable distribution of resources and to address concerns about disadvantaged communities being left behind during roll-out. Data gathered throughout the phased roll-out will provide policy makers with scientific and implementational data on the intervention's real-time impact as well as potential unintended consequences (Hemming 2018).

There are likely unforeseen challenges with large-scale implementation of cryptosporidiosis testing-and-treatment as it has not previously been attempted. Understanding the specific context is crucial in order to tailor and adapt the intervention. The gradual rollout of the intervention in a SW-CRT design permits us to identify potential challenges during local adoption and make necessary adjustments while minimizing disruption to routine care. By introducing the intervention step-by-step, we hope to mitigate potential risks and allow for adjustments based on initial lessons learned before wider project implementation in facilities that are still offering standard-of-care (i.e., clusters being observed under a control condition).

1.2.2.1.3 Pitfalls of the stepped-wedge cluster randomized trial design

We anticipate some challenges specific to the SW-CRT design. First, the duration of the study will be longer that what is required for a traditional (parallel) randomized trial. Second, generalizability depends on choosing appropriate clusters that are sufficiently representative of the target population. There is a potential risk that "intervention knowledge" can spread to clusters that are still in the control condition, leading to bias. We will take appropriate measures before and during project implementation to minimize the possible contamination between intervention and control arms. We will organise training sessions for all healthcare workers and scientific staff associated with the trial. Furthermore, we will conduct a trial run-in-period to optimise all data collection tools and to identify practical challenges with the near-patient microscopy testing or with nitazoxanide provision, permitting necessary adjustment before full trial startup.

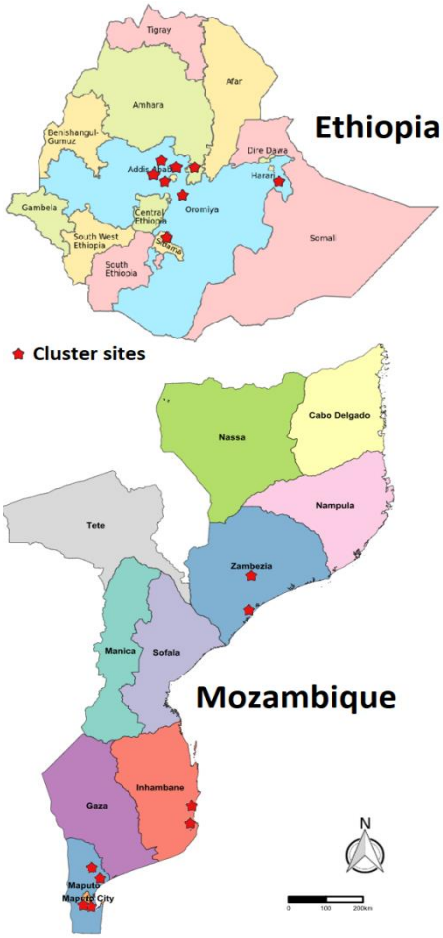


Figure 3. Map of Ethiopia and Mozambique showing the study clusters

1.2.2.2 Participants

1.2.2.2.1 Eligibility criteria for healthcare facilities (clusters)

The healthcare facilities (public hospitals and health centers) will be selected based on predefined criteria and baseline information obtained from the facility treatment records. The primary selection criteria is the annual number of children aged 12-23 months who present with diarrhoea for at the healthcare facility. District level data will be accessed to compare case numbers across facilities and to avoid selecting “outlier facilities”. Access to supportive health facilities, e.g., backup facilities in case of local disruption, or regional laboratories supervising AP staining, will also be considered, to ensure practical feasibility of the study. Candidate facilities should have basic laboratory testing capabilities (e.g., a small diagnostic lab, or at least a separate area for performing microscopy) and should provide standard care for diarrhoea and basic drug provision, e.g. treatment with oral rehydration solution. In order to minimize variation across clusters we will select facilities with comparable levels of staff expertise, and laboratory and treatment capacity. As LED-AP testing has not been rolled out in all facilities, prior availability of LED microscopes will be considered an advantage for inclusion, but will not be a criterion for inclusion. LED-microscopes will be provided by the project if necessary. We will not enforce population-level selection criteria in order to specifically target underprivileged populations/areas. However, we expect that the included facilities (and surrounding catchment areas) will be overrepresented by impoverished populations and geographical areas and areas that lack of access to clean water and sanitation (e.g., facilities who serve areas with overall low socioeconomic status), as children in these areas are likely to be at higher risk for diarrhoea and cryptosporidiosis [16].

1.2.2.2.2 Eligibility criteria for children

For all eligible children, parental or guardian consent will be obtained after providing verbal and written information translated to the local language.

1.2.2.2.2.1 Inclusion criteria

1. Children aged 12-23 months (Minimum age rationale: nitazoxanide has not been adequately evaluated for use

and is not FDA-approved for use in infants younger than 12 months. Maximum age rationale: cryptosporidiosis prevalence drops rapidly in children older than 24 months.)
2. Child is not currently enrolled as a case (meaning previously enrolled and pending 60-day visit)
    a. Reenrollment is permitted after the final 60-day visit has been completed.
3. Diarrhoea (three or more loose, or looser than normal, stools, within the previous 24 h), and/or dysentery (at least one loose, or looser than normal, stool, with stains of blood within the previous 24 h), regardless of whether these were the primary complaints leading them to seek health care.
4. Caregiver reports that that they have no plans to move out of the catchment area for at least 60 days following enrollment.
5. Caregiver permission to be visited in the home for follow-up visits up to 60 days following enrollment.

1.2.2.2.2.2 Exclusion criteria

1. The child's guardian fails to provide signed informed consent.
2. The family have plans to move out of the catchment area for >30 consecutive days during the 60 day follow-up period.
3. Children who reside further away than two hours travel by motorbike (to ensure feasibility of follow-up visits)
4. Children who are HIV positive, or whose HIV status is not known (and the caregiver does not consent to HIV testing) (Rationale: nitazoxanide is unlikely to be clinically effective in this group)
5. Children who are deemed likely to be unable to receive oral medication, based on healthcare worker assessment, e.g., where there is an ongoing aspiration risk, ongoing persistent repetitive vomiting deemed to be resolvable after rehydration, or enteropathies limiting oral absorption.
    a. Exception: if oral administration of drugs is deemed likely to be possible after initial clinical treatment (e.g. rehydration), they can be enrolled in the study.

Note that malnourished children will not be excluded from participation, but due to uncertainty about the effect of nitazoxanide in this group outcomes will be evaluated both with and without including this subgroup in the analysis. The HIV prevalence in Ethiopian children who present for healthcare with diarrhoea is <1 % [14] while in Mozambique the vertical HIV-transmission was found to be 4.4% (Fuente-Soro et al 2021).

1.2.2.2.3 Study settings

1.2.2.2.3.1 Overview

The study will be performed in Ethiopia and Mozambique. Both countries are classified as low-income countries by the World Bank. The United Nations Development Programme ranks Ethiopia as 175 and Mozambique as 185 on the Human Development Index (HDI) scale out of a total of 191 nations. The study will be conducted in hospitals and health centres where children with diarrhoea are seen. The study sites will be considered as candidate study clusters mainly based on their diarrhoea case load (see eligibility criteria, above), aiming for six clusters in each country. Unless LED-AP microscopy is already up and running for tuberculosis testing, all facilities will be equipped with a small laboratory where LED-microscopy can be performed. We will conduct the study in health facilities with previous experience of conducting clinical research. Extrapolating from caseloads from recent years the included health facilities treats more than 8000 children aged 12-23 months with diarrhoea per year.

1.2.2.2.3.2 Ethiopia

In Ethiopia, six health facilities in the central region (Addis Ababa and its surrounding area) will be included. The Ethiopian Ministry of Health (EMoH) has established a three-tier health service delivery system (a tertiary level health care, secondary level health care and a primary level health care) that requires an effective two-way referral connection and develops a strategy for an effective referral system in its national health policy. Referrals to the higher level are determined based on medical requirements or shortage of resources at the facility. Accordingly, most children with diarrhoea are treated at the primary level of health care. We have therefore selected four health centers in Addis Ababa and four primary hospitals outside Addis Ababa. There are currently 97 health centres in Addis Ababa and the four centres we chose have the highest number of children with diarrhoea. We also included four additional hospitals outside Addis Ababa.

Adama Hospital in Adama city is located in the Oromia region, 100 km southeast of Addis Ababa. Debre Berhan Comprehensive Specialized Hospital is in Debre Berhan town, North Shoa, Amhara Region, Ethiopia, 128 km from Addis Ababa. Hawassa University hospital is located in Hawassa, on the shores of Lake Hawassa, 270 km south of Addis Ababa. Hiwot Fana Specialized University Hospital, a comprehensive teaching hospital located in Harar

town, 526 km to the East of Addis Ababa Ethiopia. Table 2a summarise the health facilities that will serve as trial clusters in Ethiopia.

Table 2a. Ethiopian trial clusters			
Cluster number	**Name of center/location**	**Region**	**Estimated number of children aged 12-23 months with diarrhoea per year**
1	Kality Health Center	Addis Ababa	529
2	Bole Arabsa Health Center	Addis Ababa	310
3	Saint Gabriel	Addis Ababa	356
4	Summit	Addis Ababa	232
5	Adama Hospital	Oromia	323
6	Debre Birhan Hospital	Amhara	360
7	Hiwot Fana Hospital	Harari	245
8	Hawassa University Referral Hospital	Sidama	244
Total for Ethiopian clusters			**2599**

1.2.2.2.3.3 Mozambique

In Mozambique, the study will be conducted in hospitals and health centers in three provinces, Maputo and Inhambane in the south and Zambézia in the central region of the country. In Maputo province, we will include the Manhiça district, Matola district, Magude and Maputo city. In Inhambane the study will be conducted in the district of Massinga and Maxixe while in Zambézia, we will include the district of Quelimane and Mocuba. Hospitals from different health care levels from Central Hospitals to district level hospitals will be include in the study (Table 2b). The geographic location of each hospital is shown in Figure 3. In Manhiça and Quelimane, the already-established Health and Demographic Surveillance System (HDSS) will further facilitate the follow-up of participants.

Table 2b. Mozambican clusters				
Cluster number	**Name of health facility**	**Province**	**Estimated number of children aged 12-24 months with diarrhoea per year**	
			Hospital/ Health Center	**Cluster**
1	Hospital Distrital da Manhiça	Maputo	300	300
2	Centro de Saúde de Magude	Maputo	230	230
3	Hospital Rural de Xinavane	Maputo	139	250
	Centro de Saúde da Maragra	Maputo	55	
	Centro de Saúde da Ilha Josinha	Maputo	56	
4	Hospital Geral da Matola	Maputo	150	332
	Hospital Distrital da Massinga	Inhambane	182	
5	Hospital Distrital de Mocuba	Zambézia	197	197
6	Hospital Geral de Quelimane	Zambézia	37	257
	Hospital Central de Quelimane	Zambézia	30	
	Centro de Saúde de Micajune	Zambézia	83	
	Centro de Saúde de Sangarivera	Zambézia	63	
	Centro de Saúde de Icidua	Zambézia	44	
7	Hospital Rural de Chicuque	Inhambane	400	400
8	Hospital Central de Maputo *	Maputo	3690	3690
Grand Total			**5656**	**5656**

* To balance recruitment between clusters, and not overwhelm staff, only the first 10 eligible children per week will be recruited in this cluster.

1.2.2.3 Interventions

Testing-and-treatment for cryptosporidiosis is the intervention under study. This packaged intervention will be integrated with routine clinical care. Laboratory technicians and clinical healthcare staff will receive training in stool collection, testing, and cryptosporidiosis treatment with nitazoxanide. A standard treatment guideline will be introduced at each participating health facility, covering the testing-and-treatment pathway for diarrhoea, with

easy-to-use visual algorithms clearly specifying criteria for nitazoxanide treatment, supported by a simple checklist.
There is an intervention arm and a control arm in the study. In both arms data collection by interview, sampling and storage of sample aliquots is done in eligible children after consent. Standard diarrhoea care will also be offered. The intervention arm will additionally be offered cryptosporidiosis LED-AP testing and in those testing positive, treatment with nitazoxanide will be offered according to a standard treatment guideline developed for the study.
In the control arm, i.e., clusters that have not yet been included in the stepwise introduction of the intervention, patients will receive standard of care (Figure 4). Within 30 days of sample collection blinded LED-AP-microscopy will be performed on re-labelled and archived slides.
Children in both trial arms will be followed up daily until the end of the diarrhoeal episode to calculate total diarrhoeal duration and will have their height and weight measured after rehydration (4 days), and at 60 days after enrolment. All stool samples will be stored for later testing by targeted *Cryptosporidium* quantitative PCR (qPCR).

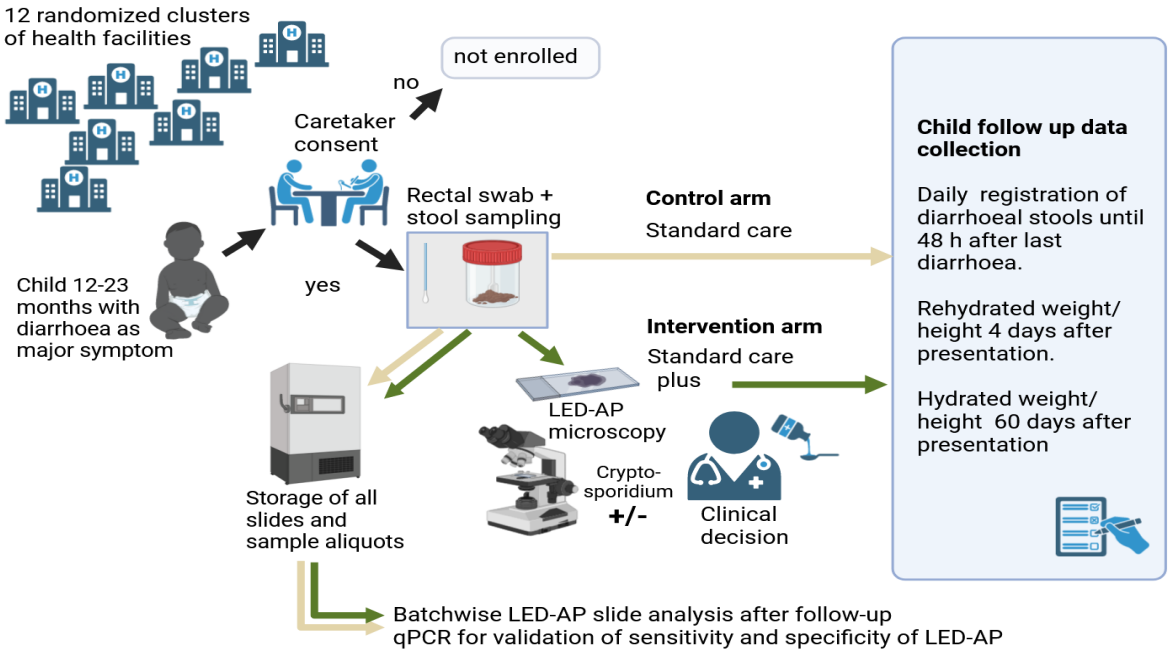


Figure 4. CryptoTT study design with patient flow, study arms and follow-up

1.2.2.3.1 Randomization (intervention allocation) procedure

The clusters (hospitals/health centres) are randomized to start the intervention, but the implementation will occur at different time points throughout the study, permitting comparison between children with and without the intervention. We will include a total of 16 clusters (figure 5). During the first three months all clusters will be in the control arm. We will then introduce the intervention in four random clusters (one in each study country), while the rest of the clusters remain as controls. A further four clusters will switch to the intervention arm every 3 months moving gradually towards inclusion of all 16 clusters in the intervention arm by the end of 15 months.

Clusters	Country	Allocation period (every three months)														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	E															
2	M															
3	E															
4	M															
5	E															
6	M															
7	E															
8	M															
9	E															
10	M															
11	E															
12	M															

13	**E**															
14	**M**															
15	**E**															
16	**M**															

	Clusters where sampling and standard care is provided after consent
	Clusters where sampling and immediate LED-AP testing is introduced in addition to standard care

Figure 5. Crypto-TT stepped-wedge cluster randomized trial design (E = Ethiopia, M = Mozambique)

1.2.2.3.2 Baseline clinical data collection

Trained clinical study nurses will use a structured Case Report Form (CRF), developed in the project planning phase, to capture clinical, socio-demographic (age, sex, ethnicity, household) and maternal data. The included children's baseline clinical history and findings will be recorded, including duration, frequency and consistency of diarrhoea, a history of antimicrobial and anti-diarrhoeal traditional medicine ingestion prior to presentation and past medical history including diarrhoeal disease, comorbidities, ongoing medications, and nutritional history. Associated symptoms and vital signs will be recorded, e.g., abdominal pain, fever, vomiting, tenesmus, anthropometric measurements (height, weight, mid-upper arm circumference), and dehydration status. Each health care facility will have a clinical coordinator who will be responsible to ensure the accuracy, completeness, and legibility of the captured data. The CRF should be completed according to instructions/guidelines developed in the beginning of the study to ensure accurate interpretation of data.

1.2.2.3.3 HIV testing and counselling

We will perform voluntary HIV-testing and counselling of children whose HIV-status is unknown, according to guidelines provided by the Ministry of Health in the respective study countries.

1.2.2.3.4 Stool sample collection

We will use standardized sample collection, handling, preparation, and storage procedures to maintain sample integrity. Stool samples will be collected in a disinfectant free, dry, leak-proof, and wide-necked container. Caregivers will be instructed in how to obtain a stool sample from the child: the child will pass stools while sitting on a potty toilet seat lined with a clean plastic bag and the stool sample is immediately collected and placed into a stool container provided by the study nurse. Caregivers will be informed that the stool sample must not come into contact with other surfaces or with materials such as urine, water, or soil before collection. With caregiver permission, a rectal swab will be collected in addition to (and usually prior to) the bulk stool sample. The patient study ID, date, and time of collection will be labelled on the container and the consistency of the stool (formed, soft, loose, watery, or bloody) will be recorded after collection. After homogenizing the stool sample by stirring vigorously in the sample container with an applicator stick, a portion of stool will be stained by auramine-phenol and examined using an LED fluorescence microscope.
Another portion of the stool sample (1-2g) will be transferred to a clean container without preservatives, then kept in a cooler box containing ice packs (alternatively, a refrigerator) and then transferred to a -80°C freezer within 6-12 hrs of collection. These samples will later be thawed for total nucleic acid extraction followed by *Cryptosporidium* quantitative PCR.
Laboratory analysis will be conducted both in laboratories in the study sites (LED-AP microscopy), and in research laboratories (qPCR) at AHRI, Addis Ababa, Ethiopia and at Centro de Investigação em Saúde de Manhiça (CISM) Mozambique.

