Study Protocol

TIMCI: Tools for the Integrated Management of Childhood Illness

Evaluation of pulse oximetry and clinical decision support algorithms in primary care

Pragmatic cluster randomised controlled trial, with embedded mixed methods, cost and cost-effectiveness studies in India and Tanzania

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Version / date	Description	Prepared by
India & Tanzania specific protocol		
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Version 0.1.6, 2nd Apr 2020	Protocol shared with PATH for independent Scientific Merit Review submission	Swiss TPH
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Authorities. It is understood that this information will not be disclosed to others without prior written authorization from the Sponsor, except where required by applicable local laws.

Contents

Abbreviations

(co)-PI	(co)-Principal Investigator
(e)CRF	(electronic) Case Report Form
ASHA	Accredited Social Healthcare Activist
BI	Burnet Institute
CDSA	Clinical Decision Support Algorithm
CE	Conformité Européenne
CG	Caregiver
CHC	Community Health Center
CS	Case Studies
CSO	Civil Society Organization
DALY	Disability-Adjusted Life Years
DB	Database
DHIS	District Health Information System
DHS	Demographic And Health Surveys
DMC	Data Monitoring Committee
DMP	Data Management Plan
EDC	Electronic Data Capture
ePOCT	electronic Point of Care Tool
ERC	Ethical Review Committee
FGD	Focus Group Discussion
GCP	Good Clinical Practice
GPS	Global Positioning System
HC	Health Center
HCP	Health Care Provider
HMIS	Health Management Information System
HMSC	Health Ministry's Screening Committee
HP	Health Post
HQ	Headquarters
IAG	International Advisory Group
ICC	Intercluster Correlation Coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICMR	Indian Council of Medical Research
ID	Identification
IDI	In-Depth Interview
IEC	Institutional Ethics Committee
IHI	Ifakara Health Institute
IMCI	Integrated Management of Childhood Illnesses
IQR	Interquartile Range
IRB	Institutional Review Board
KGMU	King George's Medical University
KII	Key Informant Interview
LMIC	Low- and middle-income countries
M&E	Monitoring and Evaluation
MedAL-C	Medical Algorithm - Creator
MedAL-R	Medical Algorithm - Reader

MedDRA	Medical Dictionary for Regulatory Activities
MEP	Monitoring and Evaluation Plan
MIS	Management Information System
MOH	Ministry Of Health
NHM-UP	National Health Ministry – Uttar Pradesh
NIMR	National Health Research Ethics Committee
NRRC	National Research Registration Committee
PHC	Primary Healthcare Center
PII	Personal Identifiable Information
QoC	Quality of Care
RA	Research Assistant
RCT	Randomised controlled trial
RHC	Rural Health Center
SAP	Statistical Analysis Plan
SNOMED CT	Systemized Nomenclature of Medicine - Clinical Terms
SOP	Standard Operating Procedure
SPA	Service Provision Assessment
SRA	Stringent Regulatory Authority
Swiss TPH	Swiss Tropical and Public Health Institute
TIMCI	Tools for integrated managment of childhood illness
ToC	Theory of Change
UCAD	Université Cheikh Anta Diop de Dakar
UoN	University of Nairobi
US FDA	United States Food and Drug Administration
VPN	Virtual Private Network
WHO	World Health Organisation

1 Summary

Background / rationale

Achieving global targets for child mortality reduction in low- and middle-income countries (LMICs) requires significant improvements in the detection and management of severely ill children. Existing guidelines are inconsistently implemented by healthcare providers and, as they are based on clinical signs, are inadequate for the detection of hypoxaemia, a strong predictor of mortality.

The overall goal of the Tools for the Management of Childhood Illness (TIMCI) project is to reduce morbidity and mortality in sick children attending primary care facilities, while supporting the rational and efficient use of diagnostics and medicines by healthcare providers. The evaluation component of the project seeks to generate evidence on the health impact, operational priorities, cost and cost-effectiveness of introducing pulse oximetry, alone or embedded into a Clinical Decision Support Algorithm (CDSA), at primary care level in LMICs, for children 0 – 59 months of age, to facilitate national and international decision-making on scale-up.

Study design

Health and quality of care impact are evaluated through pragmatic, parallel group, cluster randomised controlled superiority trials in India and Tanzania, and quasi-experimental pre-post studies in Kenya and Senegal.
In the pragmatic cluster randomised controlled trial (RCT), primary care facilities (clusters) are randomly allocated (1:1) to pulse oximetry or control in India, and (1:1:1) to pulse oximetry plus CDSA, pulse oximetry, or control in Tanzania..

The intervention package will be piloted and refined over a 3-month period prior to the start of the definitive pragmatic cluster RCT.

This will be complemented by embedded mixed methods sub-studies to evaluate key components of quality of care and gain a deeper understanding of the implementation processes, mechanisms and context following a realist approach. These studies include modified Service Provision Assessments (SPAs), a facility-based process mapping and time-flow study, qualitative studies with caregivers, healthcare providers and key stakeholders, a survey sent to selected key stakeholders on a quarterly basis, a desk-based project document and monitoring and evaluation (M&E) review, and a cost and modelled cost-effectiveness study.

Study setting

The study setting encompasses facility-based primary care level in three districts of Uttar Pradesh in India (Unnao, Sitapur, and Deoria) and in three councils in Tanzania (Mwanza, Tanga and Tabora). Caregivers often attend different types of facilities to meet their primary care needs; the study setting therefore includes a diverse range of facilities providing primary care services, including outpatient settings within larger health centres in addition to the more

traditionally-labelled primary care facilities. This includes primary healthcare centres (PHCs) and community health centres (CHCs) in India and dispensaries and health centres (HCs) in Tanzania.