1.2.2.3.5 Near-patient LED-AP microscopy testing

LED-AP microscopy will be performed as soon as possible (i.e., aiming for AP-staining and LED fluorescence microscopy ideally to be completed within 30 min) of sample collection. Stool concentration techniques will not be needed. Auramine-phenol (AP) staining is an acid-fast staining technique that shares some characteristics with conventional Ziehl-Neelsen (ZN) staining, a routine staining method for detecting acid-fast bacilli, but has greater sensitivity, specificity, and shorter staining time, than the modified ZN stain commonly used for Cryptosporidium detection in parasitology laboratories [14, 24].
The staining procedure is as follows: glass slides will be smeared directly with a tiny portion of stool, then allowed to air dry, followed by smear fixation in absolute methanol for 1 min, and AP staining (0.1% auramine-O) for 10-15 minutes. After rinsing thoroughly in tap water and decolourising in 0.5% acid ethanol for 2 minutes, a counterstain (0.1% potassium permanganate) is applied for 2 minutes. Smears will be rinsed again and allowed

to air dry for 15-30 minutes before examination under the LED fluorescence microscope. *Cryptosporidium* positive and negative controls will be used for each LED-AP microscopy examination as a quality control. *Cryptosporidium* oocysts are 4-6 µm in diameter, oval or doughnut-shaped and will fluoresce green-yellow against a dark background.
Oocysts from the other partially acid-fast parasites *Cystoisospora belli* and *Cyclospora cayetanensis* can also be visualized using the AP-staining technique, but can be reliably discerned from *Cryptosporidium* oocysts based on their shape and size: *Cystoisospora belli* oocysts are large and about 32x16 µm, oval body, elongated, and tapered at both ends; *Cyclospora cayetanensis* oocysts are spherical, measuring 8-10 µ in diameter, and variably stained.
In the intervention arm LED-AP testing will be performed on rectal swabs and stool samples as soon as possible (turn-around-time will be registered) to ensure timely result and treatment. LED-AP microscopy will be performed in addition to conventional wet microscopy for other parasites, or bacterial stool culture, if these tests have been requested as part of standard care by the responsible healthcare team.
In the control arm, air-drying of stool specimens on glass slides will be followed by AP staining, including *Cryptosporidium* positive and negative controls. Stained slides will be stored in dedicated slide boxes, i.e., protected from direct light. LED-AP will not be performed at the time of enrolment, but will rather be performed later, on the archived glass slides, after these have been re-labelled, to ensure blinding of the microscopist and other on-site study staff to the diagnostic outcome. Microscopy may be performed up to 30 days after stool collection. Each batch of slides will include a positive control, and if the strength of fluorescence has faded, re-staining with AP will be performed before examining the archived slides with an LED fluorescence microscope.

1.2.2.3.6 Treatment
LED-AP test results will be returned to the clinician using a written result slip carried by porters. If the test is positive for cryptosporidiosis, treatment with nitazoxanide will be offered to the child, with a standard dose of 100 mg twice daily for 3 days. If the AP stain is positive for *Cystoisospora belli* or *Cyclospora cayetanensis* treatment with trimethoprim-sulfamethoxazole (or, for *Cyclospora*, nitazoxanide) will be offered according to a standard treatment guideline.
LED-AP test results for control participants will be performed (blinded, independent) within 30 days after enrolment, and results of testing will be unscrambled and made available to clinical and study staff after the 60-day follow-up period is over. In the case of a positive result, study staff will contact these children, and if they still have diarrhoea, will offer re-enrolment for testing-and-treatment if the facility has since moved to the testing-and-treatment stage. Otherwise nitazoxanide treatment outside will be offered without enrolment in the trial.

1.2.2.4 Outcomes

1.2.2.4.1 Primary outcome: diarrhoeal duration
The duration of the diarrhoeal episode will be carefully captured using a combination of a diarrhoea “diary” (adapting a similar tool to what was used in the GEMS study), daily follow-up phone calls, or, alternatively, by direct home visits from health care extension workers or trained field workers, if the caregiver does not have access to a phone. Children with some or severe dehydration will receive rehydration treatment at the health facility according to standard IMCI treatment guidelines, and reassessed for resolution of dehydration. Follow-up will continue until the end of the diarrhoeal episode (defined as 2 consecutive diarrhoea-free days) or up to 14 days after presentation at the health facility, whichever comes first. Caregivers and included children will be expected to visit the health facility on day 4 after enrolment for collection of diarrhoeal diaries, assessment of treatment compliance, and to obtain anthropometric measurements from a rehydrated baseline. If caregivers cannot bring their children to the health facility on a scheduled date, study staff will conduct a home visit to assess the child and collect the required data.

1.2.2.4.2 Secondary outcomes

1.2.2.4.2.1 Diagnostic accuracy
The diagnostic accuracy of LED-AP will be evaluated by blinded comparison of LED-AP testing results to a *Cryptosporidium* qPCR reference standard conducted in a central laboratory.

1.2.2.4.2.2 Growth outcomes and case fatality at 60-day follow up
All children will receive a 60-day follow-up visit to assess growth parameters (length, weight, mid-upper arm circumference (MUAC), peripheral oedema. If the child has passed away within the 60-day follow-up period, the cause of death will be recorded, if known.

1.2.2.4.2.3 Operational outcome data

Operational data relevant for implementation will be collected, including, but not limited to:

- Total test turnaround times, i.e., the time from sample collection to an actionable result
    - broken into preanalytical, analytical and post-analytical phases.
    - Turnaround data will be recorded for both rectal swabs and bulk stool samples (see more detailed description in separate subsection)
- standardized report forms from supervision visits to health facilities
- follow-up on-site training requirements
- qualitative data (e.g., staff feedback sessions) on practical issues related to LED-AP testing

1.2.2.4.2.4 Cost-effectiveness

Cost-related data will be collected, to estimate both direct and indirect medical and non-medical costs, as well as the cost of setting up the intervention (e.g., training, supervision, equipment). A cost-effectiveness analysis (CEA) will evaluate the costs from the perspective of health care provider (only include costs incurred by the provider) and societal perspective (costs to the health care provider plus patient level costs). To assess cost from the provider's perspective, we will collect data in both the intervention and control periods on the important cost drivers such as health personnel, drugs, supplies, equipment, building space requirements and indirect costs using a standardized tool [28]. Additionally, we will include costs related to training of health personnel. We will also collect out-of-pocket expenditures related to direct medical (if any) and direct nonmedical costs including transportation, food, lodging cost born by households using exit interviews. Additionally, we will collect data on demographic characteristics and consumption expenditures that could help in disaggregated analysis across different income quintiles in both the intervention and control groups. We will collect data on demographic characteristics of the household of the patients included in the trial such as family size (number of adults and children living in the household that helps us to compute the adult equivalent) and on household consumption expenditure (expenditure on food, rent, transport, health, utilities etc. over a specified period). Based on the total household consumption expenditure, we will compute the per capita consumption expenditure using total consumption and the adult equivalent value. The per capita consumption expenditure level will then be divided into five income quintiles to allow us in disaggregated analysis.

Cost data will be collected during enrolment and follow-up visits at 4 and 60 days after enrolment. Cost data collection for subsequent visits will be harmonised with trial visits/follow-ups. Costs that are likely to be shared equally in both arms will not be included in the analysis. The total cost per individual treated will be computed for both arms based on resources consumed in each arm. We will compute unit costs (per patient) of drugs and supplies by multiplying the number of drugs or supplies consumed by their unit prices. We will use standard approaches to compute for capital costs such as equipment and building space [28]. Similarly, we will estimate health personnel costs per enrolled child. We will allocate indirect costs using allocations methods based on caseloads, floor space, laundry volume, etc.

The trial will assess the duration of diarrhoea between the intervention and control arms. Additionally, mortality differences between the two arms over a 60-day period will be assessed. These will be inputs as the health outcome measure in the CEA. We will estimate the additional disability adjusted life years (DALYs) averted due to the interventions as compared to the control arm. DALYs is a measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health. The DALYs calculations will be done as follows by accounting for both the average days of reduction in the diarrhoeal duration and also the diarrhoeal severity (mild, moderate, severe). The average days reduction in diarrhoea duration will be multiplied by a corresponding weighting factor for mild, moderate, and severe episodes, using GBD disability weights [29]. The difference in mortality rate and the average age at death between the two arms will be used to estimate life years gained due to the intervention (using a life table for Ethiopia). We will combine life years gained and disability averted to obtain a total estimate of DALY averted. Finally, we will compute the CEA as the difference in the average cost per patient in the intervention arm and the control arm divided by the difference in DALYs averted per patient between the two arms.

1.2.2.4.3 Adverse effects of treatment

Potential side effects of nitazoxanide will be monitored and recorded during and after completion of the treatment period and any significant adverse effects will be reported according to the respective drug adverse event reporting systems in Ethiopia and Mozambique.

1.2.2.5 Sample size considerations

The required sample was estimated based on our primary outcome measure; reduction of diarrhoea duration. Based on a recent study of cryptosporidiosis [30] and experience from similar studies the average duration of diarrhoea with standard care after presenting at a health facility is 4 days with a standard deviation (SD) of 5, due to a long "tail" of more prolonged diarrhoea in some of the cases. With the provision of LED-AP POC testing and nitazoxanide treatment we hypothesize that the average duration of post-presentation diarrhoea can be halved to two days, with a SD of 3.
Using the R-studio tool swCRTdesign [31] for sample size calculation, the required combined sample size for two equal study arms was estimated at an alpha level of 0.05 and 80% study power to be N=140. Considering the design effect (DE) of a stepped wedge trial design with a conservative intra-cluster correlation coefficient (ICC) of 0.19, number of clusters (k=16) and steps (t=4) the DE was 3.09, increasing the sample size to 217. Considering a study attrition rate of 10% brings this number to 241. With an expected 8% prevalence of cryptosporidiosis a total of 3013 children with watery diarrhoea will need to be enrolled.

1.2.2.6 Statistical methods

Baseline characteristics and follow up measurements will be recorded, validated, and cleaned using a digital platform (REDcap software) with export of validated datasets to STATA /R for further data wrangling and statistical analysis. The overall data analysis procedure will primarily be conducted based on the intention-to-treat Analysis approach. Thus, regardless of adherence to the intervention, all included participants and relevant data recorded during the study period will be analyzed according to the originally assigned intervention group (clustering and allocation period). Simple statistical tests (e.g. independent t-test, linear regression) will be used to compare the difference/change in mean duration of diarrhoea across the intervention groups. Important individual and cluster level characteristics will be summarised by intervention arms and compared across observation periods. We will calculate summary statistics of continuous measures, proportions for categorical variables and graphical illustrations. We will present 95% confidence intervals for all key parameters. Inferential methods (e.g., hypothesis testing, multivariable analysis will be used to estimate the effect of the intervention (test and treat strategy) and to estimate associations between potential predictor variables and our primary and secondary endpoints.
A generalised linear mixed model and/or generalised estimating equations will be employed to generate a linear model with random effect for cluster and fixed effect for each step. The incidence of cryptosporidiosis (case specific prevalence or proportion of children diagnosed with cryptosporidiosis) will be estimated and compared between intervention and control clusters at each time point using the mixed-effects regression model. A regression analysis will be used to adjust individual level confounding variables such as age, sex, and nutritional status and the effect of clustering and time variation, and coefficients of fixed effects and robust variance estimator (b, SE) will be reported. Possible heterogeneity within and between clusters will be explored and compared across intervention and control groups.
Subgroup analyses will be conducted to investigate potential effect modifiers of the intervention and primary outcome variables that include severity of diarrhoea, HIV, acute malnutrition (moderate, severe), stunting, and other facility or cluster related factors. Furthermore, we will run sensitivity analyses to assess the robustness of the results obtained from alternative models under different assumptions and parameters.
For binary outcomes, both bivariate and multivariable logistic regression models with random effects for clusters and fixed effects for each step, will be developed. Estimated difference with regard to secondary (binary) outcome measures will be reported as Relative Risk (RR) or risk difference (RD), with corresponding confidence intervals (95% CI).

1.2.3 Diagnostic accuracy of LED-AP point-of-care testing

The following diagnostic accuracy parameters of LED-AP testing will be calculated by comparing LED-AP test results (i.e., the index test) to a reference test consisting of Cryptosporidium qPCR, using quantitative cutoffs for diarrhoea-associated infection, as established previously (Johansen 2021). 95% confidence intervals for test sensitivity, specificity, and positive and negative predictive values were calculated by the Wilson method, and for positive and negative likelihood ratios with formulae from Simel and colleagues. Spearman's rank correlation will be used to quantify the association between semiquantitative scoring of positive AP slides (i.e., one to nine, ten to 50, or more than 50 oocysts per magnification field of view) with quantitative results obtained by qPCR.

1.2.3.1 Cryptosporidium qPCR reference testing

All samples tested by LED-AP microscopy will also be tested by *Cryptosporidium* qPCR, to be able to estimate key diagnostic accuracy parameters of LED-AP provided at the point-of-care, e.g. sensitivity, specificity, and

positive and negative predictive values (PPV, NPV).
After thawing frozen stool samples and pre-treatment, total nucleic acids (TNA) will be extracted using an automated extraction platform. TNA will be extracted from a weighed aliquot of stool samples followed by quantitative *Cryptosporidium* PCR to quantify the number of DNA target copies per gram of stool.
Cryptosporidium PCR will be performed blinded to the results of LED-AP testing.
The qPCR target gene will be *Cryptosporidium* oocyst wall protein (COWP) [32]. *Cryptosporidium* positive controls of known concentration will be used to generate standard curves and determine the cycle threshold (CT) to normalize the delta CT of the test sample to the delta CT of the calibrator in each sample.
All LED-AP *Cryptosporidium* positive stool samples will be tested further using a multiplex panel for viral and bacterial causes of diarrhoea to reduce case ascertainment bias due to co-pathogen diarrhoeal infections.

1.2.3.2 Diagnostic accuracy and turnaround time of rectal swabs versus bulk stool samples

1.2.3.2.1 Rationale

Rectal swab collection is an alternative faecal sampling method to conventional stool samples for the detection of intestinal pathogens and has comparable sensitivity to stool samples for some pathogens [33] The main advantage of rectal swabs is that they are considered easier and quicker to collect than a conventional stool sample. Swab sampling has the potential to reduce total test turnaround time, particularly for those young children who are not able to provide a stool sample at the time of presentation or during treatment or observation within the facility. However, the diagnostic accuracy of rectal swab testing for enteric parasites, specifically *Cryptosporidium*, has not been determined in a prospective clinical diagnostic accuracy study. There are potential limitations of the method, mainly related to analytical sensitivity: the amount of faecal material captured by the swab may not be sufficient for microscopical examination and sensitivity may be influenced by the water content of the stool (cryptosporidiosis usually leads to a profuse watery diarrhoea).

1.2.3.2.2 Design

An embedded diagnostic accuracy substudy will compare test turnaround times and diagnostic accuracy of LED-AP conducted on rectal swabs versus bulk stool samples. We will apply a paired study design to directly compare the diagnostic accuracy of rectal swabs and bulk stools from each patient and then all will be tested and compared with the reference standard (qPCR). AP-staining for rectal swabs and bulk stool will be prepared and evaluated using LED microscopy. To achieve independent examination of slides prepared from swabs versus bulk stools, all slides will be fixed, archived, and re-examined by an independent team within 1 week of the initial microscopy.

1.2.3.2.3 Participants

All participants in the SW-CRT trial are eligible for inclusion in the rectal swab evaluation substudy. Caregivers will be asked for permission to collect a rectal swab sample in addition to a bulk stool sample, both should be obtained as soon as possible to reduce turnaround times and time-to-treatment in case of a positive test. Participants from whom we receive both a rectal swab and a bulk stool sample will be included in the substudy analysis.

1.2.3.2.4 Test methods

At the facility, rectal swabs and stool samples will be processed under similar conditions and managed by the same personnel. Rectal swabs and stool samples will be collected as soon as possible after enrolment (stools will usually be obtained after rectal swab collection). Rectal swabs will be collected by the study personnel. A flocked rectal swab will be obtained by inserting the swab into the rectum (2–3 cm) and gently rotating the swab 360º before retraction. The swab will be placed into a sterile tube containing universal transport medium. As soon as the sample has arrived in the facility laboratory, a droplet will be transferred to a glass slide using a sterile transfer pipette, smeared out using a sterile inoculation loop, then air-dried. The rectal swab smear will be stained by AP and examined under an LED fluorescence microscope (LED-AP) using a similar procedure as described above for bulk stool samples.
If the rectal swab LED-AP test is positive, the child will be classified as a cryptosporidiosis case, and nitazoxanide treatment will be offered as soon as possible, without waiting for the result of bulk stool testing. If the rectal swab LED-AP test is negative, the cryptosporidiosis test result will not be issued until the LED-AP test has also been performed on the bulk stool sample. The sample tube will be stored at room temperature for maximum 12 hours before transfer to a cooler box or refrigerator, from which it will be transferred to a -80°C freezer within 72 hours from sample collection. The rectal swabs will be thawed later for batchwise qPCR, fully

blinded to the result of initial LED-AP microscopy (figure 6).

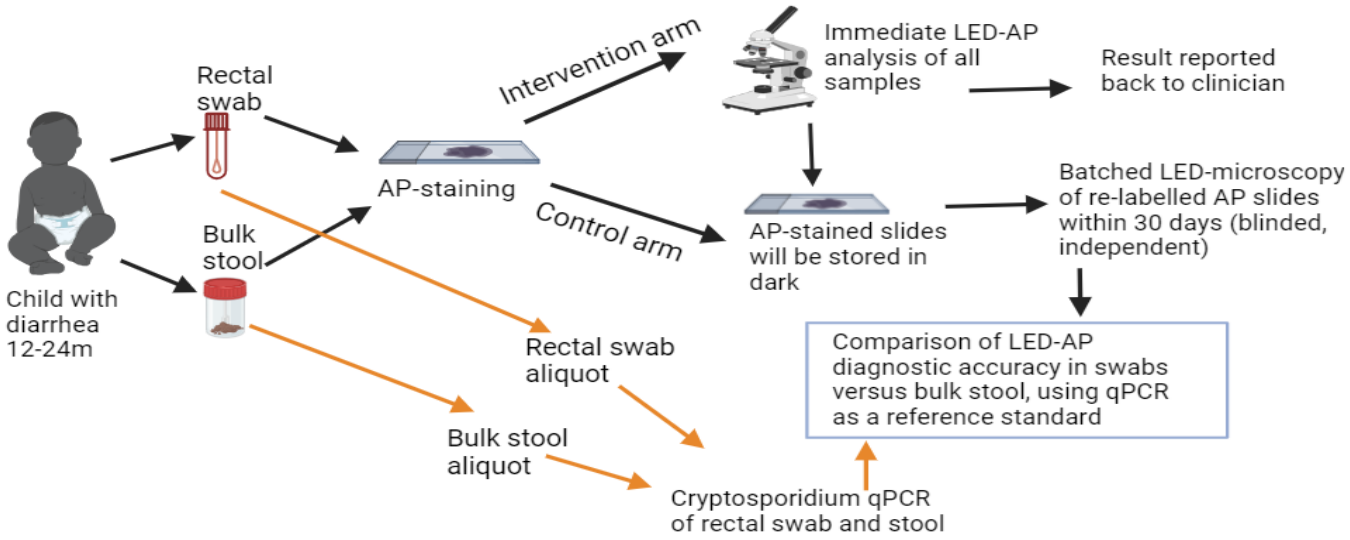


Figure 6. Stool and swab samples processing and laboratory analysis

1.2.3.2.5 Head-to-head comparison of LED-AP testing of rectal swabs versus bulk stool

To be able to perform a reliable and independent comparison of the diagnostic accuracy of LED-AP on rectal swabs versus bulk stool, the following steps will be taken:

1. All AP-stained slides (both from bulk stool and from rectal swabs) will be archived in glass slide storage boxes for later re-examination by a different staff member.
2. Samples collected in control sites will also be stained by AP, but will not be examined, instead the slides will be archived in slide storage boxes.
3. Separate staff will open the storage boxes, randomly re-arrange slides, then re-label slides using a new sequence of sample numbers within 30 days from sampling.
    a. The key will only be known to study investigators not involved in the subsequent re-analysis by LED fluorescence microscopy
    b. This procedure is intended to achieve blinding of the microscopist to which slides have been prepared from rectal swabs or from bulk stool, and which slides are from control versus intervention sites.
4. Re-examination will be performed within 30 days as the fluorescence holds well for this duration (Johansen 2021) but will start to wane gradually after this time.
    a. Control slides are included in each batch of slides and will serve as a quality control for whether the fluorescence of the stain is still at an adequate level.
    b. If the fluorescence is deemed to be too weak for re-examination, all slides in the relevant batch will be stained again using AP.
5. LED-fluorescence microscopy will be performed as described above.
6. Results will be registered in a separate data collection form to the initial laboratory findings.

1.2.3.2.6 Analysis of diagnostic accuracy

Sensitivity, specificity, positive and negative predictive values will be compared between LED-AP from rectal swabs versus bulk stool samples, by comparing both to *Cryptosporidium* qPCR as the reference standard, in paired (i.e., head-to-head) analysis, obtaining 95% confidence intervals both for the point estimates, and for the difference between estimates, using the DTComPair R package for the comparison of the accuracy of two binary diagnostic tests in a paired study design. Parasite load will be approximated by quantitative *Cryptosporidium* PCR, allowing us to compare the diagnostic accuracy of rectal swabs versus bulk stool for low-burden versus high-burden infections.

1.2.3.2.7 Analysis of test turnaround times

In addition to diagnostic accuracy, total test turnaround time (TAT) is a key marker of practical useability of a diagnostic test, is closely linked to clinician uptake of testing, patient satisfaction, and overall cost-effectiveness of testing. We will measure TAT from the time the child presents for healthcare with diarrhoea until the physician has an actionable result, i.e., is able to decide on cryptosporidiosis treatment.

The Lundberg definition of TAT [34] will be used, which include nine steps in the performance of laboratory test: ordering, collection, identification, transportation, preparation, analysis, reporting, interpretation, and action. Based on this principle, we will prepare a standardized time tracking sheet record the times of child arrival at the health facilities with diarrhoea, initial assessment by attending physician, and times for test ordering, sample collection (rectal swabs and stools) to laboratory arrival, sample preparation, analysis, reporting/result dispatch to the time the physician decided on patient treatment. This process will be applied for standard and LED-AP laboratory tests for both control and intervention arms, respectively. Time will be recorded for each part of the activity and the TAT analysis will be started from the time when the test is ordered. Data collected on patient time and activity tracking form will be registered using electronic data capture forms (REDCap).

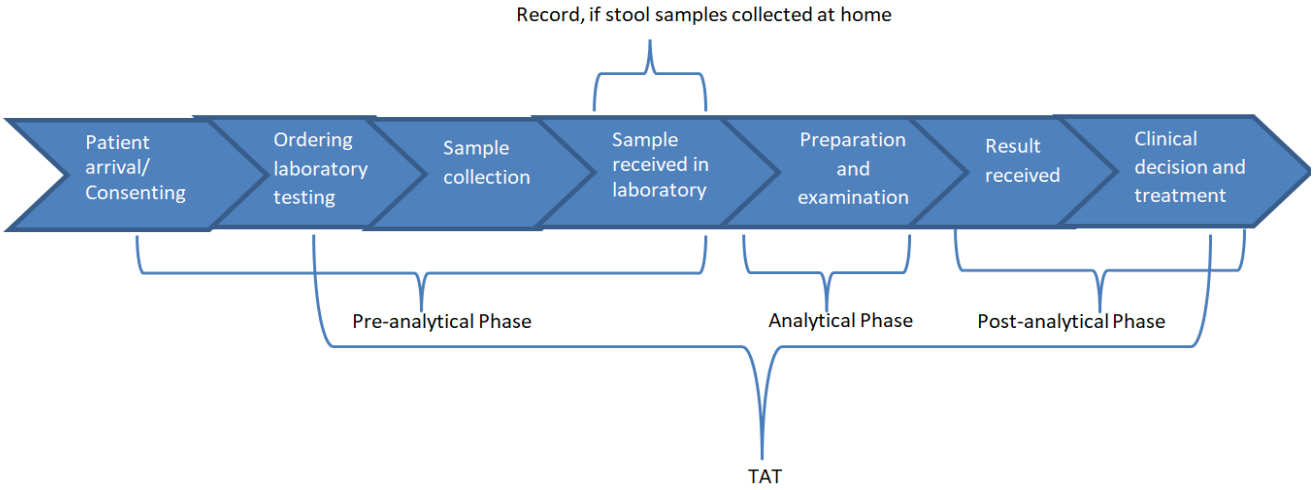


Figure 7. Analysis of TAT for rectal swab and bulk stool samples

TAT will be captured by study staff for both rectal swabs and stools, who will also document logistical or practical challenges noted during tracking of laboratory tests and clinical outcomes of children.
Time motion analysis will be performed to quantify the time impact of patients' time waiting and receiving care. Total time will be described in mean and standard deviation. TAT difference will also be calculated for the stool versus rectal swab sample tests.A standardised time tracking sheet will be used to capture the following time points:

1. Time of presentation to the healthcare facility
2. Start of assessment by clinical healthcare worker
3. Sample collection time
4. Time sample received in the local healthcare facility laboratory
5. Time sample analysis started (i.e., starting with the opening of the sample container)
6. Time sample analysis completed (i.e., time LED-AP result recorded within the lab)
7. Result received by clinical healthcare worker
8. Treatment decision time
9. (If treatment recommended): time when nitazoxanide treatment provided

The time tracking sheet will first follow the sample to the lab, and will then be attached to the LED-AP laboratory result slip, and will be filled out by the study nurses, laboratory technicians, and, finally the clinician (i.e., prescriber) receiving the result slip. Time points recorded in the standardized time tracking sheet and times recorded on clinical and laboratory data collection forms document will be cross checked as a quality control.

1.2.3.2.8 User acceptability survey

A qualitative survey will be conducted among a subset of the children and caregivers to assess user acceptability towards the rectal swab collection method. Caregivers who do not consent to obtain rectal swabs will also be invited to participate in the survey. Clinical and laboratory staff involved with the collection of rectal swabs and bulk stool samples will be included in the survey. Questions related to perceptions about testing and user preference for rectal swabs versus bulk stool samples will be registered prior to sample collection, and again after receiving the result of testing.

1.2.3.2.9 Sample size considerations of the rectal swab substudy

We also estimated a sample size for a substudy on diagnostic accuracy study of the cryptosporidium diagnosis performance of rectal swabs compared with bulk stool samples. The sample size is estimated based on a sensitivity of bulk stools 88% for the diagnosis of cryptosporidiosis using LED-AP microscopy [14] and by assuming 78% sensitivity of rectal swabs which is less than 10% of bulk stools. There were no previous studies that evaluate the sensitivity of rectal swab samples for the diagnosis of cryptosporidiosis. The sample size calculation is defined using normal approximation to construct a confidence interval for the true sensitivity value for estimating a 95% confidence and estimating the expected proportion with 10% absolute precision and power of 80%. Assuming the prevalence of cryptosporidiosis in the study sample is 8%, this substudy would require a total sample size of 824 rectal swabs and stool samples for estimating the expected proportion.

1.3 Ethical issues

1.3.1 Consenting procedures

A trained health worker will go through the informed consent process with the children's caregiver. The informed consent forms (ICF) will be written in both the officially and (if applicable) the locally used language in the study area, and additionally explained in the local language when needed to ensure that the caregiver of the child understands the consent process. The caregiver will be asked to read and review the consent form and to ask questions before signing the form. The caregiver will sign two original copies of the informed consent, one will be given to the parent and the other will be kept at the health care facility. The informed consent process will give all of the relevant information, including the study purpose, procedures, benefits, risks, how to decide whether to participate, or how to withdraw consent later. If the caregiver providing consent is illiterate, an independent witness will be present to ensure the caregiver that all the information read aloud is contained in the ICF. In this instance, the caregivers will thumbprint the ICF, which will be countersigned by the impartial witness. After the informed consent is signed a participant identification study number will be given, and will be entered into the site-specific screening log.

1.3.2 Regulatory approval process

Ethical clearance will be obtained from the Research Ethics Review Board of any University-affiliated healthcare facilities included in the study, with National Research Ethics Review Committees in Ethiopia and Mozambique, and also the Regional Committee for Medical and Health Research Ethics of Western Norway. More information regarding this is entered in the electronic application form.The clinical trial application will be submitted through the Clinical Trials Information System. LED-AP microscopy is already used for TB diagnosis, thus does not require any new regulatory approvals for market authorization. AP is currently imported and distributed by the ministry of health in Ethiopia and Mozambique according to national safety regulations.
Nitazoxanide is an FDA-approved drug. It is not included in the Ministry of Health pharmaceutical formulary in Ethiopia or Mozambique but can be imported as part of a research trial. Depending on the outcomes of the study (e.g. satisfactory efficacy, accuracy, and cost-effectiveness of an LED-AP test-and-treat strategy) full regulatory approval will be sought.

1.4 Gender issues

A risk factor study in Ethiopia found that 53% of children presenting with cryptosporidiosis were girls while only 39% of non-cryptosporidiosis diarrhoea cases were girls [16]. The reason for this difference is not clear, but gender will be considered in all statistical models as a possible confounding factor. The same study identified these gender-associated socioeconomic determinants as important risk factors for cryptosporidiosis: maternal education < 1 year, and having a primary caregiver that is not the child's mother. Particular attention will therefore be given to providing advice to both primary and secondary caregivers on appropriate home-based management of diarrhoea and malnutrition. Caregiver instruction is considered part of normal care in many healthcare facilities, but effort will be made to tailor verbal and written teaching material to young mothers with variable or low level of formal education. The study also found that the proportion of children who failed to submit a stool sample was higher among girls than boys [16]. During training and supervision of study staff we will therefore highlight that there might be gender-related reasons why children might fail to provide a stool sample within reasonable time, and that extra encouragement and support should be provided to caregivers in order to minimise the risk of gender selection bias.

Equal opportunity is a key issue in the CryptoTT project, and particular attention to gender issues will be taken over the lifetime of the project. In the collaborative work to establish the team a majority of males have signalled their interest, with the balance being further tilted towards male majority when the female scientific coordinator of our first stage proposal was offered a position outside AHRI. In this situation the project will focus on facilitating opportunities for female researchers. Specific mentorship and training will be offered to female junior researchers.

1.5 Data management

1.5.1 Oversight of collection and storage of data

During the study a carefully designed paper case report forms (CRFs) will be used to collect baseline- and follow up data. All study personnel collecting and processing data will receive trained in data handling and ethical issues related to data collection. Data collected using CRFs at each participating site will be imported using tablets to the Research Electronic Data Capture (REDCap) daily, by staff assigned for this activity, each user will have a username and password authentication to prevent unauthorized access to the project database, and paper CRFs will be kept/archived at the site, as per the data management plan (DMP) to be developed for this trial in the beginning of the project (see below). During storing/archiving the trial data, all the confidentiality and data protection principles will be applied. CRF completion guidelines explaining how to record the required data, timeline for transmission of data, data queries and query resolution will be prepared for the trial. Armauer Hansen Research Institute in Ethiopia will be responsible for centralized data management in Ethiopia whereas Fundacao Manhica will be responsible for the centralized data management in Mozambique. The clinical data management team will ensure that access to the data will be restricted only to authorized personnel (i.e. data entry, monitor or statistician) through user and passwords. In addition, the database architecture, the access to the application servers and the servers will be protected through a firewall. Only essential access will be permitted and only systems will only allow the creation and use of strong passwords.

1.5.2 Data capture

We will collect sociodemographic, clinical, and laboratory data on both paper and electronic case report forms, as well as observation checklists, and consent forms. All personnel involved in data collection and processing will receive training on ethical data handling practices. Quantitative data, whether collected on paper or electronically, will be consolidated into RedCap for data cleaning and processing.

1.5.3 Data storage

For secure data storage and collaboration, we will utilize a designated project folder on the Armauer Hansen Research Institute's encrypted cloud server, ensuring the protection and integrity of the data. This approach underscores our commitment to ethical standards, data security, and the efficient management of study data.

To uphold data security and integrity, multimedia files and transcriptions will be securely stored on designated researcher computers within encrypted folders, accessible only to authorized study personnel. Electronic data collection, facilitated through Android devices and RedCap software, will incorporate stringent password protection measures on each device used for data capture. Additionally, all data will be systematically removed from audio recorders and tablets upon the conclusion of the study period, minimizing the risk of data breaches or unauthorized access.

Paper consent forms, essential documents safeguarding participant consent, will be securely stored at site-partner offices and archived for a period of 10 years following the study's conclusion. These forms will be stored within locked filing cabinets, located within offices equipped with additional security measures to prevent unauthorized access.

1.5.4 Data access

1.5.4.1 Open access

In accordance with FAIR (Findable, Accessible, Interoperable, Reusable) principles and ethical guidelines, research data will be archived at the conclusion of the study. Subject to ethical approvals, datasets will be made openly available for scrutiny by other researchers and policy-makers, promoting transparency and fostering scientific collaboration. Furthermore, all research reports and academic publications will be made accessible through open-access platforms, ensuring unrestricted access to research findings without financial barriers.

Information describing the anonymized data will be shared for other researchers and policy makers when required will be included in the participant information sheet (PIS/ICF) and reviewed for ethical approval in order to address the requirement for data sharing. All research reports and academic publications will be made open access, to ensure anyone can access them without financial costs.

1.5.4.2 Data management plan

A detailed Data Management Plan (DMP) will be developed within six months of project start. This plan will delineate objectives for data generation, processing, accessibility, curation, storage, and preservation, aligning with FAIR principles and regulatory requirements. Furthermore, the DMP will outline robust measures for safeguarding sensitive data, affirming our commitment to ethical research conduct and data stewardship.

1.6 Capacity building

Need for capacity building in diagnostics of diarrhoeal diseases and health economics

As part of the study logistics two study nurses and two laboratory technicians from each hospital/health centre will be trained on the study protocol and data collection tools.

We will arrange refresher training from clinicians at health facilities on national standard treatment guidelines for the **management of diarrhoea** in children. These guidelines will be supplemented with specific guidance on the correct use of LED-AP-testing and indication for nitazoxanide treatment.

We will provide training on the **LED-AP method for laboratory technicians** at each health care facility and sample delivery/result communication will be specifically addressed. Refresher training will be provided depending on staff turnover. Laboratory staff will also be trained on qPCR for onsite detection of Cryptosporidium using molecular biology technologies.

Skills to perform economic impact analyses are scarce in Ethiopia and Mozambique. The trial will also be an opportunity to build capacity at the healthcare facility management level, ministry of health level and in academic institutions **to perform health economic evaluations**. To achieve this we plan to conduct successive workshops on the basic principles of economic evaluations and their relevance for roll-out of diagnostic and therapeutic interventions.

The project will create opportunities for master and PhD-students in both Ethiopia and Mozambique. As part of CRYPTO TT's capacity building we will train one PhD student from Ethiopia in cost-effectiveness research, and two PhDs from each country (Ethiopia and Mozambique) in the epidemiology of diarrhoeal disease and point-of-care diagnostics. The students will be enrolled in a joint PhD program between local Universities and the University of Bergen. The students will be jointly supervised by project partners. The PhD students will also be trained in research methodology and data analysis. They are expected to publish their work in peer-reviewed journals.

1.7 Local innovation and sustainability

After WHO recommended the use of light-emitting diode fluorescence microscopy (LED-FM) as an alternative to conventional light microscopy using Ziehl-Neelsen staining in 2011, a significant number of LED microscopes have been rolled out in many SSA countries including Ethiopia and Mozambique. However, many of these microscopes are now out of use, and are not being used for the diagnosis of TB as initially intended. Since we are planning to re-purpose the use LED microscopes in CryptoTT we want to solve this problem through involvement of a small enterprise called Simbona Africa Engineering Solutions in Ethiopia.

Our preliminary assessment indicates that the main reason for failure of the LED microscopes is malfunction of the power supply unit and lack of replacement from the local market. In addition, there is poor end-user skills and lack of preventive and corrective maintenance since the capacity of local biomedical engineers for maintaining these microscopes is limited. Simbona will therefore be involved in maintenance of the LED microscopes during the project period. In addition, training will be provided to local biomedical engineers and laboratory technologists in the installation and maintenance of LED-microscopes.

To solve the problem of damaged power supply units, Simbona will produce a prototype and initial small-scale production of a locally manufactured low-cost power supply unit which will be able to match local voltage requirements and withstand power fluctuations. These activities will ensure sustainable usage of the LED microscopes both for the diagnosis of TB and cryptosporidiosis.

2 Impact

2.1 Project's pathways towards impact

2.1.1 Expected Outcome and Impacts

CryptoTT aims to revolutionize the current syndromic treatment of diarrhoea by introducing a cost-effective diagnostic method for a major treatable pathogen. Here we outline outline a test-and-treat intervention in a diagnostic CRT, which serves as an optimal evaluation of the operational utility of the LED-AP test for cryptosporidiosis at technology readiness level 7.
CryptoTT anticipates demonstrating the feasibility of transitioning from syndromic management to targeted therapy for common diarrhoeal causes in children, treatable with affordable medication. This aligns with the WHO's integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD), which advocates a unified approach to prevent pneumonia and diarrhoea deaths. Similarly, the WHO's Integrated Management of Childhood Illness (IMCI) aims to reduce preventable mortality, minimize illness and disability, and promote healthy growth and development in children under five years of age.
The project's objectives align well with these WHO initiatives, as it aims to provide access to a Point-of-Care (POC) diagnostic and treatment for a significant cause of severe childhood diarrhoea and long-term sequelae. The project is expected to achieve the following major impacts:

2.1.2 Scientific impacts

2.1.2.1 Diagnosis and treatment of cryptosporidiosis

CryptoTT is anticipated to provide evidence on the effectiveness of the diagnostic testing and the targeted test-and-treat strategy. Furthermore, it will generate insights on the impact of linking diagnostic testing with targeted treatment on health outcomes of children with diarrhoea. Given the absence of robust screening and testing algorithms and international standard methods for diagnosing cryptosporidiosis, CryptoTT is expected to contribute new scientific discoveries on cryptosporidiosis diagnosis.
CryptoTT is also expected to generate robust evidence on the applicability of LED-AP for diagnosing cryptosporidiosis. The cryptosporidiosis LED-AP test could be implemented at the primary healthcare level, where it is already in use for TB diagnosis and monitoring in many Sub-Saharan African (SSA) countries. Considering the dual burden of TB and diarrhoeal diseases in many SSA countries, CryptoTT will generate scientific evidence on dual-use technology for diagnosing tuberculosis and cryptosporidiosis that can be easily integrated with pre-existing laboratory infrastructure for tuberculosis testing.
Although nitazoxanide is an effective treatment option for cryptosporidiosis, its provision will need to be supported by accurate POC cryptosporidiosis testing incorporated into clinical treatment guidelines. Additionally, new evidence on the potential impact of using rectal swabs as an alternative to bulk stool samples on the turnaround time for diagnosing diarrhoeal diseases will also be generated.