Key Eligibility Criteria

Consenting government-designated healthcare facilities providing outpatient curative primary care services for children 0 – 59 months of age will be included. Facilities will be excluded if they use pulse oximetry as a routine part of outpatient consultations of children prior to the start of the intervention.

Children 0 – 59 months, for whom caregivers provide consent, will be eligible if attending any study facility with an illness, excluding those admitted as inpatients within the facility, or attending for a consultation related to trauma only.

Caregivers of enrolled children, and healthcare providers at study sites involved in the care of children 0 – 59 months of age, and stakeholders involved in or affected by the intervention, will be eligible for inclusion in the applicable studies.

Interventions

The TIMCI project will introduce pulse oximetry, alone or embedded into a CDSA, into primary care facilities, supported by targeted training and embedded into monitoring, supportive supervision and maintenance systems. Refresher training will be provided to healthcare providers in the routine care arm.

The pulse oximeters provided in the study will be UNICEF-approved handheld pulse oximeters with paediatric and neonatal probes. Healthcare providers will be provided with guidance (paper-based, or within the CDSA) and trained on the following criteria for pulse oximetry use:

- All children under 2 months of age
- Children 2 – 59 months of age presenting with cough / difficulty breathing
- Children 2 – 59 months of age with Integrated Management of Childhood Illness (IMCI) signs of moderate / severe disease (IMCI 'yellow' or 'red' classification)

Healthcare providers will be advised to use a cut-off of SpO2 <90% for referral, unless specific national guidance states otherwise. Different SpO2 cut-offs for referral for sites at high altitude will be finalised with the International Advisory Group (IAG) and Ministries of Health (MoHs).

The tablet-based CDSA, provided to facilities in arm 1, guides healthcare providers through medical consultations with an algorithm called electronic point-of-care tool (ePoct+). The clinical algorithm will be adapted to reflect national guidelines for the management of children 0 – 59 months of age in primary care (based on IMCI and additional relevant case management guidelines), and will be validated through consultation of international and national experts in each country.

Outcomes

Two primary outcomes will be assessed in order to improve the ability to detect a difference between each of the intervention arms (pulse oximetry alone, or embedded into a CDSA) and the control arm, given the relatively low occurrence of severe outcomes at primary care level:

- Proportion of children with a severe complication (death or secondary hospitalisation) by Day 7
- Proportion of children admitted to hospital within 24 hours of the Day 0 primary care consultation and as a result of a referral

Important secondary and other outcomes include:

- Proportion of children with severe complication (death or secondary hospitalisation) by Day 28
- Proportion of children cured (defined as caregiver reported recovery from illness) at Day 7 follow-up
- Proportion of children referred by a primary care healthcare provider to a higher level of care (either to a hospital or to an inpatient part of a larger primary healthcare facility) at Day 0 consultation
- Proportion of children who completed referral, as reported at day 7 follow-up
- Proportion of children with hypoxaemia (according to differing cut-offs) with severe complication
- Proportion of children prescribed an appropriate antibiotic at Day 0 consultation

Sub-group analyses will include age (under 2 months, 2 – 12 months, 13 – 59 months), sex, and clinical presentation (with cough / difficulty breathing, fever, other). Other exploratory analysis will be conducted of individual and health system factors associated with health and patient-centred outcomes.

Mixed methods sub-studies will mostly be exploratory, to evaluate quality of care outcomes and explore perceptions, values, attitudes and beliefs. Process evaluation criteria will be evaluated according to the Medical Research Council criteria.

Cost and modelled cost-effectiveness will assess:

- Full implementation cost of the intervention per focal country (cost to health system as well as direct costs paid by the household to the health system)
- Cost per child assessed using pulse oximetry devices and CDSA per country; where applicable, compared to cost per child in routine care
- Modelled cost per DALY averted attributed to the introduction of pulse oximetry and CDSAs

Sample size

The sample size for the pragmatic cluster RCT is calculated separately for each country to compare each of the intervention arms with the control arm. In order to detect a 30% reduction in the severe complication primary outcome (from 1.1% to 0.77%) with 80% power, we estimate a sample size in each country as follows:

- India – Initial sample size calculation for the three arm trial was 0 facilities per arm, recruiting an average of 510 children over the 12 month period, with an average of 110 per CHC per month and 20 children per PHC, and a facility ratio of CHC : PHC of 1:3, equating to 20,400 children per arm over the study. Following the decision not to introduce the CDSA plus pulse oximetry arm, a decision was made to reallocate facilities to the remaining to arms up to 60 facilities per arm.

- Tanzania – 22 facilities per arm, recruiting an average of 1680 children over the 12 month period, with an average of 350 per health centre per month and 70 per dispensary per month, and an average ratio of health center : dispensary of 1:3, equating to 36,960 children per arm over the study

Service provision assessments and process mapping will be conducted in 6 facilities per arm per country, stratified by rural / urban location and facility type, at 5 time points (once per quarter in each facility). At each facility at each time point, 10 – 30 children per facility will be included, resulting in an estimated sample size of 600 clinical observations, time-flow observations and exit interviews per arm in each country over the study period.

Final sample size for qualitative studies will be determined by reaching thematic saturation. Per country, an estimated total of 70-90 in-depth interviews (IDIs), 6 – 8 walking interviews and 12 focus group discussions (FGDs) will be conducted with caregivers, spread across the study period. Similarly, 70-90 IDIs and 12 FGDs will be conducted with healthcare providers, and approximately 45-55 key informant interviews with stakeholders.