2.1.2.2 Contributing towards EU-EDCTP3's joint undertaking research agenda

In line with the Horizon Joint Undertaking Global Health EDCTP3's Framework Programme and strategic

research agenda, our proposal involves the implementation of a POC testing for cryptosporidiosis. This easy-to-use, affordable test can rapidly diagnose cryptosporidiosis, leading to more timely treatment and thereby reducing morbidity and transmission of diseases. The POC diagnostic could be easily deployed and readily used at primary care and community healthcare centers in resource-limited communities in Low and Middle-Income Countries (LMIC). Performing this study in Ethiopia and Mozambique, where the disease burden is high, will generate robust evidence for its wider implementation in other SSA countries.

2.1.2.3 Fostering diffusion of knowledge and Open access.

CryptoTT is expected to generate more than 10 publications, fostering the diffusion of knowledge and scientific evidence generated through a well-designed study. The manuscripts are expected to be published in open access journals, thereby facilitating wider access to the scientific community. In addition, CryptoTT will work towards updating existing diagnosis and treatment guidelines based on the project's results. These guidelines will be accessible both to health practitioners and the scientific community.

2.1.3 Societal impacts

2.1.3.1 Reduced morbidity and mortality

Evidence from previous trials indicates that targeted cryptosporidiosis treatment can reduce both morbidity and mortality [5]. Cryptosporidiosis in early childhood, if untreated, can lead to malnutrition, impaired physical and cognitive development, and increased risk of death. Therefore, timely and appropriate treatment is crucial. Currently, prompt diagnosis and suitable therapy are the most effective ways to reduce morbidity and transmission of Cryptosporidium infections in endemic areas.

An ideal diagnostic test for countries with limited resources should be inexpensive, user-friendly, quick, portable, not requiring refrigeration, and have high sensitivity and specificity. A POC diagnostic test can reduce the time to adequate treatment and care. CryptoTT aims to provide data to assess the impact of a low-cost diagnostic tool on morbidity and mortality related to cryptosporidiosis. Treatment is also expected to reduce the time for Cryptosporidium oocyst shedding, thereby limiting transmission. The project will contribute to the UN Sustainable Development Goal 3 “Ensure healthy lives and promote well-being for all at all ages” in Ethiopia and Mozambique. The method's low investment and running cost make it easily transferable to other SSA countries.

2.1.3.2 Reduced use of antibiotics

Watery diarrhoea is often over-treated with empirical antibiotics in LMIC, increasing the risk of anti-microbial resistance development. Access to a diagnostic method would enable clinicians to prescribe targeted therapy, thereby avoiding unnecessary antibiotic prescriptions for children who do not need them. This would help curb the progressive emergence of antimicrobial resistance, a significant global problem, especially in low-resource settings.

In addition, the LED-AP POC test for cryptosporidiosis would help decrease irrational use of antibiotics in children with severe diarrhoea as we expect that access to a test result will lead to more targeted therapies. Experiences from the GEMS study indicates that *Cryptosporidium* usually occurred without bacterial co-pathogens that would require antimicrobial treatment (Liu J, Platts-Mills JA, 2016). CryptoTT is therefore expected to facilitate appropriate treatment of diarrhoea

2.1.3.3 Improved public health data and surveillance

The reported association between cryptosporidiosis and stunting and cognitive impairment has significant repercussions on the health of future generations. These severe consequences can translate to reduced future productivity and economic impact. An accurate diagnostic test for cryptosporidiosis would provide health authorities and healthcare systems with prevalence data for a major cause of diarrhoeal illness. Such data is essential for developing and implementing informed health policies, improving clinical surveillance of diarrhoeal diseases, and reducing the burden of cryptosporidiosis. CryptoTT will facilitate the estimation of the true burden of cryptosporidiosis and the potential future application of LED-AP for routine diagnosis. The experience gained from this project will facilitate trials of potential new treatment options for cryptosporidiosis in LMIC.

2.1.3.4 Policy change in treatment of children with diarrhoea and cryptosporidiosis

The results from this project will be of great interest to the ministries of health in Ethiopia and Mozambique. In Ethiopia, the diarrhoea management guidelines are set up by the National Newborn Child Health and

Development Technical Working Group, while national standard treatment guidelines are made by the Ethiopian Food and Drug Administration. In Mozambique, these functions are performed by the Department of Public Health in the Ministry of Health. We will engage with the authorities and ministries in the planning and implementation. The proposed project will provide high-quality data about the feasibility and cost-effectiveness of using LED-AP in testing for cryptosporidiosis.

2.1.3.5 Capacity building

Physicians, nurses, and laboratory technicians working in healthcare centers will receive upgraded knowledge and capacity in the management and diagnosis of diarrhoeal diseases and cryptosporidiosis. Additionally, the PhD level training will help develop a critical mass of researchers in Ethiopia and Mozambique and strengthen the capacity related to validation, optimization, and implementation of diagnostic tools and test and treat strategy not only for cryptosporidiosis but also for other poverty-related diseases.

2.1.3.6 Knowledge exchange and community practice

We will establish stakeholder forums to ensure knowledge exchange to clinicians, nurses etc working at local health facilities. In addition to health care staff, also governmental agencies will be invited to these fora. Using stakeholder engagement forums, intense engagement and interaction will be created and this will foster knowledge exchange. In addition the project will create an opportunity for north-south and south-south collaboration and networking between partners in Norway, Ethiopia and Mozambique. Since AHRI is found in close proximity with Africa Centers for Disease Control and Prevention this will be harnessed as an opportunity to create platforms for knowledge exchange and dissemination and scaling up of the results in other African countries. Further engagement with World Health Organization Regional Office for Africa (WHO-AFRO) will enhance knowledge exchange and community practice across Africa and other LMIC where the burden of diarrhoeal disease is high.

2.1.4 Economic/technological impacts

2.1.4.1 Repurposing diagnostic testing

The goal of this project is to repurpose a diagnostic tool that is already available and has been deployed by primary health care centers based on a recommendation from WHO.

2.1.4.2 Lower health care expenses

For a cryptosporidiosis test to be cost-effective, a sensitivity of at least 70% would be necessary [35]. The CryptoPOC study from Ethiopia showed sensitivity of 88%, well above this threshold. The next step to show the potential for impact of this test is to determine the **diagnostic operational utility** and cost-effectiveness in a large multi-site study involving several types of health facilities, which is something that aligns with the objectives of CryptoTT. A test-and-treat study will create valuable data comparing two stool collection procedures, turnaround times, and treatment provision, in addition to treatment efficacy. These are important operational complexities hugely benefitting from a scaled-up evaluation to refine a large-scale roll-out of testing. Improved overall patient management as a result of the reduced turnaround times, accurate diagnosis and disposition for cryptosporidiosis, will reduce cost.

2.1.4.3 Business opportunities for local companies

CryptoTT will involve local SMEs. In both Mozambique and Ethiopia the maintenance/service agreement of LED-microscopes is done by local enterprises that will be engaged in this project.In Ethiopia an SME will be partnering to engage deeply with the project to improve durability and maintenance of LED-microscopes with particular focus on developing robust power supplies. This will knowledge is transferable to other LMICs. Laboratory consumables and reagents will be purchased locally whenever possible, to strengthen local ownership and ensure sustainability of this diagnostic tool.

2.2 Measures to maximize impact

2.1.5 Dissemination and exploitation

The results of this project will provide vital data on how the LED-AP test can facilitate clinical decisions about targeted treatment of an important cause of severe diarrhoea, and to avoid overuse of antibiotics in cases where the

test is positive. Routine LED-AP testing in children with diarrhoea can inform health authorities about the prevalence of this pathogen to guide public health measures and monitor effects of interventions.
Results of the study will be communicated widely as described in WP6. In the planning of this project, we have discussed with health facilities and health authorities about caseload, current laboratory facilities and current guidelines. We will engage WHO, WHO-Afro, Africa CDC, Ministries of health in Ethiopia and Mozambique through a series of stakeholder engagement forums.
The results of the project will be disseminated through presentations in national, regional and international conferences. Project partners will also attend EDCTP forum. In addition, CryptoTT will publish a minimum of 10 manuscripts in open access journals and we will make use of the H2020 guide on open access. in all publications and presentations, the funding by EU-EDCTP3 will be duly acknowledged.

2.1.6 Communication

A communication plan of the results of the CryptoTT project to policy makers and the public will be developed.
The constant engagement with policy makers during proposal development will continue during the implementation of the project and beyond. Stakeholders including the Ministries of Health from both Ethiopia and Mozambique, Africa CDC, WHO and WHO-AFRO and other relevant organizations will be constantly communicated. Since the Armauer Hansen Research Institute works directly under the Ministry of Health Ethiopia, this will facilitate communication with policy makers. The Manhica Health Research Centre also has its own Health and Demographic Survey Site and through close interaction with the Ministry of Health (Mozambique) led to guide the health authorities and decision-making bodies to define or adjust health policies. These existing linkages will therefore be leveraged in CryptoTT.
In order to communicate the results of the project with the wider public, we will develop a dedicated website. Project information and news will be posted on the website, the website of partner institutions and organizations. The dedicated website and websites of the partner organizations will serve to disseminate news and achievements of the project to the scientific community and the wider public. The website will also be used to acknowledge and promote the funding agency, EU-EDCTP3. The website will provide information about the project partners and the funding organization, about the projects' aim and structure, outcomes (published via briefing notes to especially inform lay people and policy makers) and with up-to-date information about project work progress (e.g. upcoming work-shops, publications, current research actions). We will publish results of the study through the website. Thus, other researchers elsewhere will be able to access the results to build up on the work of the project. Moreover, we will use appropriate social media channels to disseminate interim results, request for suggestions and feedbacks, etc. In addition, press releases and TV/radio- interviews will be used as means of communication to the general public.

2.1.6.1 Management of intellectual property

All researchers that participate within CryptoTT will have the right for the ownership of data, findings and intellectual property related of the project and the details of the specific rights will be identified through discussion and negotiation

2.1.7 Intellectual property exploitation

Any new discoveries within the project will be available for exploitation through open access, licensure and commercialization to other partners following IP access regulations of the institutions involved within CryptoTT. The final decision on the conditions for exploitation will be dependent on the agreement between the consortium members.

2.1.8 Knowledge management and protection

Management and protection of data and discoveries within the project will be properly handled based on regulations that will be included within the Consortium Agreement and will be done based on agreement between all consortium members.

2.1.9 Data ownership, protection and access rights

The consortium agreement will be used as a blueprint for governing for questions relating to data and results ownership and sharing. Any data that is generated within the project and generated solely by a single partner and that lies within the scope of the project will be owned by the partner that generated it. Any data that is jointly generated by all consortium members will have a joint ownership.

For results generated within the project and that will have potential for business opportunities by the consortium members, necessary steps will be taken to protect them. Any patenting and other deliberation will be handled based on regulations included within the consortium agreement.
Access rights to data generated within the project will be based on stated obligation within the consortium agreement.
#§COM-DIS-VIS-CDV§#

2.3 Summary

2.1.10 Key elements of the impact section

SPECIFIC NEEDS	EXPECTED RESULTS	KEY STAKEHOLDERS
What are the specific needs that triggered this project? * Lack of appropriate diagnostic tests for cryptosporidiosis Long turnaround time of diagnostic tests * Lack of data regarding the cost of a diarrhoeal episode * Weak integration between diagnosis, treatment and follow up of diarrhoea/cryptosporidiosis. * Inappropriate use of antibiotics due to lack of specific diagnostic tests * Lack of robust data on the impact of cryptosporidiosis on the growth of children * Lack of trained workforce in the health sector. * Insufficient local production of drugs	What do you expect to generate by the end of the project? *** New product: i**mplementation of LED-AP for the diagnosis of cryptosporidiosis. * Implementation of test ad treat strategy for cryptosporidiosis * Publication of scientific data and discoveries on reduction of turnaround time, impact of cryptosporidiosis on growth failure and reduced antibiotic use. *** 4 MSc students trained.** *** 4 PhD students trained.** *** 50 laboratory technicians trained on the use LED-AP** for the diagnosis of cryptosporidiosis. * A business model for engagement of SMEs involved in pharmaceuticals and repair of biomedical equipment	*Who will use or further up-take the results of the project? Who will benefit from the results of the project?* *** Ethiopian Ministry of Health**. *** Ministry of Health Mozambique.** *** Africa CDC** *** WHO-AFRO** * Families/caregivers * **Patients**: >1500 children to whom diagnostic service will be provided *** Health care workers**: >100 physicians, nurses, and laboratory technicians *** Scientific community** working on diagnostics, diarrhoeal diseases, parasitology and cost-effectiveness.

D/C/E ACTIVITIES	TARGET OUTCOMES	WIDER IMPACTS
What dissemination, exploitation and communication measures will you apply to the results? *** Dissemination towards the ministry of health and policy makers**: * Using policy briefs and guidelines on the diagnosis of cryptosporidiosis and repurposing LED-AP. *** Dissemination through Africa CDC and WHO** *** Dissemination towards the scientific community**: * Scientific publication in open-access journals, presentation in local and international conferences and the EDCT forum. *** Communication towards public:** Website, press release, community engagement forum, interviews on radio/TV and social media. *** Exploitation of the re-purposed diagnostic tool for implementation**	*What change do you expect to see after successful dissemination and exploitation of project results to the target group(s)?* *** Change of policy:** Ministries of health in Ethiopia and Mozambique to revise guidelines for the diagnosis and treatment of cryptosporidiosis and diarrhoeal diseases. *** High interest in the scientific discovery** (citation of project publications). *** Improved health outcomes** for children with diarrhoea and cryptosporidiosis *** Reduced** use of antibiotics for treatment of diarrhoeal diseases in children **Improved capacity** of local SMEs in availing treatment drugs and servicing microscopes	*What are the expected wider scientific, economic and societal effects of the project contributing to the expected impacts outlined in the respective destination in the work programme?* *** Scientific:** New data on feasibility of LED-AP test and treat strategy, accuracy of LED-AP in a scaled up trial, acceptability of rectal swab testing and its accuracy compared to bulk stool, turnaround time for LED-AP testing and impact of test and treat strategy on short and long term health outcomes. *** Integration into healthcare systems:** Provide actionable data for potential integration of the test and treatment strategy into existing healthcare system *** Economic/Technological:** Lower health care expenses through increased diagnostic accuracy for cryptosporidiosis, and less

*** Exploitation of the business model** for engagement of SMEs		inappropriate use of antimicrobial drugs *** Societal:** Reduction in morbidity and mortality associated with diarrhoeal diseases and cryptosporidiosis * Improved quality of life and childhood development, by limiting prolonged diarrheal illness and growth faltering

#§IMP-ACT-IA§

3 Quality and efficiency of the implementation

3.1 Work plan and resources

To achieve the objectives indicated in section 1, CryptoTT has been structured into 9 work packages (WP, table 3.1a).

Each WP has one lead, and all partners will contribute to the work. The consortium consists of physicians, nurses, laboratory technologists, pharmacists, biomedical engineers and researchers.

3.1.1 List of work packages

Table 3.1 a List of work packages

Work package No.	Work package title	Lead participant no.	Lead participant short name	Person-months	Start month	End month
1	Coordination and management	1	UiB		1	48
2	Scientific project leadership	2	AHRI		1	48
3	Diagnostic cluster randomised trial	2	AHRI		1	36
4	Optimising TAT by rectal swab sampling	2	AHRI		9	36
5	Capacity building	1	UiB		6	48
6	Data management and analysis	2	FM-CISM		3	48
7	Cost-effectiveness analysis	4	ACEPS		1	48
8	Technology development and grassroots innovation	2	Simbona		1	48
9	Dissemination, Exploitation and Communication	2	FM-CISM		1	48

3.1.2 GANTT chart

	Year 1				Year 2				Year 3				Year 4			
Task	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
WP1																
WP2																
WP3																
WP4																
WP5																
WP6																
WP7																
WP8																
WP9																

3.2 Capacity of participants and consortium as a whole

The CryptoTT consortium is a partnership between University of Bergen, Norway; Armauer Hansen Research Institute, Ethiopia; Fundacao Manhica, Mozambique; Addis Center for Ethics and Priority Setting (ACEPS) and the small enterprise Simbona Africa Engineering Solutions, Ethiopia.

The members of the consortium have complementary expertise which will be critical for the success of the project.

The consortium members were carefully selected based on their expertise in LED-AP microscopy, diarrheal diseases and intervention trials, cost-effectiveness and local maintenance and adaptation of microscopes.

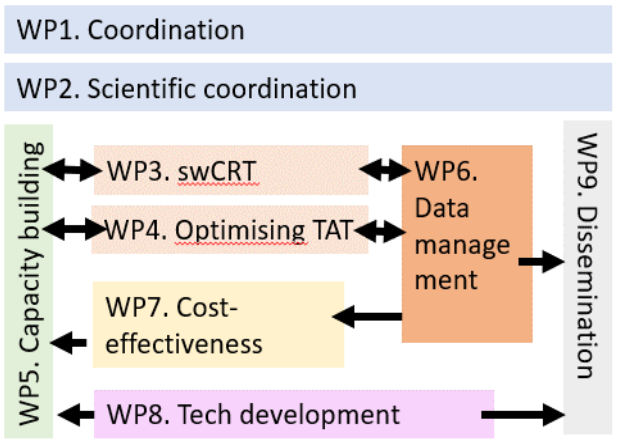


Figure 8. Inter-relationship between work packages with main links indicated

The **consortium** partners have the necessary infrastructure to carry out the project. Surveys have shown enough eligible children with diarrhea to be present in the proposed trial clusters. Many of the cluster sites have already LED microscopes and additional LED micoscopes and AP-stain will be provided to sites that need it. Short term freezer facilities for samples are available at the cluster sites and longer term storage at minus 80C is available at AHRI and FM-CISM. Laboratory facilities for DNA extraction and qPCR are available at FM-CISM and AHRI. Preferably most laboratory work will be done at these sites, but laboratories at UiB can be used for piloting methods and specific investigations by visiting PhD-students. UiB will contribute expertise in statistics and intervention trial.

The University of Bergen (UiB) is a medium sized university with about 18 000 students and 4,000 faculty and staff. It is engaged in the European Union's Framework programmes for research, technological development and innovation and has been designated as a European Research Infrastructure and a Research Training Site in several scientific fields. The university has been part of 177 projects in Horizon 2020 and Horizon Europe. It is currently involved in 109 FP7 projects – being the coordinator of 38 of these. Through a priority area on global challenges, UiB works to promote interdisciplinary and cross-faculty research and education that has an impact on how we meet these challenges globally and locally. In 1988 UiB established a **Centre for International Health** to do research and training contributing to improved health and equity. It offers master and PhD programs in global health, and hosts the **Centre for Intervention Science in Maternal and Child Health (CISMAC)** which is a Centre of Excellence funded by the Norwegian Research Council (https://cismac.uib.no). Since 2013, this centre has pursued research to promote equitable improvements in maternal, newborn and child health low-income populations in Asia and Sub-Saharan Africa. CISMAC encompasses research institutions elsewhere in Norway and in India, Nepal, South Africa, Uganda and Zambia and interacts closely with the WHO.

The CryptoTT project is coordinated by **Professor Kurt Hanevik** at the Department of Clinical Science. He is a medical doctor with a specialization in infectious diseases, and leads a research group focusing on diarrhoea

caused by enterotoxigenic *Escherichia coli* and protozoan parasites. He has experience from LMIC through work with Médecins Sans Frontières and has been involved in several clinical trials in Norway, Uganda, Tanzania and Ethiopia. He coordinated the CryptoPOC study in Jimma, Ethiopia, funded by the Research Council of Norway (RCN) and the Bill and Melinda Gates Foundation. Professor Hanevik has worked on CISMAC projects and been a member of the EU COST action on waterborne parasites 2014 – 2018. He is responsible for parasitology in the Scientific Affairs Subcommittee of the European Society of Clinical microbiology and infectious diseases (ESCMID). Professor **Halvor Sommerfelt** is a medical doctor and epidemiologist with a wide range of experience in randomized controlled trials, including to assess treatment strategies for childhood diarrhoea in LMIC. He has been centrally involved in many studies in LMIC, including the GEMS study, which provided robust data on the importance of *Cryptosporidium* in young children in LMICs. Professor Sommerfelt is the Director of CISMAC.
Clinical microbiologist **Øystein H Johansen** is a Medical Doctor and did his PhD in the CryptoPOC project in Ethiopia. He has lived in Ethiopia for 4 years and knows the country well. He has developed expertise in evaluating diagnostic testing accuracy and will analyse the trial results, especially with regard to the diagnostic value of LED-AP. Junior scientist **Christina Saghaug** is a pharmacist with a PhD in intestinal parasite detection, drug metabolism and resistance. She will take part in Nitazoxanide purchase, storage, evaluation of side effects and in setting up qPCR analyses for *Cryptosporidum*. Statistician **Janne Mannseth** holds a PhD in statistics from 2019, and have since worked on various projects within epidemiology and medical statistics, both with RCT, swRCT and health register data. She will provide statistical assistance in planning and analysis of the clinical trial.

The **Armauer Hansen Research Institute (AHRI)** is the scientific project lead of CryptoTT. AHRI is a biomedical research institute under the Ministry of Health in Ethiopia. It was established in 1970 and is is mandated to perform innovation and basic, epidemiological and translational research on related to clinical research, genetics, biotechnology, biomedical technology, bioinformatics, on all poverty related diseases. In addition, it has a string clinical trial directorate with experience in performing large scale clinical trials. Recently AHRI has also been mandated to perform innovation and research in vaccines, diagnostics, traditional medicine and pharmaceutical development. AHRI has a strong clinical network with academic institutes, healthcare facilities, research institutes and international organizations. It is responsible for ensuring sustainability of clinical and diagnostic intervention to fight against poverty related infectious diseases. Because of its position under the Ministry, it is also well positioned to engage with policy makers, make recommendations and follow up implementation of research outputs with an impact on policy. AHRI will therefore leverage its position and experience in CryptoTT to generate policy briefs and recommendations from results with potential policy implications and engage with policy makers.
AHRI is the Ethiopian representative of the EDCTP Association,and has successfully participated in EDCTP2 projects such as Evaluation of the feasibility, accuracy and effectiveness of a rapid point of care serological triage test for active TB (**SeroSelectTB**) and Important data on COVID-19 profile in Africa (**AIDCO**). It has ongoing projects from Horizon EU including: A holistic approach in patient management and epidemic surveillance through convergence of diagnostic technologies, capacity building and stakeholder engagement (**HoliCare**) and Serological Testing and Treatment for P vivax: From A Cluster-Randomized Trial to A Mobile-Technology Supported Intervention (**PvStatem**). It has also recently been awarded two grants from EDCTP3: Building Scalable Pathogen Genomic Epidemiology For Ethiopia (**EpiGenEthiopia**) and Optimizing severe pneumonia management in children through scaleup of bCPAP technology in low resource settings (**OPT-BCPAP**).
The research team at AHRI includes senior scientist **Rawleigh Howe**, MD, PhD, who has more than 30 years of experience on infectious diseases and diagnostic accuracy trials; Senior scientist **Alemseged Abdissa**, PhD is an expert in clinical microbiology and participated in the CryptoPOC study in Jimma, Ethiopia; Senior researcher **Adamu Bayissa**, MD, expert in large scale clinical trials; Senior researcher **Hawult Taye**, PhD, an epidemiologist with experience in implementation research and experimental studies; Postdoctoral researcher **Fregenet Tesfaye**, PhD with experience in performing diagnostics research and Postdoctoral researcher **Abel Abera**, PhD with a training in Molecular Biology and Microbiology and experience in conducting clinical studies and comparison of point-of-care diagnostic assays.
AHRI has excellent research laboratory facilities that enables working on tropical diseases and is currently leading the Ethiopia Cholera Control and Prevention (ECCP) Project, an ambitious project aimed at vaccinating more than 100,000 residents in areas at risk of cholera and surveillance of cholera and other diarrhoeal diseases. In addition to previously established advanced diagnostic tools.

Fundação Manhiça-Centro de Investigação em Saúde de Manhiça (FM-CISM) is a biomedical research institute with headquarters in Manhiça district (in Southern Mozambique). Established in 1996, it has solid experience on infectious diseases research, and currently plays a pivotal role at the national level in contributing to

the development of the Mozambican Ministry of Health's overall policy. The core research portfolio includes malaria, HIV, tuberculosis, bacterial, viral and neglected tropical diseases, maternal, sexual and reproductive health and population studies (Demography and Social and Behavioural Sciences). CISM has been running a Health and Demographic Surveillance System (HDSS) since its establishment, covering the district population with a detailed registry of demographic events, in addition CISM has a morbidity surveillance system that includes systematic collection of demographic, clinical, outcome and treatments for children <15 years of age at the Manhiça District Hospital (MDH). CISM has Laboratory, Information Technology, Data Management Centre and analysis, social and behavioural research, and regulatory unit services. CISM has participated in and coordinated several EDCTP funded projects, including the Trials of Excellence in Southern Africa (TESA) Network and the Stopping the Transmission Of intestinal Parasites (STOP) Consortium. The team of CISM includes **Dr. Delfino Vubil,** PhD, who has a background in Molecular Biology and Microbiology. He has been working for CISM for over 15 years in diarrhoeal diseases and other invasive bacterial infections, having contributed to the epidemiological description and characterization of different pathogens. Senior researcher **Inácio Mandomando**, PhD, is an expert in diarrhoeal diseases, and the main coordinator of the Bacterial, Viral and Neglected Tropical Diseases (DBVTN) research area, who has more than 20 years of experience. Dr Mandomando has been involved in several studies, from surveillance, intervention and impact evaluation. He was the site principal Investigator for the Global Enterics Multicenter Study (GEMS) which aimed to quantify the burden and microbiological etiology of diarrhoeal diseases in children under 5 years conducted from 2007-2012. Clinical coordinator **Áuria de Jesus**, MD, is the medical coordinator in the DBVTN group, coordinating clinical trials on diarrhoeal diseases and currently involved in the Trivalent *Salmonella* Conjugated Vaccine trial for children under one year. **Alberto Chaúque**, MSc is a statistician from CISM's Statistical Analysis unit and has over 10 years of experience in data management and analysis in studies that evaluated the impact of the introduction or change of the pneumococcal vaccines formulation..

Addis Center for Ethics and Priority Setting (ACEPS) is a center under the College of Health Sciences at Addis Ababa University (AAU) and its main objectives are: 1) Generate economic evaluation evidence to enhance evidence informed efficient policy decision making in Ethiopia; 2) Provide country support for transparent, ethically acceptable, fair, and efficient priority setting for improved population health and wellbeing in national health systems; 3) Conduct short and advanced courses on economic evaluation, health technology assessment and essential health services package design (EHSP); 4) Support the medical ethics teaching under the College of Health Sciences, AAU. ACEPS is also engaged in capacity building through supporting master's and PhD level students.
Solomon Tessema Memirie (MD, PhD) is a pediatrician and health economist and is currently the director of Addis Center for Ethics and Priority Setting (ACEPS). His main research focus is health economics and priority-setting and examining the cost and cost-effectiveness of health interventions in Ethiopia. He has assessed household out-of-pocket expenditures and associated impoverishment for vaccine preventable diseases, analysed cost-effectiveness of maternal and child health interventions, and analysed cost-effectiveness of introducing the birth doses of hepatitis B- vaccine into the expanded immunization program in Ethiopia. The research outputs have been used to populate essential health services packages in Ethiopia. He is a member of the National Immunization Technical Advisory Group of Ethiopia, the Research Advisory Council of the Ministry of Health of Ethiopia and technical working group member of the implementation of case-based provider payment mechanism being led by the Ethiopian Health Insurance Services. He had a key role in the revision of the Ethiopian essential health services package.
He has supervision experience both form UiB and from Addis Ababa University having completed supervision of 2 master's students and 4 PhD students, and currently supervising 4 PhD students.

Simbona Africa Engineering Solutions has extensive experience over the last 8 years in medical device design, installation, production, maintenance, repair, and health professional training. With such experience and expertise, Simbona can play a critical role in the sustainable use of LED-APs for the diagnosis of TB and cryptosporidiosis in Ethiopia. Simbona's participation in CryptoTT will be led by Mr. **Habtamu Abafoge** who has extensive experience in the designing and development of medical equipment. He has been selected as 2020 Africa Youth Award Winner, under Technology Category and in 2023 has won the African Youth Award for SDG by ECA/Economic Commission of Africa. In CryptoTT, Simbona will contribute preventive and corrective maintenance training on LED microscopes, training of laboratory technician and biomedical engineers and power supply adaptor design and deployment for sustainable use
Simbona has been previously completed the design and production of solar-powered neonatal LED phototherapy units, LED-based adult and neonate vein finders, affordable infant radiant warmers for low-resource settings that work with alternative power sources, and the and the manufacturing of ultraviolet technologies for hospital-acquired infection prevention in Ethiopian health facilities.

3.3 Supplementary tables and lists

3.3.1 Work package descriptions (list)

Table 3.1b Work Package description
To achieve the objectives of CryptoTT the work plan has been divided into 9 work packages.

Work package number	**01**	**WP lead:** UiB	Participating: AHRI, FM, ACEPS	Duration: 1 – 48
Work package title	**Coordination and project management**			

Objective
Coordination and management of the project, including administrative, financial, monitoring, legal and contractual tasks.

The project management structure
University of Bergen with project coordinator Kurt Hanevik will spearhead the overall coordination and financial management. This includes signing agreements with Horizon Europe, disbursement of funds, contractual reporting, and audits. The project coordinator, the project manager (to be appointed), and the financial and legal staff at UiB will collaborate closely with the scientific coordinator to ensure the project's administrative, legal and financial management. This includes administering the Grant Agreement, establishing the Consortium Agreement, and ensuring financial management and project reporting.
A steering committee (SC) will be established, comprising the coordinator, the scientific project leader and a representative from each partner institution. The SC will monitor interactions between WP leads and institutional leads, track the project's milestones and deliverables, and hold bi-weekly digital meetings to discuss the project's progress, identify problems and outstanding issues, suggest solutions, and make decisions. All SC members will ratify the minutes from SC meetings.

Advisory board
An advisory board, consisting of three members, will be established to provide advice on scientific and ethical issues within the project. The advisory board members (all confirmed) are:

- Sitara Rao Ajjampur, Professor of Microbiology at The Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India
- Kåre Mølbak, Executive vice-president and director of the Division of Infectious Diseases Preparedness at Statens Serum Institut, Copenhagen, Denmark
- Robert Choy is Director for Research & Development at PATH, a non-profit funding agency working to accelerate progress toward universal health coverage.

Tasks
T1.1 Efficient management and coordination of the CryptoTT project, timely achievement of all deliverables and milestones in accordance with contractual requirements and objectives
T1.2 Financial management, including resource allocation and distribution, and expenditure monitoring
T1.3 Ensure efficient communication between consortium members and the EU and act as the key contact point for the GH EDCTP3.
T1.4 Internal communication and project meetings: provide tools and support for internal communication, set up regular meetings on a digital platform, and organize project kick-off meeting and final meeting.
T1.5 Develop a risk management plan and monitor, analyse, prioritize and handle risks, including consideration of external events of political, ethical, scientific, technological or socio-economic nature.
T1.6 Prepare project reports according to contractual requirements

Deliverables
D1.1. Project risk management plan
D1.2 Final project report

Milestones

M1.1 Consortium agreement signed by all partners
M1.2 Kick-off meeting
M1.3 Final meeting

Work package number	**02**	**WP lead:** AHRI	Participating: AHRI, FM, ACEPS	Duration: 1 – 48
Work package title	**Scientific project leadership**			

Objectives

- Organize and lead project progress meetings.
- Serve as the primary contact point for the GH EDCTP3 on all matters related to scientific action governance.
- Spearhead the development of scientific actions, ensuring the achievement of deliverables and maintaining scientific quality.
- Facilitate initial ethical clearance approval for the protocol in collaboration with project partners and work package leads and ensure adherence to ethical standards during implementation.
- Develop guidelines for the dissemination of project outputs, including authorship in manuscripts, conference and workshop participation.

Description of work

This WP encompasses the scientific leadership and management of the project. The objectives include leading all scientific action governance issues of the project, spearhead the development of scientific actions, ensuring the achievement of deliverables, maintaining scientific quality; facilitating initial ethical clearance approval and preparing guidelines for dissemination of project outputs.

Tasks

T2.1 Leading project meetings: The leader will organise and lead project meetings, both during the proposal development and throughout the project period. Biweekly meetings will be held virtually during the first six months of the project, transitioning to monthly meetings from month 7 to month 48 will be held virtually. The WP leader will prepare an agenda for scientific action points to be discussed at the meetings and share them in advance.

T2.2 Co-lead development of consortium and legal agreements: collaborate with the coordinator and other beneficiaries on drafting and negotiating the consortium agreement and other legal agreements among the beneficiaries

T2.3 Monitoring scientific actions: Support and collaborate with the coordinator on monitoring activities and the adoption of appropriate internal measures to ensure that beneficiaries fulfill their obligations regarding budget, timeline, deliverables, and scientific quality.

T2.4 Submission and approval of the study protocol for ethical review committees: a detailed study protocol, be based on the initial proposal, will be developed from month 1-6 of the project. At month 6, the protocol will be submitted to all the ethical review committees and institutional review boards. The WP leader will lead the development of the protocol and submission among all partners. Approval is expected to be obtained from all consortium members at month 12.

T2.5 Development of guidelines for dissemination of project outputs: Guidelines for the dissemination of project outputs, including authorship in manuscripts, conference participation, and workshop involvement, will be developed by month 3. These guidelines will be reviewed by all consortium members and approved by the steering committee.

Deliverables:

D2.1 Monitoring reports
D2.2 Developed study protocol for ethics approval
D2.3 Developed guidelines for dissemination

Milestones

M2.1 First consortium meeting
M2.2 Ethical approval obtained

M2.3 Completion of guidelines for all scientific actions

Work package number	**03**	**WP lead:** AHRI	Participating: FM, UiB, ACEPS	Duration: 1 – 30
Work package title	**Diagnostic stepped-wedge cluster randomised trial**			

Objectives

- Ensure standard-of-care for diarrhoea is implemented according to national standard diarrhoeal treatment guidelines across all the study facilities.
- Develop standardized procedures and training material for the implementation of cryptosporidiosis testing-and-treatment in all study facilities
- Oversee the implementation of testing-and-treatment for cryptosporidiosis according to the stepped-wedge cluster randomized trial design

Description of work

Tasks

T3.1 Conduct an initial stakeholder analysis and pre-implementation site visits
T3.2 Develop a study manual of operations, including SOPs, CRFs, adverse effects report forms, and visual aids (e.g. algorithms and flowcharts) outlining key steps during study enrolment, for the clinical management of children with diarrhoea, and the test-and-treat intervention
T3.3 Establish trial supervision systems (clinical supervision, laboratory supervision)
T3.4 Develop laboratory SOPs for handling and storage of stool samples, LED-AP microscopy, quality control systems for staining and microscopy, long-term storage and shipment of stool samples, nucleic acid extraction, and qPCR
T3.5 Manage procurement and supply chain, including consumables for collecting stool samples, LED-microscopes with backup power supply, laboratory reagents (e.g.AP stains), consumables, and Nitazoxanide.
T3.6 Conduct a trial run-in period to refine all of the above manuals and SOPs before full implementation of the trial
T3.7 Randomize sites and conduct trial recruitment, sampling, intervention and follow up as planned with continuous supervision to ensure a low attrition rate

Deliverables

D3.1 Stakeholder analysis and forum report
D3.2 Clinical study initiation package (before enrolment of the first study participant) including:

a. Registration number of the clinical study in the European Clinical Trials Information System
b. Final version of study protocol as approved by the regulators and ethics committees
c. Regulatory and ethics approvals required for the enrolment of the first study participant

D3.3 Midterm recruitment report when 50% of the study population is recruited.
D3.4 Trial completion report

Milestones:

M3.1 preparation of all materials, manuals and forms
M3.2 Completion of the run-in period
M3.3 Completion of the trial
M3.4 Completion of Lab analyses
M3.5 Deposition of summary results in the Clinical Trials Information System

Work package number	**04**	**WP lead:** AHRI	Participating: FM, UiB	Duration: 1 – 30
Work package title	**Improving total test turnaround time with rectal swabs for cryptosporidiosis testing**			

Objectives

- Accelerate diagnosis: minimize the duration from them moment the patient presents for healthcare with diarrhoea to the availability of the test result and the subsequent treatment decision (total test turnaround times)
- Alternative sampling method: Establish an alternative sample collection method for children who cannot provide a conventional stool sample
- Standardized procedures: formulate standardized procedures and training material for rectal swab collection and its integration into the cryptosporidiosis testing-and-treatment workflow
- Qualitative evaluation: conduct a qualitative evaluation of rectal swab sample collection involving patients, caregivers, healthcare workers, and clinicians

Description of work

Tasks

T4.1 Develop a standardised time tracking tool to monitor all samples
T4.2 Create visual aids to assist caregivers and healthcare staff in rectal swab collection
T4.3 Formulate subsections within the laboratory SOPs for handling rectal swab specimen staining, archiving and blinding
T4.4 Design questionnaires for a rectal swab user satisfaction survey
T4.5 Supervise all study personnel during sampling and LED-AP microscopy analysis

Deliverables

D4.1 Rectal swab substudy report
D4.2 User satisfaction survey report

Milestones

M4.1 Substudy sections in study manuals, questionnaires and SOPs completed
M4.2 Finalization of SOPs based on feedback from the run-in-period
M4.3 Completion of LED-AP blinded slide re-examination
M4.4 Completion of qPCR reference testing on frozen samples

Work package number	**05**	**WP lead:** UiB	Participating: FM, ACEPS, AHRI	Duration: 6 – 36
Work package title	**Capacity building**			

Objectives

- Train healthcare workers (laboratory staff, nurses and physicians) in the use of LED-AP for the diagnosing and treating cryptosporidiosis
- Build research capacity on cost-effectiveness and clinical intervention trials at participating institutions

Description of work
This work package aims to provide short- and long-term training to enhance the competence of healthcare workers at participating health facilities in managing diarrhoea and diagnosing cryptosporidiosis.