Ethics Review

Following independent scientific merit review, the protocol will be submitted to all relevant research ethics committees / institutional review boards in each country and the WHO ethical review committee.

Estimated study timeline

Pending all relevant ethical approvals, first enrolment is anticipated to be in January 2021, with completion of data collection in March 2022.

Depending on the evolution of the Covid-19 pandemic, we will keep implementation, research processes and timelines under review and inform the necessary bodies and institutions accordingly of any possible adaptations.

2 General information

2.1 Trial registration

The trial is registered on clinicaltrials.gov, with the main register ID: NCT04910750. The study is also registered at Clinical Trial Registry of India (CTRI) with registration number CTRI/2022/03/041325.

2.2 WHO Trial Registration Data Set

To be uploaded once approved

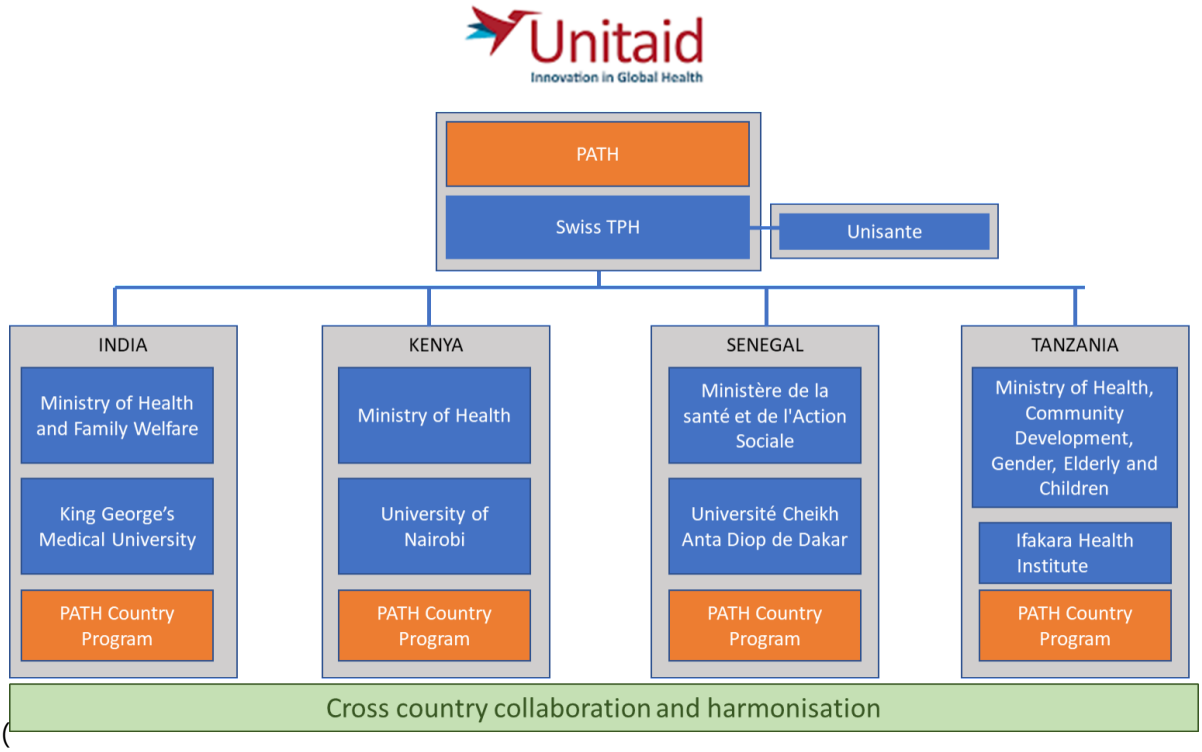
2.3 Funding

The TIMCI project and associated research described in this protocol are funded by UNITAID. PATH (Seattle) is the primary recipient of the funds and manages the project, with distribution of funds for project implementation to PATH Country offices. All research partners are sub-contracted by and accountable to PATH. PATH is responsible for all procurement related to implementation (including medical supplies and consumables). Pulse oximeters used within the study will be procured through and delivered by UNICEF.

2.4 Roles & responsibilities

PATH headquarters (Seattle) lead the project, including strategic direction and decision-making, project oversight and compliance, global communications, risk monitoring and mitigation, quality/change management, as well as serving as liaison with UNITAID, the International Advisory Group and other relevant global partners, such as WHO and UNICEF. Additional details on project governance are described below. PATH retain overall

responsibility for the project, but have sub-contracted



(**Fig. 1**): the Swiss Tropical and Public Health Institute (Swiss TPH) to coordinate research design and analysis, which includes collaboration with UniSanté, who lead the design and development of the clinical decision support algorithm (CDSA); University of Waterloo (UoW) to conduct cost-effectiveness analysis; and the following research partners leading country research activities: King George's Medical University (KGMU, India); University of Nairobi (UoN, Kenya); Université Cheikh Anta Diop de Dakar (UCAD, Senegal); and Ifakara Health Institute (IHI, Tanzania). As this protocol relates only to research activities in India and Tanzania, other country research leads will not be further detailed in this document.