T5.1 We will organise practical trainings to health care staff involved in the study. These trainings will be planned by UiB in collaboration with AHRI and FM, and will be carried out at central health facilities in the project. The trainings will adhere to national guidelines of Ethiopia or Mozambique and trial site circumstances. Pediatricians at CryptoTT partner institutions will conduct the trainings.

- lab technicians: - A two-day course plus three days of supervised hands-on practice in slide preparation, staining and LED-microscopy will be provided.
- Nurses: A two-day course will be provided on handling children with diarrhea, including sampling, supportive care, LED-AP diagnostic method and advising caretakers of children with diarrhea.
- Medical doctors: A one-day training will be provided in general management of diarrheal diseases, clinical signs and symptoms, sampling, supportive treatment, LED-AP diagnostic method, interpretation of laboratory results and Nitazoxanide treatment in *Cryptosporidium* positive children.

T5.2 UiB and ACEPS will organize a one-week course in health economics in Addis Ababa. The course will focus on principles and methods in cost effectiveness analysis, health technology assessment, costing methodologies and valuation of benefits in health economic evaluation. The target group includes researchers in project institutions, junior researchers at other academic institutions and interested officials at relevant governmental departments.

T5.3 UiB and FM will arrange a one week course in clinical intervention trial design and implementation in Maputo. The course will build on a course in Intervention Science in maternal and child health provided by UiB but take a broader approach. The target group includes researchers in partner institutions and as junior researchers at other academic institutions in Ethiopia sand Mozambique.

T5.4 ACEPS in collaboration with the Health economics unit of the School of Public Health, Addis Ababa University (AAU) will identify a candidate doctoral student. The candidate will be involved in WP 7 (Cost-effectiveness analysis) from initial conceptualization and design, through data collection, into analysis and dissemination. The candidate will be jointly supervised by Dr. Memirie (ACEPS) and senior health economists from AAU. Two PhD students will also be selected from both Ethiopia and Mozambique to be trained in research on diarrhoeal diseases epidemiology and point-of-care diagnostics. FM and AHRI are not academic institutions, and cannot provide master and PhD degrees. However, they regularly provide a good training environment for students from academic institutions in their countries. The master and PhD students will be recruited and integrated in the FM and AHRI project teams in work package 3 and 4 and take part in data collection and data analysis for their degrees. They will receive supervision from senior researchers at CryptoTT partner institutions, as well as their home academic institutions. They will be encouraged to participate in the CryptoTT workshops, relevant international meetings, and a research stay at UiB for 3-6 months to learn laboratory procedures including qPCR and/or receive training in statistical analyses and writing.

Deliverables
D5.1 Trainings for health facility staff before and during the clinical trial
D5.2 Training materials for workshops

Milestones
M5.1 Completion of cost-effectiveness workshop
M5.2 Completion of clinical intervention trials workshop
M5.3. Completion of five PhD degrees

Work package number	**06**	**WP lead:** FM	Participating: ACEPS, AHRI, UiB	Duration: month 1 – 48
Work package title	**Data management and analysis**			
Objectives				

- harmonize data collection across all sites.
- develop and manage comprehensive data management and analysis plans.
- facilitate robust and accurate data analysis.
- To facilitate the preparation and deposit of data in public repositories

Description of work

This work package aims to establish a comprehensive roadmap on data collection, analysis, cleaning, management procedures, transformation and results presentation. Coordinated by the FM-CISM data management and analysis team, we will develop the study database in collaboration with the team leading the design of the diagnostic cluster clinical trial (WP3) protocol. The protocol and forms for the study will be shared with the partners for approval. This includes defining the hosting location for the electronic database and designing the data sharing and management plan. The unified database will streamline integration and facilitate comparison of results across sites.

Tasks:

T6.1 Assess the trial sites capabilities for data collection and determine the information technology requirements (eg, tablets or PCs for data entry, routers and other devices for internet access).
T6.2 Design a unified database and a data sharing and management plan, detailing all data cleaning and management procedures, and defining the tasks and responsibilities of each study team member.
T6.3 Formulate a data analysis plan in line with the diagnostic cluster clinical trial's requirements.
T6.4 Establish regular data management meetings to ensure adherence to the data management plan across all sites and ensure data harmonization.
T6.5 Demonstrate the database of all sites before study commencement.
T6.6 Conduct regular data cleaning to resolve missing data and discrepancies.
T6.7 Perform the final data analysis and prepare the results for the study report and the publications.
T6.8 Prepare data for deposit in a public repository with persistent unique identifiers (e.g. Infectious Disease Data Observatory - IDDO)

Deliverables:

D6.1 Report on sites' data collection capabilities, existing data handling and storage infrastructure, and identified needs.
D6.2 Comprehensive data sharing and data management plan.
D6.3 Detailed data analysis plan.
D6.4 Guidelines for harmonized database structure, features,usage, and report on training sessions.
D6.5 Harmonized trial database.
D6.6 Dataset for public repository

Milestones:

M6.1 Entry of first participant data into the database
M6.2 Entry and cleaning of data for 50% of required participants
M6.3 Entry of last participant into the database
M6.4 Completion of final database cleaning and database lock

Work package number	**07**	**WP lead:** ACEPS	Participating: AHRI, FM, UiB	Duration: 1 – 48
Work package title	**Cost-effectiveness analysis**			

Objectives

- To assess the cost and cost-effectiveness of the combined test and treat strategy using LED-AP POC test followed by treatment against cryptosporidiosis
- To assess the incremental cost-effectiveness of rectal swab as compared to bulk stool samples

Description of work

We will conduct a cost-effectiveness analysis (CEA) from the perspective of both the health care provider (only include costs incurred by the provider) and societal perspective (costs to the health care provider plus patient level costs) to evaluate the cost-effectiveness the combined test and treat strategy using LED-AP POC test as compared

to the usual care for diarrhoea patients. Furthermore, we will evaluate the additional cost and effectiveness of rectal swab as compared to bulk stool testing, where the incremental cost of rectal swab, per additional cryptosporidium cases identified, will be computed.

Tasks
T7.1 Develop and integrate a standardized cost data collection tool into clinical trial CRF and pilot test it.
T7.2 Train study staff in of collecting cost data
T7.3 Conduct cost data collection
T7.4 Supervision and data quality assurance

Deliverables
D7.1 Final report on cost and cost-effectiveness analysis

Milestones
M7.1 Cost data collection tools developed and pilot tested
M7.2 Cost data collection completed
M7.3 Cost and cost-effectiveness analysis completed.

Work package number	**08**	**WP lead: Simbona**	Participating: AHRI, UiB	Duration: 1-48
Work package title	**Technology development and grassroot innovation**			

Objectives
- To facilitate technology transfer in installation and maintenance of LED microspcopes
- To enhance sustainability in the use of LED-AP for the diagnosis of cryptosporidiosis
- To promote local innovation of diagnostic tools
- To increase involvement of local SMEs in introducing diagnostic solutions

Description of work
In this WP, the CryptoTT consortium will enhance technology transfer and involvement of local small and medium-sized enterprises in innovation and sustainability of the LED-AP. The main activities within this WP include corrective ad preventive maintenance, training to laboratory technicians and biomedical engineers and the design and production of power supply units for LED microscopes.

Tasks
T8.1 Training: To facilitate technology transfer, local SMEs involved in the project will train laboratory technicians and biomedical engineers in the installation and maintenance of LED-AP.
T8.2 Installation and maintenance of LED microscopes: we will therefore liaise with the local SME that will be involved in installation and maintenance.
T8.3 Production of power adapter prototype: Simbona Africa Engineering Solutions will lead the development of a prototype power supply adapter for LED microscopes aiming to locally produce adapters.
T8.4 Workshops: We will also hold two workshops to engage other local innovators and SMEs to promote innovation on locally made point-of-care diagnostic tools.

Deliverables
D8.1 Training course material
D8.2 Maintenance report
D8.3 LED Microscope charging adapter prototype.

Milestones
M8.1 Short term training completed.
M8.2 First prototype developed.
M8.3 Innovation promotion workshops conducted.

Work package number	09	WP lead: FM	Participating: UiB, AHRI, ACEPS, Simbona	Duration: month 1-48
Work package title	**Dissemination, Exploitation and Communication**			

Objectives

- To develop a communication plan, including detailed plans for communication to different target groups
- To implement an appropriate dissemination of the research outcomes to the scientific community, public health officials and policy makers.

Description of work

In this WP, the CryptoTT consortium will ensure effective communication of the project messages and activities at national, regional and international level. It will engage with stakeholders and decision makers at the local, national and international level to make sure that the results are translated into evidence-based policies

Tasks

T9.1 Create a communication and dissemination plan for the project including a scientific publication plan
T9.2 Participation in national, regional, and international conferences to share research outcomes
T9.3 Prepare templates and materials for communication and dissemination to different target groups
T9.4 Provide information and project updates on the website and appropriate social media platforms
T9.5 Have regular contact with the Ministries of Health and engage with international bodies such as WHO and UNICEF
T9.5 Use of the EDCTP Forum for dissemination of the results of the project.

Deliverables

D9.1 Communication, dissemination and exploitation plan
D9.2 Communication, dissemination and exploitation report summarizing activities carried out throughout the project period
D9.3 Dissemination materials

Milestones

M9.1 Completed dissemination, exploitation and communication plan
M9.2 First draft of the dissemination materials
M9.3 Functional Website and logo of the project

3.3.2 Deliverables (list)

Table 3.1c: List of deliverables

Number	Deliverable name	Short description	Work package number	Short name of lead participant	Type	Dissemination level	Delivery date (in months)
1.1	Risk management plan	Monitor, analyse, prioritize and handle risks	01	UiB	R	PU	M2
1.2	Final report	Final report of CryptoTT	01	UiB	R	PU	M48
2.2	Monitoring reports	Minutes of meetings	02	AHRI	R	PU	M48
2.3	Study protocol	Protocol for ethics approval of the clinical studies in project	02	AHRI/FMI	R	PU	M6
2.4	Guidelines for	Guidelines for dissemination of	02	AHRI	R	PU	M3

	dissemination	project outputs					
3.1	Stakeholder analysis and forum report	Stakeholder analysis and report from stakeholder forum	03	AHRI/FM	R	PU	M6
3.2	Clinical study initiation package	Registration number, study protocol and regulatory and ethics approvals	03	AHRI/FM	R	PU	M9
3.3.	Midterm recruitment report	Report when 50% of study population is recruited	03	AHRI/FM	R	PU	M19
3.4	Trial completion report	Trial completion report	03	AHRI/FM	DATA	PU	M30
4.1	Rectal swab substudy report	Report on the rectal swab substudy	04	AHRI	R	PU	M12
4.2	User accpetability survey report	Report from user acceptability survey	04	AHRI	R	PU	???
5.1	Training for health facility staff	Practical training for facility staff	05	UiB	COURSE	PU	M18
5.2	Training materials	Training materials for workshops	05	UiB	R	PU	M17
6.1	Report on sites' data collection capabilities	Report on data collection capabilities, data handling and storage infrastructure and needs	06	FM-CISM	R	PU	M9
6.2	Data sharing and data management plan	Comprehensive data sharing and data management plan	06	FM-CISM	R	SEN or C-UE/ EU-C	M6
6.3	Data analysis plan	Detailed data analysis plan	06	FM-CISM	R	SEN	M12
6.4	Guidelines for harmonised database structure	Guidelines for harmonized database structure, features, usage and report from training session	06	FM-CISM	R	SEN	M8
6.5	Harmonised trial database	Harmonized trial database	06	FM-CISM	R	PU	M12
6.6	Dataset for public repository	Prepare data for deposit in a public repository	06	FM-CISM	R	PU	M48
7.1	Cost and cost-effectiveness	Cost and cost-effectiveness analysis report	07	ACEPS	R	PU	M45

	analysis report						
8.1	Training course material	Training course material	08	Simbona	R	PU	M6
8.2	Maintenance report	Report form installation and maintenance	08	Simbona	R	PU	M12
8.3	Charging adapter prototype	LED Microscope charging adapter prototype	08	Simbona	PRO TOT YPE	PU	M32
9.1	Communication , dissemination and exploitation plan	Communication, dissemination and exploitation plan	09	FM-CISM	R	PU	M5
9.2	Communication , dissemination and exploitation report	Communication, dissemination and exploitation report	09	FM	R	PU	M48
9.3	Dissemination materials	Dissemination materials	09	FM	R	PU	M33

3.3.3 Milestones (list)

Table 3.1d: List of milestones

Milestone number	**Milestone name**	**Related work package(s)**	**Due date (in month)**	**Means of verification**
M1.1	Consortium agreement signed	01, 02	3	signed agreement
M1.2	Kick-off meeting	01, 02	3	Kick off meeting report
M1.3	Final meeting	01, 02	48	Final meeting report
M2.1	Kick-off meeting	01, 02	3	Kick-off meeting report
M2.2	Ethical approval	02	6	Approval documents
M2.3	Guidelines for scientific actions	02	3	Guidelines document
M3.1	All materials, manuals and forms prepared	03	10	Manuals made tor run-in
M3.2	Run-in period completed	03	12	Report of adaptations made
M3.3	Trial completed	03	30	Trial completion report
M3.4	Lab analyses completed	03	40	Dataset finalised
M3.5	Summary results deposited	03	47	Confirmation from depository
M4.1	Acceptance study completed	04	30	Report on findings

M4.2	Finalized SOPs	03	12	SOP documents available
M4.3	LED-AP blinded slide re-examination completed	04	30	Last slide examines
M4.5	qPCR reference testing completed on frozen samples	04	40	Last sample analysed
M5.1	Cost-effectiveness workshop	05	18	Workshop report
M5.2	Clinical intervention trials workshop	05	30	Workshop report
M5.3	Five PhD degrees completed	05	48	PhD theses published
M6.1	Entry of first participant data into the database	06	12	Entry dates recorded in the database and updates at clinical trial registries' webpages
M6.2	Entry and cleaning of data for 50% of required participants	06	20	Entry dates recorded in the database and updates at clinical trial registries' webpages.
M6.3	Entry of last participant into the database	06	31	Entry dates recorded in the database and updates at clinical trial registries' webpages.
M6.4	Completion of final database cleaning and database lock	06	35	Verifiable by extract from the database
M6.5	Completion of final data analysis	06	48	Verifiable by the delivery of final study/trial report.
M7.1	Cost data collection tools developed and pilot tested	07	10	Collection tools available
M7.2	Cost data collection completed	07	30	Complete cost data
M7.3	Cost and cost effectiveness analysis completed	07	48	Analysis results available
M8.1	Short term training completed	08	8	Training report
M8.2	First prototype developed	08	25	Prototype available
M8.3	Innovation promotion workshops conducted	08	32	Workshop report
M9.1	First draft of dissemination materials	09	6	First drafts of dissemination materials available
M9.2	Project website up and running	09	3	CRYPTO TT website up and running

3.3.4 Critical risks for implementation (table)

Table 3.1e Critical risks for implementation

Description of risk (indicate level of (i)	Work	Proposed risk-mitigation measures

likelihood, and (ii) severity: Low/Medium/High)	package(s) involved	
Decline in staff knowledge and motivation over time	WP3	Provide refresher training and clear standard SOPs and guidelines for LED-AP test and treat strategy
Poor recruitment	WP3	Provide regular monitoring and supportive supervision and identifying areas for improvement. and increase supervision of staff. Increase community awareness.
Low recruitment rate	WP3, WP4	The trial cannot easily be extended in time due to the swCRT design. Early intervention to establish community engagement, extended hours of recruitment and widen recruitment area in affected clusters.
Delays in ethics approval	WP1	Carefully include and consider all possible ethical issues. Consult with ethics committee before submission to clarify potential concerns.
Equipment failure	WP3	Keep a backup LED-microscope in each region for rapid replacement during intervention phase. Use voltage stabilisers.
Inter-observer variability and risk of contamination or degradation could affect the reliability/validity of data collection	WP3, WP4, WP7	Optimize LED-AP test and treat strategy through providing adequate training
Power outage	WP3	Use battery packs or hospital generators
Effect of cross-over information contamination	WP3 WP4	Choosing appropriate clusters that represent the target population and ensuring consistent adherence to allocated interventions across clusters and time points
Risk of misclassification, measurement error and bias estimates o Skill/experience of healthcare worker o Existing healthcare inequalities o Effect of other interventions	WP3, WP4, WP7	Implement quality control measures to ensure . Conduct pre-implementation site visits and trial run-in-period to refine implementation protocol/procedures and perform interim data analysis and make careful adjustment. Consistent supervision and training for adherence to treatment protocols
Disrupted supply of intervention drug	WP3	Continuous monitoring of remaining drug supply. Rapid replacement from central backup storage in each trial country
Delayed and shortage of supplies for sampling, testing and supportive therapies	WP3, WP4	Establish efficient logistics and supply chains to ensure consistent availability of LED-AP test kits, supportive care supplies
Political instability	WP3, WP4, WP7	Targeting safest areas. Temporarily exclude clusters.

3.3.5 Summary of staff effort and purchase costs (tables)

Table 3.1f: Summary of staff effort

Participant Short Name	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	WP9	Total
UiB	20		28	10	10				4	**72**
AHRI	11	81	695	174	58	69	-	35	35	**1158**

FM-CISM	18	0	1035	0	0	41	0	0	12	**1106**
ACEPS							60			**60**
Simbona								14		**14**

Table 3.1g: 'Subcontracting costs' items : None

Table 3.1h: 'Purchase costs' items (travel and subsistence, equipment and other goods, works and services)

Participant Number/Short Name		
01/ / UiB	**Cost (€)**	**Justification**
Travel and subsistence	92500	Management meetings, annual meetings, Travel subsidies for workshop participants, supervision visits, Scientific advisory board travel, Conference presentations,
Equipment	0	
Other goods, works and services	417500	Bulk purchase of DNA extraction/qPCR reagents, rectal swabs, nitazoxanide, shipping, backup LED-microscopes, laptop
Remaining purchase costs (<15% of pers. Costs)	0	
Total	510000	

Participant Number/Short Name		
02 / AHRI	**Cost (€)**	**Justification**
Travel and subsistence	166000	Trial site visits & supervision, conferences, management meetings
Equipment	0	
Other goods, works and services	150000	Cold boxes, plastics, Auramine phenol, Ethics fees, Freezer space rent, tablets for RedCap, website, voltage stabilizer,
Remaining purchase costs (<15% of pers. Costs)	0	
Total	316000	

Participant Number/Short Name		
03/FM-CISM	**Cost (€)**	**Justification**
Travel and subsistence	53900	Trial site visits & supervision, conferences, management meetings
Equipment	0	
Other goods, works and	473361	Cold boxes, plastics, Auramine phenol, Ethics fees, Freezer space

services		rent, tablets for RedCap, website, voltage stabilizer
Remaining purchase costs (<15% of pers. Costs)	0	
Total	527261	

Participant Number/Short Name		
04/ ACEPS	**Cost (€)**	**Justification**
Travel and subsistence	29000	Trial site visits & supervision, conferences, management meetings
Equipment		
Other goods, works and services	3000	Software lisence, visa,
Remaining purchase costs (<15% of pers. Costs)		
Total	32000	

Participant Number/Short Name		
05/ Simbona	**Cost (€)**	**Justification**
Travel and subsistence	3650	Trial site visits & supervision, management meetings
Equipment		
Other goods, works and services	18450	Electronic components,
Remaining purchase costs (<15% of pers. Costs)		
Total	22100	

4 References

1. Kotloff, K.L., et al., *Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study.* Lancet, 2013. **382**(9888): p. 209-22.
2. Collaborators, G.B.D.D.D., *Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016.* Lancet Infect Dis, 2018. **18**(11): p. 1211-1228.
3. Animut, A., et al., *Febrile illnesses of different etiology among outpatients in four health centers in Northwestern Ethiopia.* Jpn J Infect Dis, 2009. **62**(2): p. 107-10.
4. Tessema, G.A., et al., *National and subnational burden of under-5, infant, and neonatal mortality in Ethiopia, 1990-2019: Findings from the Global Burden of Disease Study 2019.* PLOS Glob Public Health, 2023. **3**(6): p. e0001471.
5. Khalil, I.A., et al., *Morbidity, mortality, and long-term consequences associated with diarrhoea from Cryptosporidium infection in children younger than 5 years: a meta-analyses study.* Lancet Glob Health, 2018. **6**(7): p. e758-e768.
6. Johansen, O.H., et al., *Oocyst Shedding Dynamics in Children with Cryptosporidiosis: a Prospective Clinical Case Series in Ethiopia.* Microbiol Spectr, 2022. **10**(4): p. e0274121.
7. Sow, S.O., et al., *The Burden of Cryptosporidium Diarrheal Disease among Children < 24 Months of Age in Moderate/High Mortality Regions of Sub-Saharan Africa and South Asia, Utilizing Data from the Global Enteric Multicenter Study (GEMS).* PLoS Negl Trop Dis, 2016. **10**(5): p. e0004729.
8. Kirkpatrick, B.D., et al., *Childhood cryptosporidiosis is associated with a persistent systemic inflammatory response.* Clin Infect Dis, 2006. **43**(5): p. 604-8.