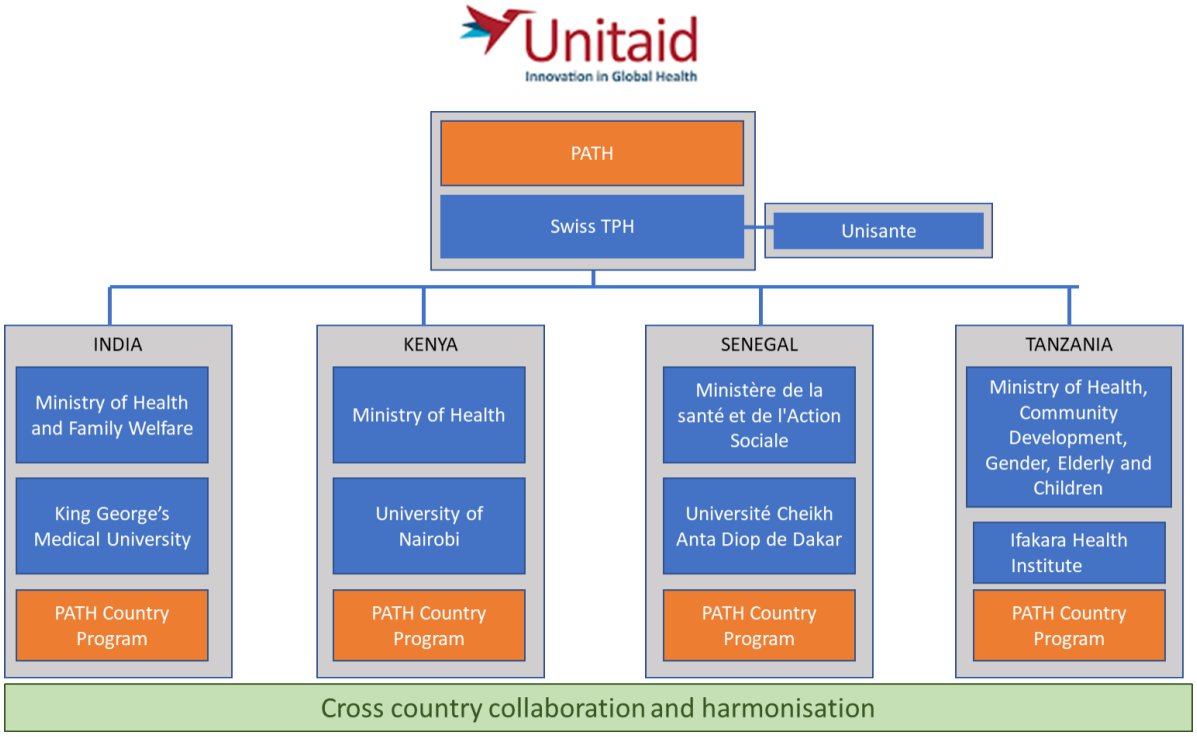


Fig. 1. TIMCI project partners

PATH is the Sponsor of the research but is delegating certain responsibilities to Swiss TPH and country research partners, outlined in Tab. 1. Through that delegation Swiss TPH, in collaboration with the research partners in each country, will be responsible for the initiation and management of the research. Each of the study countries has a separate tri-partite agreement between the country research partner, PATH and Swiss TPH. Within this agreement, Swiss TPH has the lead in development and design of the research. The respective in-country research partner will be responsible for the adaption of the design to the country specific context, in close collaboration with Swiss TPH and PATH.

Tab. 1. TIMCI Sponsor responsibilities and delegation

	PATH	**Swiss TPH**	**Research Partners**
Investigator selection	Lead		
Medical expertise	Review	Lead	Participates
Trial design	Review	Lead	Participates
Submission to WHO ethical review	Lead	Review	Review
Submission to country ethical review	Review	Review	Lead
Preparation of study sites	Review	Participates	Lead
Trial management		Lead	Participates
Research conduct		Participates	Lead
Data collection		Participates	Lead
Quality assurance & control	Review	Lead	Lead
Safety reporting		Lead	Lead
Data analysis (country specific)		Participates	Lead
Data analysis (cross-country)		Lead	Participates
Dissemination	Review	Lead	Lead

Compensation	Review	Lead	Participates
Financing	Lead		
Insurance	Lead		

2.4.1 Protocol development

Swiss TPH leads the study design and protocol development in close collaboration with all other partners. The University of Waterloo leads the development and conduct of the cost-effectiveness component of the research, in close collaboration with Swiss TPH, PATH and the country research partners. The RCT will be conducted in two countries, India and Tanzania. In each country, Swiss TPH and PATH collaborate with research institutions, both of which have extensive experience in implementing and conducting large-scale projects in their respective study settings. PATH central contributes to the protocol development, ensuring alignment of the proposed research with the intervention and the training packages, which are led by PATH. In both study countries, the local PATH office interlinks with the research partners. Tab. 2 outlines the investigators and contributors to the protocol.

Tab. 2. TIMCI investigators and contributors for India and Tanzania study

	Name	**Role**	**Input**
Swiss TPH	Prof. Kaspar Wyss	Co-PI	Oversight & overall responsibility for research design for Swiss TPH
	Prof. Valérie d'Acremont	Co-PI	Oversight & overall responsibility for research design for Swiss TPH
	Dr. Fenella Beynon	Clinical Research Scientist, Co-I	Quantitative study design and analysis, clinical input for algorithm
	Dr. Hélène Langet	Data Manager, Co-I	Study design, data management oversight, technical input for algorithm, link CDSA into research design
	Dr. Leah F. Bohle	Social Scientist, Co-I	Lead on qualitative study design & analysis
	Dr. Fabian Schär	Project Manager, Co-I	Study design, Ethics approval, timelines and link with research partners
	Dr. Tracy Glass	Biostatistician	Input into study design, data management and analysis
	Silvia Cicconi	Biostatistician	Input into study design, data management and analysis
	Dr. Gillian Levine	Clinical Researcher	Development of clinical content for young infants; input into study design; qualitative study design and analysis for young infants; data analysis
	Dr. Kristina Keitel	Senior Clinical Scientist	Input in development of clinical content for algorithm, input on study design
	Dr. Elisabeth Reus	Clinical Operations	Development of monitoring plan, ethics input
	Dr. Vânia Oliveira	Clinical Operations	Monitoring of study conduct
	Anja Orschulko	Social Scientist	Qualitative study design & analysis
	Dr. Gaurav Kumar	Country Coordinator India	In-country link between Swiss TPH, Research Partner and PATH

	Dr. Lena Matata	Country Coordinator Tanzania	In-country link between Swiss TPH, Research Partner and PATH
Unisanté	Vincent Faivre	Deputy head of IT department	Software development
	Alan Vonlanthen	Project Manager	UniSanté Project Management, IT department
UoW	Prof. Susan Horton	Cost-effectiveness PI	Oversight and analysis of cost-effectiveness study
	Dr. Nnachebe Michael Onah	Cost-effectiveness Co-I	Design and conduct of cost-effectiveness study in collaboration with country research partners
KGMU	Prof. Shally Awasthi	National PI	Lead for research activities in India
	Dr. Divas Kumar	Country Research Coordinator	Lead coordination of in country research team
	Mansi Tyagi	Country Lead Social Scientist	Lead qualitative study implementation & analysis
	Anmol Jacob	Country Data Manager	Data Manager, Quantitative study implementation & analysis
	Dr. Gidhar Agarwal	Senior Biostatistician	Statistical analysis
	Dr. Ved Prakash	GM Child Health & Immunization	Programmatic support
	Prof. Monika Agarwal	Professor, Dept of Community Medicine	Technical support
IHI	Dr. Honorati Masanja	National PI	Oversight &and overall responsibility for research design for Tanzania
	Dr. Irene Masanja †	Former Country Coordinator/co-investigator	Contributed to the development of the protocol and led the IHI research team
	Dr. Grace Mhalu	Country Coordinator/Social Scientist	Contribute to the implementation of the protocol and coordinate the IHI research team / Lead qualitative study implementation & analysis
	Dr. Abdallah Mkopi	Senior Research Scientist	Data Manager, Quantitative study implementation & analysis
	Samwel Lwambura	Country Data Manager	Data Manager, Quantitative study implementation & analysis
	Mr Ibrahim Mtebene	IT/Software and software developer	IT/Software development
	Suzan Makawia	Research scientist / Economist	Conduct of cost effectiveness study
	John Maiba	Social Scientist	Qualitative study implementation and coordination
	Charles Festo	Research Scientist	Assist in quantitative data management, analysis and study coordination

PATH	Mr Mike Ruffo	TIMCI project director	Oversight & overall responsibility for TIMCI
	Ms Mira Emmanuel-Fabula	TIMCI Project Manager	Global Project Management
	Dr. Helen Storey	Senior Research Officer	Lead research PATH on Output 2
	Dr. Manjari Quintanar Solares	Senior Program Officer	Training Lead
	Ms Tara Herrick	Senior Market Analytics Officer	Cost-Effectiveness Lead
	Mr Zachary Clemence	Market dynamics Senior Associate	Implementation development
	Ms Tanya Lalwani	Senior Monitoring Evaluation and Learning Officer	Monitoring & Evaluation Lead
	Dr. Kovid Sharma	PATH-India	TIMCI Country Lead
	Dr. Kanishk Gupta	PATH-India	TIMCI Program Officer
	Dr. Amos Mugisha	PATH-Tanzania	PATH-Tanzania Country Representative
	Dr. Deusdedit Mjungu	PATH-Tanzania	TIMCI Country Lead

2.4.2 Project governance

The TIMCI project has several different working groups for governance of implementation and research activities, described in Tab. 3 below. As shown in Fig. 2, the research governance for the RCT is shared with the longitudinal observational study (conducted in Kenyaand Senegal) through a Research Steering Committee (RSC). The RSC is chaired by an independent expert, and will include two sub-groups, which act as management groups, one for the RCT and one for the longitudinal observational study. The Management groups will facilitate the day-to-day running of the RCT and escalate issues to the RSC. Thematic Working Groups will consist of thematic experts from all study countries. An independent Data Monitoring Committee (DMC) will be established for the RCT.

Tab. 3. TIMCI project and research governance

Project Governance		
Group	Membership	Function
International Advisory Group	Unitaid*, ALIMA, WHO, UNICEF, USAID, experts in paediatrics and IMCI, CHAI *Unitaid is an observer in this group	Strategy and guidance focused; shared with ALIMA – recipient of parallel UNITAID award
Country Implementation Working Groups	PATH in-country project lead, leaders of Swiss TPH and research/implementation partners for research activities, key implementation and/or management staff, MOH representatives	Project management focused at country level; ensures close country-level collaboration across multiple organizations and implementation partners; important link to MOH.
Global Implementation Team	PATH country- and HQ-based leadership, Swiss TPH, Country Implementation Working Group leaders	Pan-country strategic and management function; forum to build relationships between countries, share learnings, and ensure alignment.