9. Steiner, K.L., et al., *Species of Cryptosporidia Causing Subclinical Infection Associated With Growth Faltering in Rural and Urban Bangladesh: A Birth Cohort Study.* Clin Infect Dis, 2018. **67**(9): p. 1347-1355.
10. Kabir, F., et al., *Impact of enteropathogens on faltering growth in a resource-limited setting.* Front Nutr, 2022. **9**: p. 1081833.
11. Molbak, K., et al., *Cryptosporidiosis in infancy and childhood mortality in Guinea Bissau, west Africa.* BMJ, 1993. **307**(6901): p. 417-20.
12. Nasrin, D., et al., *Pathogens Associated With Linear Growth Faltering in Children With Diarrhea and Impact of Antibiotic Treatment: The Global Enteric Multicenter Study.* J Infect Dis, 2021. **224**(12 Suppl 2): p. S848-S855.
13. Guerrant, D.I., et al., *Association of early childhood diarrhea and cryptosporidiosis with impaired physical fitness and cognitive function four-seven years later in a poor urban community in northeast Brazil.* Am J Trop Med Hyg, 1999. **61**(5): p. 707-13.
14. Johansen, O.H., et al., *Performance and operational feasibility of two diagnostic tests for cryptosporidiosis in children (CRYPTO-POC): a clinical, prospective, diagnostic accuracy study.* Lancet Infect Dis, 2021. **21**(5): p. 722-730.
15. Nhambirre, O.L., et al., *Intestinal Parasites in Children up to 14 Years Old Hospitalized with Diarrhea in Mozambique, 2014-2019.* Pathogens, 2022. **11**(3).
16. Johansen, O.H., et al., *A comparison of risk factors for cryptosporidiosis and non-cryptosporidiosis diarrhoea: A case-case-control study in Ethiopian children.* PLoS Negl Trop Dis, 2022. **16**(6): p. e0010508.
17. Zangenberg, M., et al., *Prolonged and persistent diarrhoea is not restricted to children with acute malnutrition: an observational study in Ethiopia.* Trop Med Int Health, 2019. **24**(9): p. 1088-1097.
18. Ashigbie, P.G., et al., *Use-case scenarios for an anti-Cryptosporidium therapeutic.* PLoS Negl Trop Dis, 2021. **15**(3): p. e0009057.
19. Schneider, A., et al., *Current pharmacotherapy of cryptosporidiosis: an update of the state-of-the-art.* Expert Opin Pharmacother, 2021. **22**(17): p. 2337-2342.
20. Amadi, B., et al., *Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial.* Lancet, 2002. **360**(9343): p. 1375-80.
21. Love, M.S. and R.K.M. Choy, *Emerging treatment options for cryptosporidiosis.* Curr Opin Infect Dis, 2021. **34**(5): p. 455-462.
22. Checkley, W., et al., *A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium.* Lancet Infect Dis, 2015. **15**(1): p. 85-94.
23. Chalmers, R.M., et al., *Comparison of diagnostic sensitivity and specificity of seven Cryptosporidium assays used in the UK.* J Med Microbiol, 2011. **60**(Pt 11): p. 1598-1604.
24. Khurana, S., et al., *Evaluation of Ziehl-Neelsen staining, auramine phenol staining, antigen detection enzyme linked immunosorbent assay and polymerase chain reaction, for the diagnosis of intestinal cryptosporidiosis.* Trop Parasitol, 2012. **2**(1): p. 20-3.
25. O'Leary, J.K., R.D. Sleator, and B. Lucey, *Cryptosporidium spp. diagnosis and research in the 21(st) century.* Food Waterborne Parasitol, 2021. **24**: p. e00131.
26. Hawkins, R.C., *Laboratory turnaround time.* Clin Biochem Rev, 2007. **28**(4): p. 179-94.
27. Hemming, K., et al., *Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration.* BMJ, 2018. **363**: p. k1614.
28. Drummond, M., *Methods for the economic evaluation of health care programmes*. 2nd ed. 1997, Oxford: Oxford University Press.
29. GBD, I. *Global Burden of Disease Study 2019 (GBD 2019) Disability Weights*. 2019 [cited 2024 01.04.2024]; Available from: https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights.
30. Hossain, M.J., et al., *Clinical and Epidemiologic Features of Cryptosporidium-Associated Diarrheal Disease Among Young Children Living in Sub-Saharan Africa: The Vaccine Impact on Diarrhea in Africa (VIDA) Study.* Clin Infect Dis, 2023. **76**(76 Suppl1): p. S97-S105.
31. Xia, F., et al., *Power and sample size calculation for stepped-wedge designs with discrete outcomes.* Trials, 2021. **22**(1): p. 598.
32. Van Lint, P., et al., *Detection of Giardia lamblia, Cryptosporidium spp. and Entamoeba histolytica in clinical stool samples by using multiplex real-time PCR after automated DNA isolation.* Acta Clin Belg, 2013. **68**(3): p. 188-92.
33. Maasch, J., et al., *Rectal Swabs as an Alternative Sample Collection Method to Bulk Stool for the Real-Time PCR Detection of Giardia duodenalis.* Am J Trop Med Hyg, 2020. **103**(3): p. 1276-1282.
34. Lundberg, G.D., *Acting on significant laboratory results.* JAMA, 1981. **245**(17): p. 1762-3.
35. Ricci, K.A., et al., *Reducing stunting among children: the potential contribution of diagnostics.* Nature, 2006. **444 Suppl 1**: p. 29-38.

INFORMATION ON CLINICAL STUDIES

(For calls that involve clinical studies[1], project participants must add this document to the application and upload it as separate annex to the proposal part B in the Submission System.)

Clinical studies have a number of methodological, operational and regulatory specificities. Information on these issues is crucial for evaluators to assess the scientific quality and operational feasibility of the proposal. The following set of section headings guide applicants to provide essential information on clinical studies in a standardised format.

Applicability:

For **HE collaborative research and innovation:**

Single-stage and stage-2 proposals: The use of this template is mandatory for single-stage or stage-2 proposals, if the application includes a clinical study[1] AND it concerns a topic including clinical studies[2].

For these topics, you will have the possibility to upload the completed template as a separate part of your application in the submission system.

Stage-1 proposals: In the limited frame of a stage-1 proposal, not all methodological details of clinical studies can be fully elaborated. Depending on the characteristics of the study, however, key aspects of clinical study have to be convincingly addressed already at stage 1. This template cannot be uploaded as a separate document at stage 1, but relevant aspects of this information should be integrated in part B of the stage 1 proposal template.

For **HE IHI Joint Undertaking and Global Health-EDCTP3 Joint Undertaking:**

Single-stage and **stage-2** proposals: The use of this template is mandatory for all clinical studies. You can upload the completed template as a separate part of your application in the submission system.

Stage-1 proposals: see under Horizon Europe collaborative research and innovation

For each[3] clinical study performed within the scope of the proposal, essential information according to the below structure should be provided and compiled into one single document per proposal. Each section must be addressed briefly and concisely. In case one or more sections do not apply to a particular study, please provide a short explanation.

When the requested information is currently not available (e.g. a clinical study is planned for a later stage of the project and it will be based on or influenced by future results of other studies), the source and the collection of the relevant input should be described.

Information provided in this template does not need to be repeated elsewhere in the proposal but can be referred to.

There are no page limitations for this template, but explanations should be as concise as possible.

---

1 Clinical study covers clinical studies/trials/investigations/cohorts and means, for the purpose of this document, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by Regulation 536/2014 (on medicinal products), clinical investigation and clinical evaluation as defined by Regulation 2017/745 (on medical devices), performance study and performance evaluation as defined by Regulation 2017/746 (on in vitro diagnostic medical devices).

2 For proposals containing clinical studies submitted to topics *not* foreseeing clinical studies, you may use the section headings of this template as an orientation and provide the related information in sections B.1 and B.3 of the proposal, if the submission system does not provide the possibility to upload the template.

3 If the proposal contains more than one clinical study, each study should be described separately, e.g. study A, study B, etc.

Information outside the scope of this template will not be taken into account in the proposal evaluation. No other chapters or annexes (containing e.g. complete study protocols) can be added to this template. Section headings should not be changed.

Ethics considerations have to be addressed in the appropriate section of the proposal. Similarly, risks and mitigation measures have to be addressed in the respective section of the proposal (part B.3.1 and table 3.1e) and not in this template!

The below three **mandatory deliverables** apply to each clinical study included in the proposal:

1. Study initiation package (before enrolment of the first study participant) including:

    - Registration number of the clinical study in a registry meeting WHO Registry criteria[4] (see also references given in subheading 1.1 of this template)[5]

    - Final version of study protocol as approved by the regulator(s) / ethics committee(s)

    - Regulatory and ethics (if applicable, institutional) approvals required for the enrolment of the first study participant (In case of multicentre clinical studies, submission of approvals for the first clinical site is sufficient.)

2. Midterm recruitment report

    This report is due when 50% of the study population is recruited. The report shall include an overview of the number of recruited participants by clinical sites, any problems in recruitment and, if applicable, a detailed description of implemented and planned measures to compensate for any incurred delays.

3. Report on the status of posting results

    Irrespective of the successful completion of the clinical study, summary results must be posted in the applicable registry/ies (where the study was registered) even if the timing of posting of results falls outside of the grant period. The report is to be scheduled for the time results posting is expected or for the last months of the project, whichever comes earlier.

[4] https://www.who.int/clinical-trials-registry-platform/network/registry-criteria

1 Description of the clinical study

1.1 Title, acronym, unique identifier (e.g. EUCT Number[5], or identifier from ISCRTN[6], ClinicalTrials.gov[7] if available) of the clinical study

The below information pertains to the clinical trial in WP3 of the proposal "Impact of a cryptosporidiosis point-of-care test-and-treat strategy in children with diarrhoea (Crypto-TT). Registration in clinical trials database will be done if funding is approved.

1.2 Study rationale

Please provide the overall rationale for conducting the proposed study.

The intestinal protozoan parasite Cryptosporidium is a major cause of severe diarrhoea in low and middle income countries, and is associated with increased risk of death. Over the last decades it has become increasingly clear that it also leads to impaired linear growth and development. Despite this very large health burden in Africa and Asia, and an available treatment option, it is rarely diagnosed and treated. Strikingly, no studies have yet assessed the impact of diagnosing and treating symptomatic cryptosporidiosis in young children in reducing diarrhoea duration and explored the impact on the severe sequels. There is a dire need for low-cost accurate point-of-care diagnostics for the important diarrheal pathogen Cryptosporidium

LED-microscopes recommended for follow-up of TB-treatment in LMIC can be used also for AP-stained faecal smears to accurately detect Cryptosporidium. An intervention designed to diagnose and treat Cryptosporidium infection in children younger than 5 years would be very beneficial for public health.

1.2.1 Extent and evaluation of current knowledge directly linked to the scientific question(s) to be answered by the clinical study

The intervention in this study is a combined test and treat strategy. Thus, current knowledge on the diagnostic test (microscopy of auramine-phenol stained slides using a LED-microscope (LED-AP)) and the efficacy of the drug Nitazoxanide is linked to the outcomes of this study.

The CryptoPOC study in Jimma, Ethiopia, showed that LED-microscopy of AP-stained stool smears had good sensitivity (88%) and specificity (99%) for the diagnosis of cryptosporidiosis in children. This was the first adequately powered, prospective, diagnostic accuracy study for cryptosporidiosis in children who present for health care with diarrhoea in a low-resource setting (Johansen OH, 2021). The diagnostic accuracy estimates were consistent with estimates from a previous study conducted in a high-income country (Chalmers RM, 2011), and a small study in HIV-positive adults in India (Khurana S, 2012).

The clinical efficacy of Nitazoxanide against Cryptosporidiosis has been demonstrated in healthy patients but has been found to be ineffective in immunocompromised HIV-positive patients (Schneider A et al 2021). Specifically on study showed that diarrhea was resolved after 7 days in 22% in the placebo group versus 56% improvement in Nitazoxanide group in Zambian children (Amadi et al. 2006). Nitazoxanide received initial FDA approval in 2002, and was was approved *as a generic medication in 2020. Nitazoxanide is currently available in two oral dosage forms: a tablet (500 mg) and an oral suspension (100 mg per 5 ml when reconstituted). It is approved in children down to 12 month of age, due to lack of data for younger age groups. However, it has been used in a study against rotavirus in children down to 5 months without any particular adverse reactions (Rossignol et al. 2006). Side effects of Nitazoxanide has not differed from placebo treatment (Stockis et al. 2002).*

---

[5] Please note that from 31.1.2023 all applications for clinical trials in the EU will need to be submitted through the Clinical Trials Information System (CTIS) as per the Clinical Trials Regulation (536/2014): https://euclinicaltrials.eu/

[6] https://www.isrctn.com/

[7] https://clinicaltrials.gov/

1.2.1.1 Outcomes (efficacy, safety) of completed and number of ongoing clinical studies utilising the same intervention in the same indication (including review of public registers)

There are to our knowledge no studies evaluating a test and treat strategy for cryptosporidiosis currently. One ongoing NIH funded study (1U01AI167788-01A1) is testing the safety and efficacy of nitazoxanide in infants between 6 and 12 months of age at the ICDDRb in Bangladesh. If found safe and effective also in this age group the relevance of a point-of-care diagnostic test for Cryptosporidium will be even larger.

1.2.1.2 Level of evidence related to the mechanism of action of the intervention in the planned clinical study population

There are to our knowledge no studies evaluating a test and treat strategy for cryptosporidiosis currently. Detection of Cryptosporidium by various methods followed by Nitazoxanide treatment has been shown to be effective in several studies mentioned above. The mechanism of action for Nitazoxanide is disruption of the energy metabolism by inhibition of the pyruvate: ferredoxin/flavodoxin oxidoreductase (PFOR) cycle in protozoans. Nitazoxanide also induces lesions in the cell membranes and depolarizes the mitochondrial membrane while inhibiting quinone oxidoreductase NQO1, nitroreductase-1 and protein disulphide isomerase enzymes.

1.3 Objective(s) of the clinical study

Please differentiate between primary and secondary objective(s)

Primary objective
Estimate the effectiveness of a low-cost point-of-care test followed by targeted cryptosporidiosis treatment with nitazoxanide on diarrheal duration in children presenting to health care facilities with diarrhoea

Secondary objectives
1. *To **validate the sensitivity, specificity, positive and negative predictive values (PPV and NPV),** of LED-AP cryptosporidiosis POC-testing scaled-up real-life clinical settings, compared with quantitative PCR as a reference test*
2. *To assess sensitivity, specificity, PPV and NPV, and reduction in total test TAT of using **rectal swab specimens** instead of bulk stool samples*
3. *To assess the **cost-effectiveness** of an LED-AP based test-and-treat strategy against cryptosporidiosis*
4. *To explore differences in **mortality and growth parameters** 60 days after enrolment in children in the intervention arm with LED-AP based testing-and-treatment compared with children in the control arm*
5. *To explore the effectiveness of an LED-AP-based test-and-treat strategy in **vulnerable groups** such as children with acute malnutrition or prolonged or persistent diarrhoea*

1.4 Characteristics of the study population (size, age group, sex distribution, inclusion and exclusion criteria; all items with justification!)

Inclusion criteria
1. *Children aged 12-23 months (Minimum age rationale: nitazoxanide has not been adequately evaluated for use and is not FDA-approved for use in infants younger than 12 months. Maximum age rationale: cryptosporidiosis prevalence drops rapidly in children older than 24 months.)*
2. *Child is not currently enrolled as a case (meaning previously enrolled and pending 60-day visit)*
    a. *Reenrollment is permitted after the final 60-day visit has been completed.*
3. *Diarrhoea (three or more loose, or looser than normal, stools, within the previous 24 h), and/or dysentery (at least one loose, or looser than normal, stool, with stains of blood within the previous 24 h), regardless of whether these were the primary complaints leading them to seek health care.*
4. *Caregiver reports that that they have no plans to move out of the catchment area for at least 60 days following enrollment.*
5. *Caregiver permission to be visited in the home for follow-up visits up to 60 days following enrollment.*

Exclusion criteria

1. *The child's guardian fails to provide signed informed consent.*
2. *The family have plans to move out of the catchment area for >30 consecutive days during the 60 day follow-up period.*
3. *Children who reside further away than two hours travel by motorbike (to ensure feasibility of follow-up visits)*
4. *Children who are HIV positive, or whose HIV status is not known (and the caregiver does not consent to HIV testing) (Rationale: nitazoxanide is unlikely to be clinically effective in this group)*
5. *Children who are deemed likely to be unable to receive oral medication, based on healthcare worker assessment, e.g., where there is an ongoing aspiration risk, ongoing persistent repetitive vomiting deemed to be resolvable after rehydration, or enteropathies limiting oral absorption.*
    a. *Exception: if oral administration of drugs is deemed likely to be possible after initial clinical treatment (e.g. rehydration), they can be enrolled in the study.*

Note that malnourished children will not be excluded from participation, but due to uncertainty about the effect of nitazoxanide in this group outcomes will be evaluated both with and without including this subgroup in the analysis.

1.4.1 Details on sample size and power calculation

The required sample was estimated based on our primary outcome measure; reduction of diarrhoea duration. Based on a recent study of cryptosporidiosis [30] and experience from similar studies the average duration of diarrhoea with standard care after presenting at a health facility is 4 days with a standard deviation (SD) of 5, due to a long "tail" of more prolonged diarrhoea in some of the cases. With the provision of LED-AP POC testing and nitazoxanide treatment we hypothesize that the average duration of post-presentation diarrhoea can be halved to two days, with a SD of 3.