Consortium Executive Board	PATH and Swiss TPH executive-level leaders, Program Director, Senior Project Manager	Strategic advisory and dispute-resolution committee for PATH and Swiss TPH.
Country-Level Technical Working Groups	Depends upon country; link with most applicable existing group, such as a child health TWGs. Key influencers with MOH, policy, operations	Existing working groups that will provide essential review and oversight in each country; builds and maintains linkages with country operators.
Manufacturers Advisory Group	Influential organizations involved with product development for pulse oximetry, multimodal devices, O2, and possibly clinical or procurement functions	Inform development of TPP, design manufacturer incentive programs, and ensure alignment with market forces.
Research Governance		
Research Steering Committee	Independent external chair, with representation from Swiss TPH, and research parners	Regular review of research progress in all four countries with particular focus on trial and longitudinal study
Subgroup one: RCT management group	Swiss TPH, KGMU, IHI	Internal working group for management of RCT study activities
Subgroup two: LS management group	Swiss TPH, UoN, UCAD	Internal working group for management of LS study activities
Data Monitoring Committee	Independent Chair, Clinician and Biostatistician with relevant experience	Monitoring of the RCT conduct
Thematic Working Groups	Thematic experts Swiss TPH, BI, UoN, UCAD, and IHI, KGMU	Exchange on content-specific topics across all research partners

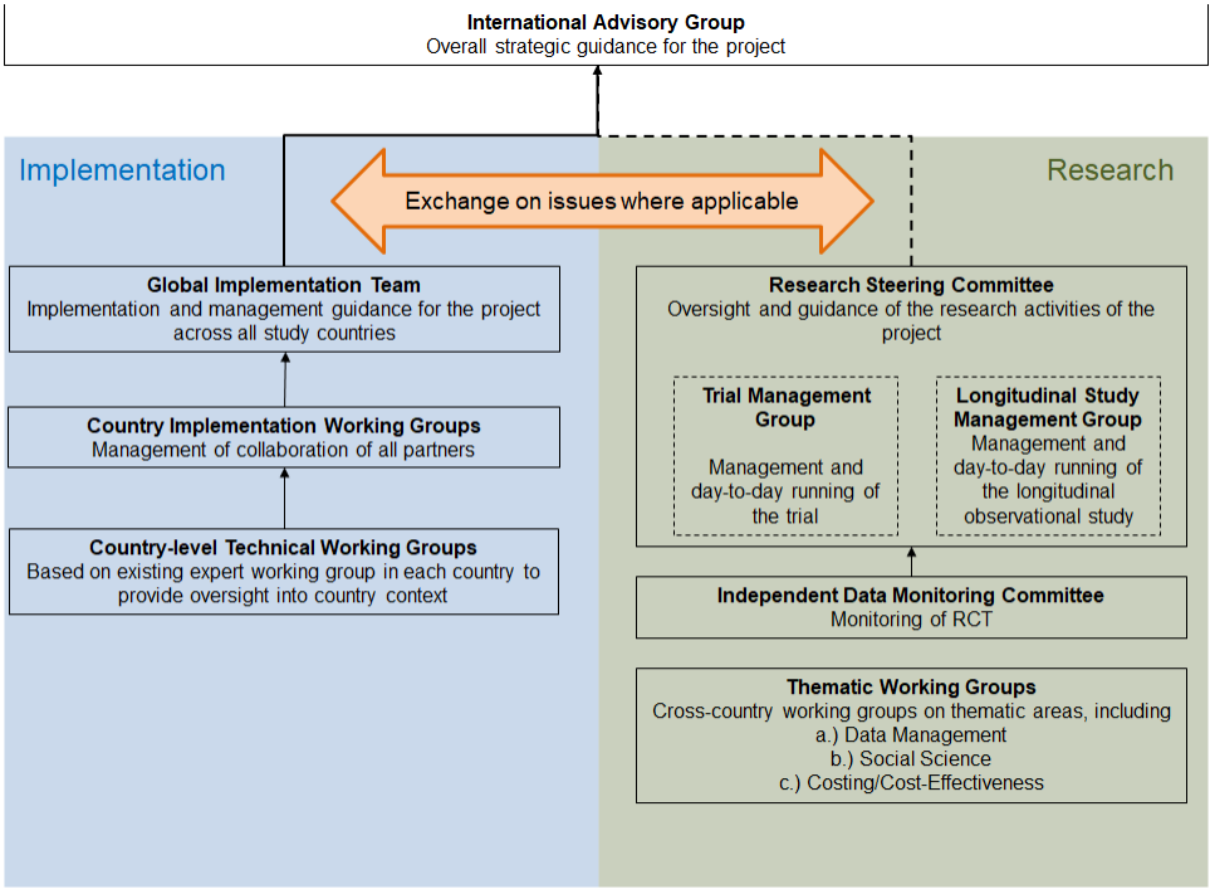


Fig. 2. TIMCI governance overview

3 Background & rationale

Despite progress in reducing child mortality in the last few decades, an estimated 5.3 million children under five years of age died of preventable causes in 2018.[1] If we are to achieve the Sustainable Development Goal 3.2 by 2030, all countries must reduce under-five mortality to at least as low as 25 per 1,000 live births and neonatal mortality to at least as low as 12 per 1,000 live births.[2] Strengthening systems to identify and appropriately treat sick children, alongside health prevention and promotion activities, is critical to achieving this goal.

The Integrated Management of Childhood Illness (IMCI) guidelines, launched in 1995 and now adopted by over 100 countries, responded to the need to systematise the implementation of evidence-based health interventions for children under five in primary care and the community.[3] The case management component provides a simple, structured approach to assessment, classification and treatment of the sick child, with a particular focus on severe illness.[4]

Yet despite the intention of IMCI to have high sensitivity for detection of severe disease, many studies have demonstrated poor identification and management of severely ill children due to both non-adherence by health workers[5–9] and intrinsic problems of guidelines based on clinical signs alone[10–14]. The Tools for the Integrated Management of Childhood Illness (TIMCI) project seeks to address these issues by introducing clinical decision support algorithms (CDSAs) and pulse oximetry to strengthen guideline implementation and accuracy in order to improve quality of care and reduce morbidity & mortality.

3.1 Rationale for pulse oximetry

Hypoxaemia, a reduction in blood oxygenation, has a myriad of causes in children – both respiratory and non-respiratory, but regardless of the cause, is strongly associated with mortality.[15] A meta-analysis of 13 studies on 13,928 children found a 5.5 fold increased risk of death among children with acute lower respiratory infection (ALRI) with oxygen saturation (SpO2) below 90%.[15] The association of hypoxaemia with mortality in non-respiratory conditions is less extensively documented, but a recent large study in Nigeria found adjusted odds of death in hypoxaemic children to be 7.1 in ALRI, and range from 5.9 to 6.6 in the next most common causes of hypoxaemia (malaria, acute febrile encephalopathy, sepsis, seizures).[16]

The prevalence of hypoxaemia is estimated to be around 13% among children with WHO defined suspected pneumonia.[17] Prevalence is also high among sick neonates (18 – 23%), malaria (3 – 17%), meningitis (3 – 15%) and malnutrition (2 – 8%).ibid Studies have further demonstrated the importance of hypoxaemia in children with asthma, sepsis, malaria, sickle cell disease, tetanus and a variety of neonatal illnesses.[16,18–22] However, the relative contribution of different diseases to the burden of hypoxaemia is highly variable in different settings[17], and likely to reflect the local burden of disease. For example, in the aforementioned study of 23,926 hospitalised children in Nigeria, among all children (28 days – 14 years) with hypoxaemia, 37% had ALRI, 33% malaria, 32% acute febrile encephalopathy, 27% sepsis and 18% seizures. In

countries facing a lower burden of malaria, such as India (2.2% of under 5 deaths are attributed to malaria, compared to 13.2% in Nigeria), whilst systematic data on hypoxaemia burden is not available, this distribution is likely to be different.[23]

Given the prevalence of hypoxaemia and its role in mortality, a number of studies have sought to evaluate the predictive power of clinical signs to detect hypoxaemia and guide oxygen therapy. But no single sign or combination of signs has reliably been found to detect hypoxaemia with adequate sensitivity or specificity.[24] Using clinical signs alone thus leads to a failure to identify all children who need oxygen and unnecessary administration of oxygen (which is often in scarce supply) for children who do not need it.[24]

Pulse oximeters provide a non-invasive, accurate and easy to use method of evaluating hypoxaemia. A number of observational studies at hospital level have shown significant reductions in child mortality, referrals and triage time following the introduction of pulse oximetry and associated interventions.[13,25,26] Furthermore, a recent modelling study estimated that implementing pulse oximetry could avert up to 148,000 deaths per year of children under-5 in fifteen high-burden pneumonia countries, far more than the potential deaths averted by IMCI alone.[27] In addition to the potential impact on child morbidity and mortality, there are potential resource savings through the reduction in unnecessary oxygen use – up to two thirds of children eligible for oxygen based on WHO criteria are not hypoxic.[14]

Whilst most data and guidance relating to pulse oximetry pertains to hospital settings, there is emerging evidence on the benefit in primary care. In Malawi, provision of pulse oximetry to rural health centres and community health workers resulted in increased referral rates among children with WHO-defined severe pneumonia. They also found that pulse oximetry enabled the identification of hypoxaemic children who otherwise would have been categorised as having non-severe pneumonia.[13] Whilst their study was implemented before the 2014 modification to WHO IMCI guidelines, retrospectively applying the criteria to their dataset revealed that 69% of hypoxaemic children would not have been categorised as requiring referral. Pulse oximetry therefore provides the opportunity to improve the sensitivity of IMCI guidelines for severe disease. Implementation of pulse oximetry could also be a strategy to rule-out severe disease and therefore reduce unnecessary hospital referrals and admissions, though the exact oxygen saturation cut-off requires further validation.[28]

This potential to improve the detection and referral of children with severe disease has led to strengthened interest in the potential to rollout pulse oximetry to primary care. However, before significant investment is made in this area, it is critical to understand what health impact pulse oximetry has, for which children in which contexts, and with what consequences – such as over-referral to already stretched hospital resources. Impact is likely to depend on a number of factors, including burden of hypoxaemia in primary care, choice of criteria for pulse oximetry use (to optimise detection of hypoxaemic children whilst avoiding false positives and over-burdening clinic staff) and pre-existing quality of care.

3.2 Rationale for clinical decision support algorithm

Whilst the introduction of pulse oximetry can improve the identification of sick children in primary care, it does not provide a comprehensive approach to improve adherence to evidence-based guidelines. Observational studies have indicated that IMCI-trained healthcare providers only correctly classify children according to IMCI guidelines 33 – 87% of the time.[5] This lack of correct classification likely stems from incomplete assessments. Pooled data from the Service Provision Assessment surveys in Namibia, Kenya, Tanzania and Uganda found health workers conducted a complete danger signs assessment in less than 33% of 6856 children assessed.[6] In Malawi, fewer than 1% of children had an assessment including all 16 elements of the history and examination.[9] In the same study, respiratory rate was only checked in 16% of children presenting with cough or difficulty breathing.

Failure to assess key signs can result in under-classification of severity and inadequate management of children with severe disease, leading to a higher mortality risk. For example, in the above study in Malawi, clinical officers did not refer 41% of children with severe / very severe pneumonia, and requested oxygen for only 23% of those that met criteria.[9] Similarly, in a study in South Africa, only 47% of children with severe disease were correctly identified by a health worker.[7]

Even when health workers do recognise severe disease, they do not necessarily treat and refer according to guidelines. In a study in Tanzania, only 38% of children with severe disease were referred by IMCI-trained health workers, despite 95% having been recognised as having severe pneumonia, severe malaria or both.[8] The authors surveyed health workers and found that 91% believed that referral was not a necessary component of management for certain severe conditions.