Using the R-studio tool swCRTdesign (Xia, 2021) for sample size estimation, the required combined sample size for two equal study arms was estimated at an alpha level of 0.05 and 80% study power to be N=140. Considering the design effect (DE) of a stepped wedge trial design with a conservative intra-cluster correlation coefficient (ICC) of 0.19, number of clusters (k=16) and steps (t=4) the DE was 3.09, increasing the sample size to 217. Considering a study attrition rate of 10% brings this number to 241. With an expected 8% prevalence of cryptosporidiosis a total of 3013 children with watery diarrhoea will need to be enrolled.

1.5 Design of the clinical study (controlled / uncontrolled; randomised; open / blinded; parallel group / cross over / other, including innovative trial designs e.g. for personalised medicine, small study populations, or adaptive platform trials; please justify the appropriateness of the selected design)

A stepped wedge cluster randomized trial (SW-CRT, Hemming 2018) design has been chosen for this study. It will be conducted at hospitals and health centers in Ethiopia and Mozambique.

A SW-CRT design is in some respects similar to large-scale implementation programmes for roll-out of a new diagnostic test (in our case, a repurposed test). Due to the randomised sequence determining the time point for the intervention at a given site, we are able to gather important implementational evidence, with a formal evaluation of the clinical efficacy and cost-effectiveness of the whole test-and-treat package.

Alternative study designs would be a traditional diagnostic RCT (D-RCT), where individual participants are randomised to receive either the test, the treatment, or both, or a conventional cluster randomised trial, where whole facilities are randomized to either receive the intervention or to continue with standard-of-care. However, as there is already an approved drug available for cryptosporidiosis it seems ethically problematic to offer placebo or to withhold treatment. We also anticipate a risk of bias due to lower participation and buy-in from local healthcare staff involved in the study unless they are able to offer both the test and the treatment. The SW-CRT design allows us to address these concerns: although the timing will vary between facilities, all clusters will receive the testing-and-treatment package.

The SW-CRT design allows for a phased rollout of cryptosporidiosis testing-and-treatment. Larger-scale rollout will be considered as a next step, based on the findings from the study. Resource

allocation should be based on data-driven insights from the early stages of a programme with an aim to ensure equitable distribution of resources and to address concerns about disadvantaged communities being left behind during roll-out. Data gathered throughout the phased roll-out will provide policy makers with scientific and implementational data on the intervention's real-time impact as well as potential unintended consequences (Hemming et al 2018).

There are likely unforeseen challenges with large-scale implementation of cryptosporidiosis testing-and-treatment as it has not previously been attempted. Understanding the specific context is crucial in order to tailor and adapt the intervention. The gradual rollout of the intervention in a SW-CRT design permits us to identify potential challenges during local adoption and make necessary adjustments while minimizing disruption to routine care. By introducing the intervention step-by-step, we hope to mitigate potential risks and allow for adjustments based on initial lessons learned before wider project implementation in facilities that are still offering standard-of-care (i.e., clusters being observed under a control condition).

We anticipate some challenges specific to the SW-CRT design. First, the duration of the study will be longer that what is required for a traditional (parallel) randomized trial. Second, generalizability depends on choosing appropriate clusters that are sufficiently representative of the target population. There is a potential risk that "intervention knowledge" can spread to clusters that are still in the control condition, leading to bias. We will take appropriate measures before and during project implementation to minimize the possible contamination between intervention and control arms. We will organise training sessions for all healthcare workers and scientific staff associated with the trial. Furthermore, we will conduct a trial run-in-period to optimise all data collection tools and to identify practical challenges with the near-patient microscopy testing or with nitazoxanide provision, permitting necessary adjustment before full trial startup.

1.6 Type of intervention (medicinal product / advanced therapy medicinal product / medical device / in vitro diagnostic medical device / surgical or other invasive procedure / other medical intervention, including, e.g., counselling)

Testing-and-treatment for cryptosporidiosis is the intervention under study. This packaged intervention will be integrated with routine clinical care. Laboratory technicians and clinical healthcare staff will receive training in stool collection, testing, and cryptosporidiosis treatment with nitazoxanide. A standard treatment guideline will be introduced at each participating health facility, covering the testing-and-treatment pathway for diarrhoea, with easy-to-use visual algorithms clearly specifying criteria for nitazoxanide treatment, supported by a simple checklist.

There is an intervention arm and a control arm in the study. In both arms data collection by interview, sampling and storage of sample aliquots is done in eligible children after consent. Standard diarrhoea care will also be offered. The intervention arm will additionally be offered cryptosporidiosis LED-AP testing and in those testing positive, treatment with nitazoxanide will be offered according to a standard treatment guideline developed for the study.

1.7 Description and timing of study procedures

Please provide an overview, preferably in a tabular format, about the schedule of study procedures. Please give a simple statement on how long individual patients or healthy volunteers participate in the clinical study.

	STUDY PERIOD					
	Screening	**Enrolment**	**Intervention**	**Follow up**		
TIMEPOINT	***Day 0***	**Day 0**	***Day 0***	***Diarrhoea diary***	***Day 4***	***Day 60***
ENROLMENT:						
Eligibility screen	all					
Informed consent	all					
Rectal/stool sampling		all				

INTERVENTIONS:						
LED-AP microscopy			intervention arm			
Nitazoxanide treatment start (*Cryptosporidium* positive children)			Intervention arm			
ASSESSMENTS:						
Demographics		all				
Clinical variables		all		all	all	all
Diarrhea duration				all	all	
Rehydrated height/weight					all	all
Death					all	all

Each participating child will be part of the study for two months from enrolment to last follow-up timepoint. Children in both trial arms will be followed-up until the end of the diarrhoeal episode, in order to calculate total diarrhoeal duration, and will have their height and weight measured after rehydration (4 days), and at 60 days after enrolment. All stool samples will be stored for later testing by targeted Cryptosporidium quantitative PCR (qPCR).

2 Preparedness status

2.1 Development of the clinical study protocol

Please describe how the below aspects have been or will be addressed in developing the clinical study protocol (if applicable):

2.1.1 Scientific advice from regulatory and health technology assessment bodies

Our consortium members have critical expertise in intervention studies and diarrhoea studies in general. They have all the necessary expertise including clinical, epidemiological science. Having performed clinical studies for many years all institutions possess the necessary knowledge and skills to prepare all the details of the study protocol.

2.1.2 Clinical efficacy, safety, and methodological guidelines (including guidelines on statistics)

The proposed study is an intervention study of the clinical efficacy of an well documented low-cost diagnostic methods combined with an approved drug treatment for the study population. The primary outcome of interest is efficacy of the combined test and treat strategy, while also monitoring for potential side effects or adverse events. The overall data analysis procedure will primarily conduct based on the intention-to-treat Analysis approach. Simple statistical tests (e.g. independent t-test, linear regression) will be used to compare the difference/change in mean duration of diarrhoea across the intervention groups. We will calculate summary statistics of continuous measures, proportions for categorical variables and graphical illustrations. We will present 95% confidence intervals for all key parameters. Inferential methods (e.g., hypothesis testing, multivariable analysis will be used to estimate the effect of the intervention (test and treat strategy) and to estimate associations between potential predictor variables and our primary and secondary endpoints. A generalised linear mixed model and/or generalised estimating equations will be employed to generate a linear model with random effect for cluster and fixed effect for each step. A regression analysis will be used to adjust individual level confounding variables such as age, sex, and nutritional status and the effect of clustering and time variation, and coefficients of fixed effects and robust variance estimator (b, SE) will be reported. Possible heterogeneity within and between clusters will be explored and compared across intervention and control groups. Subgroup analyses will be conducted to investigate potential effect modifiers of the intervention and primary outcome variables that include severity of diarrhoea, HIV, acute malnutrition (moderate, severe), stunting, and other facility or cluster related factors. Estimated difference with regard to secondary (binary) outcome measures will be reported as Relative

Risk (RR) or risk difference (RD), with corresponding confidence intervals (95% CI).quantitative data will be analysed using STATA and R softwares.

2.1.3 Involvement of citizens / patients, carers in drawing up the clinical study protocol

We will be involving all relevant stakeholders including clinicians and caregivers along the steps of the protocol development and during the clinical study. Feedback from health facility personnel and patient caretakers will be gathered during the run-in period and adaptations made.

2.2 Regulatory intelligence to ensure timely regulatory approval and ethics clearance of the clinical study in all jurisdictions where its implementation is planned

Please provide information on the following regulatory and ethics aspects:

2.2.1 How the consortium will ensure access to regulatory expertise necessary to get advice on, and management of, regulatory affairs activities in all concerned jurisdictions?

All the consortium members are clinical researchers and are well versed with all relevant national and international ethical and regulatory requirements for doing clinical research. In addition, some of the consortium members are also serving as institutional and national ethics committee members in their respective countries. Thus, they will be providing their expertise in this regard. We have had discussions with drug regulatory authorities in both Ethiopia and Mozambique, and been reassured there will be no regulatory hurdles regarding importation and use of this drug in these countries.

2.2.2 How the consortium will ensure access to ethics expertise necessary to get advice on current proceedings and documentation requirements of all concerned ethics committees?

All the consortium members are clinical researchers and are well versed with all relevant national and international ethical and regulatory requirements for doing clinical research. In addition, some of the consortium members are also serving as institutional and national ethics committee members in their respective countries. Thus, they will be providing their expertise regarding documentation requirement of ethics committees.

2.3 How the scientific and operational governance of the clinical study will be ensured?

2.3.1 Please give details about the sponsor(s) (name, type of entity, seat or country of residence).

University of Bergen (UiB) will be coordinating this project. UiB is located in Norway and has ample experience in conducting multi-centre and multi-country clinical trials and a diverse portfolio of clinical studies.

2.3.2 Please describe the composition, the role and the functioning of the planned board(s), governing bodies.

The project will be led by a steering committee (SC) that consists of the coordinator, scientific project leader and leads from each partner institutions. The SC will monitor the interaction between WP leads and institutional leads and track the project's milestones and deliverables. The SC will have a bi-weekly virtual meeting to discuss the project's progress, identify problems and outstanding issues, suggest solutions, and make decisions.

3 Operational feasibility

3.1 Please describe how the availability of the intervention(s) (including comparators) is secured throughout the entire implementation phase (give details on manufacturing, packaging / labelling operations, storage, logistical, import/export issues, etc.)

Facilities that do not currently have or use a LED microscopes will be supplied one from this project. Sources of AP stain have been identified from local purchasers/government supplies. Nitazoxanide tablets or oral suspension is available from several well-reputed generic producers in India (Sun Pharmaceutical Industries Ltd. or Macleods Pharmaceuticals LTD. Comparator is not needed in this study.

The drug will be purchased in bulk by UiB, to ensure uniformity, with quality certificates. Study treatment packages of one full treatment course will be made, labelled with unique identifier and donated Ethiopian and Mozambican partners accompanied with the necessary paperwork for importation distributed to clinical study sites from a central storage in each of the two countries.Treatment package identifier will be recorded when treatment is given to a study participant.

3.2 Please describe how the study population will be recruited

Please give details on the recruitment strategy, monitoring of progress and potential mitigation measures

Potential study participants will be identified and approached by trained nurses and physicians at study health facilities in Ethiopia and Mozambique. After checking for eligibility criteria, the clinician/nurse will provide complete study information to parent/caregiver of potential children then obtain written informed consent. For those who decline to consent, the reasons will be recorded if caregivers are willing to give their reasons.

We will do ongoing follow up of the status of recruitment and if the rate is not found to be as planned, we will analyse the reasons for slow recruitment and act accordingly. This could be refresher training on informed consent process, engagement of caregivers etc.

3.2.1 How many clinical sites will contribute to the recruitment of the study population in which countries? Are these clinical sites part of an established clinical trial network? Please also describe the selection criteria of the clinical sites.

A total of 8 hospitals in Ethiopia, and 8 sites in Mozambique will be recruiting the study participants. Most of the study hospitals are part of clinical research network within their respective country. The sites are selected based on criteria of case load of children with diarrhoea, and experience with LED-AP microscopy. Case load data from previous years have been collected in order to include sites with similar number of cases per year.

3.2.2 Will recruitment of the study population be of competitive nature between the clinical sites? (Please describe how underperformance of individual clinical sites in recruitment will be managed.)

The recruitment of patients will not be competitive, and all eligible children will be recruited. If a single site is found to be performing poorly, increased supervision and trainings will be attempted first. If no improvement, we will replace the site with an equivalent health facility within the same country.

3.2.3 What evidence supports the ability of the individual clinical sites to recruit the required number of study participants within the planned timeline (e.g. documented performance in previous clinical studies of similar complexity targeting very similar study population)?

The number of patients /participants per site was determined based on previous case load of children with diarrhoea within the age range 12-23 months, in the previous year.

3.3 Please describe what additional supply (e.g. an electronic device for remote data capture, a specific instrument for administering the investigational product, etc.) is necessary to carry out the required study procedures and how this supply will be made available to the clinical sites

Ten of the sites will need an added or backup LED-microscope with power adapter and voltage stabilizing unit. Nitazoxanide oral suspension treatment packages will be purchased through the coordinator and distributed to each study site from a central storage in both Ethiopia and Mozambique. A tablets will be provided for electronic data capture at each site.

3.4 Please provide plans on data management aspects (data standards, type of data capture, verification of data, central data collection, cleaning, analysis, reporting, security)

We will capture data using different data collection tools: a) Paper case report formats; c) Electronic Data capturing format; d) Observations checklists and e) Paper consent forms. All study personnel collecting and processing data will be trained on ethical considerations in data handling. A central data manager at each country will be responsible for ensuring data quality and creating and sending out data queries to sites and resolve issues.

The team will set up a shared project folder at an encrypted cloud server. Electronic data will be collected on Android devices, using RedCap. Each data collector will use a password protected device for data collection. All data forms will be kept in a locked filing cabinet, within an office that can be locked. We will import all paper and electronically collected quantitative data into RedCap for further data cleaning and processing before making it ready for analysis.

3.5 Please give details on how reporting obligations (regarding study initiation, safety of study participants, ethical concerns, quality issues, integrity of data, study results) to regulatory bodies and ethics committees will be met.

The study will be initiated after obtaining ethical clearance from each participating country. The scientific coordinator will be providing progress reports and safety reports to respective ethics committees based on the local requirements. Data quality and integrity will be checked by investigators during their monitoring visits to the sites in addition to data quality check by central data manager.

3.6 Please list all items of the sponsor's responsibilities (e.g. monitoring clinical sites, meeting regulatory obligations, data management, etc.) that will be supported by entities that are not part of the sponsor's organisation. Please describe how the sponsor will ensure oversight of these activities.

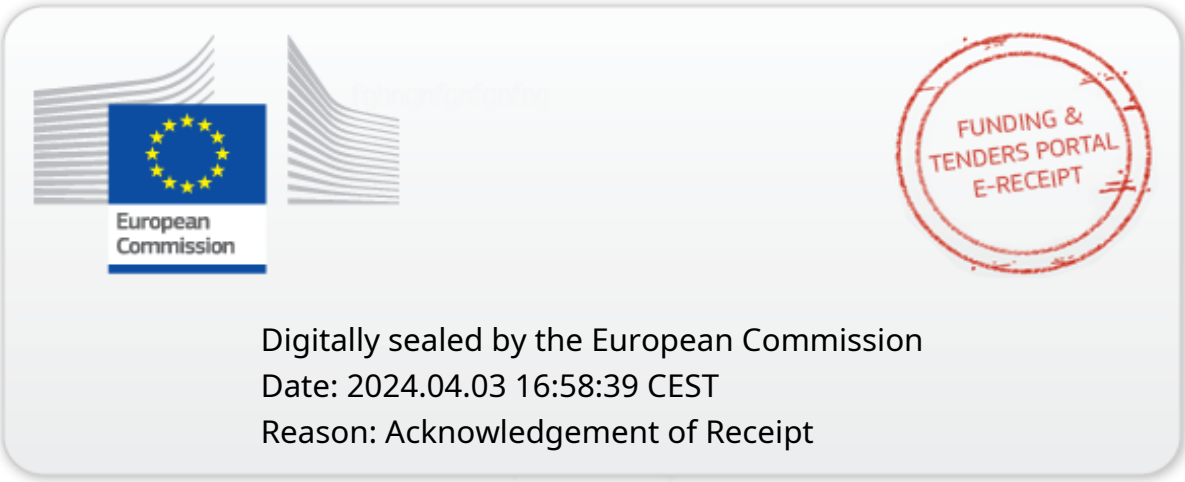
Monitoring of clinical sites, data management and regulatory obligations will be handed by consortium members in each participating country. However, UiB will verify those activities are accomplished according to the management plan. This will be done through bi-weekly steering committee meetings, close collaboration with the scientific coordinator and at least three monitoring visits every year.

3.7 What are the plans for major study milestones and what evidence supports its feasibility?

Please describe a realistic plan (based on prior experience) detailing the time necessary for (i) compiling the required regulatory and ethics submission package, (ii) receipt of regulatory and ethics approval, (iii) initiation of clinical site(s), (iv) completion of recruitment of the study population, (v) final assessment of all study participants, (vi) analysis and reporting of the study results.

We will compile the detailed protocol and all the necessary regulatory and ethics documents within 6 months of the project initiation. We anticipate to have ethics approvals from all countries within 6 months of submission. We plan to prepare training materials, and train study staff, lab-technicians, and clinicians for one run-in site in each country so that a run-in period can be performed as soon as ethical approvals are in place. After necessary adjustments have been undertaken the sites will be randomized with regard to timing of introduction of the intervention, and trainings commenced at all sites. The stepped wedge cluster randomized trial will start at all sites around 14 months after the project initiation. The trial will include patients for 14 months, and end follow up of the last participants two months later, at around the 30th month of the project. Thereafter analyses of study results will be performed during the next 12 months and be ready at the 42th month of the project. Remaining project time will be used for writing publications and reports and dissemination of results among stakeholders and community.

HISTORY OF CHANGES		
VERSION	PUBLICATION DATE	CHANGE
1.0	24.03.2021	Initial version (included in the standard HE proposal template)
1.1	08.04.2021	Reference to ‘sex distribution’ added in section 1.4.
2.0	13.10.2021	Standalone template document.
3.0	15.01.2022	Reformatting changes and change of document name.
4.0	01.05.2022	Removed reference to specific topics for a more generalised template
4.1	13.05.2022	Added reference to Global Health-EDCTP3 Joint Undertaking
4.2	01.04.2023	Added reference to mandatory use of CTIS and complex trials



This electronic receipt is a digitally signed version of the document submitted by your organisation. Both the content of the document and a set of metadata have been digitally sealed.

This digital signature mechanism, using a public-private key pair mechanism, uniquely binds this eReceipt to the modules of the Funding & Tenders Portal of the European Commission, to the transaction for which it was generated and ensures its full integrity. Therefore a complete digitally signed trail of the transaction is available both for your organisation and for the issuer of the eReceipt.

Any attempt to modify the content will lead to a break of the integrity of the electronic signature, which can be verified at any time by clicking on the eReceipt validation symbol.

More info about eReceipts can be found in the FAQ page of the Funding & Tenders Portal.

(https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/support/faq)