Electronic clinical decision support algorithms (CDSAs) provide an electronic step-by-step guide through a clinical consultation for healthcare providers, supporting the integrated disease management approach promoted by WHO. Recent studies of two such tools, based on IMCI and national guidelines, have demonstrated potential for significant improvements in health outcomes and large reductions in unnecessary antimicrobial prescribing.[29,30] The use of one such tool by healthcare providers in consultations for all acutely unwell children was found to improve cure rate at day 7 (97% compared to 92% in routine care) whilst reducing antibiotic prescriptions from 84% to 15%.[29] Another tool, ePOCT, used for children with fever and integrating point of care diagnostic tests, reduced clinical failure rate to 2% (compared to 5% in routine care) and antibiotic prescriptions to 11% (from 95%).[31]

The mechanisms by which CDSAs impact health worker practice may stem from the fact that the electronic algorithms, by design, provide support in decision making for any combination of clinical findings, whereas paper-based IMCI or national guidelines are, by necessity, reductionist.[10] In a mixed-methods exploration of the reasons for non-adherence to IMCI guidelines by health workers, Lange and colleagues described "cognitive overload" as a contributory factor to non-adherence.[32] In such circumstances, support to the complex clinical

decision making process with CDSAs can facilitate health workers to provide higher quality care. This is likely to be particularly true in the case of introducing novel technology such as pulse oximetry, which adds an additional level of complexity to the integrated clinical assessment of children.

Implementing pulse oximetry embedded into a CDSA has the potential to improve the detection of children with severe disease and improve the adherence of healthcare providers to evidence-based, integrated disease management guidelines. We hypothesise that these interventions will result in a reduction in adverse health outcomes through better treatment and referral decisions, and an improvement in quality of care through the rational use of essential medicines and improvements in the health worker and caregiver experience.

3.3 The TIMCI project

The Tools for Integrated Management of Childhood Illness (TIMCI) project builds on this hypothesis to form part of the response to the need for better mechanisms to detect and manage children with severe illness in LMICs. It is a 4 year UNITAID-funded project, focused on the interventions of pulse oximetry and CDSAs in primary care, organised into four main outputs: (1) introduction of pulse oximetry and CDSAs in four countries (India, Kenya, Senegal and Tanzania); (2) evidence generation for pulse oximetry and CDSA introduction; (3) market strengthening for adapted multi-modal devices; and (4) creating conditions for national and global scale-up and sustainable use of these tools.

This protocol focuses on the evidence generation component of the TIMCI project in India and Tanzania (a separate protocol has been developed for Kenyaand Senegal to reflect a different study design).

To our knowledge, no large scale studies have systematically evaluated the health impact, cost-effectiveness and optimal implementation approaches of pulse oximetry, alone or embedded into a CDSA, for children with a broad range of clinical diagnoses in primary care.

4 Goal & objectives

The overall goal of the TIMCI project is to reduce morbidity and mortality in sick children attending primary care facilities, while supporting the rational and efficient use of diagnostics and medicines by healthcare providers. The evaluation component of the project seeks to generate evidence on the health impact, operational priorities, cost and cost-effectiveness of introducing pulse oximetry, alone or embedded into a CDSA, into primary care in LMICs, for children 0 – 59 months of age, to facilitate national and international decision-making on scale-up. Specific objectives, according to these themes, include:

Health and quality of care impact

To evaluate the impact on health and quality of care outcomes of sick children 0 – 59 months of age of introducing pulse oximetry, alone or embedded into a CDSA, for facility-based primary care, compared to routine care, including on:

- Mortality and hospitalisations
- Adherence by primary healthcare providers to key components of assessment, classification and management guidelines, in particular on referral decision-making and antimicrobial prescription

To assess severe, moderate and mild hypoxaemia prevalence among sick children attending intervention primary care facilities, and understand the association of different hypoxaemia cut-offs with adverse outcomes, according to sociodemographic and clinical features.

Implementation and process

- To understand the facilitators and barriers to uptake, acceptability of the intervention and behaviour change by health care providers, caregivers and their children, and a variety of stakeholders at community, health facility, national and international levels
- To evaluate characteristics of children, caregivers, healthcare providers and health facilities associated with uptake and impact of the interventions
- To understand how the interventions affect patient flow and patient-provider interactions, including change in care processes, consultation time, and communication between caregivers and healthcare providers

Cost and cost-effectiveness

- To determine the cost and estimate any cost savings and/or additional costs of introducing pulse oximetry with or without CDSAs into primary care in four countries
- To estimate cost effectiveness of the interventions compared to routine care and other interventions aimed at improving the management of severe illness in children 0 – 59 months of age

5 Study design

Health and quality of care impact are evaluated through pragmatic, parallel group, cluster randomised controlled superiority trials in India and Tanzania, and quasi-experimental pre-post studies in Kenya and Senegal.

In the pragmatic cluster randomised controlled trial (RCT), primary care facilities (clusters) are randomly allocated (1:1) to pulse oximetry or control in India, and (1:1:1) to pulse oximetry plus CDSA, pulse oximetry, or control in Tanzania.This assessment of the health impact of the intervention will be complemented by embedded mixed methods sub-studies in both countries to evaluate other key components of quality of care[33] and gain a deeper understanding of the implementation mechanisms and context. These studies include modified Service Provision Assessments (SPAs), a facility-based process mapping and time-flow study, qualitative studies with caregivers, healthcare providers and key stakeholders, a regular survey sent to selected key stakeholders, a desk-based project document and monitoring and evaluation (M&E) review, and an economic evaluation (Fig. 3, Tab. 8). Data from the mixed-method studies will be triangulated in order to generate in-depth insights into implementation.

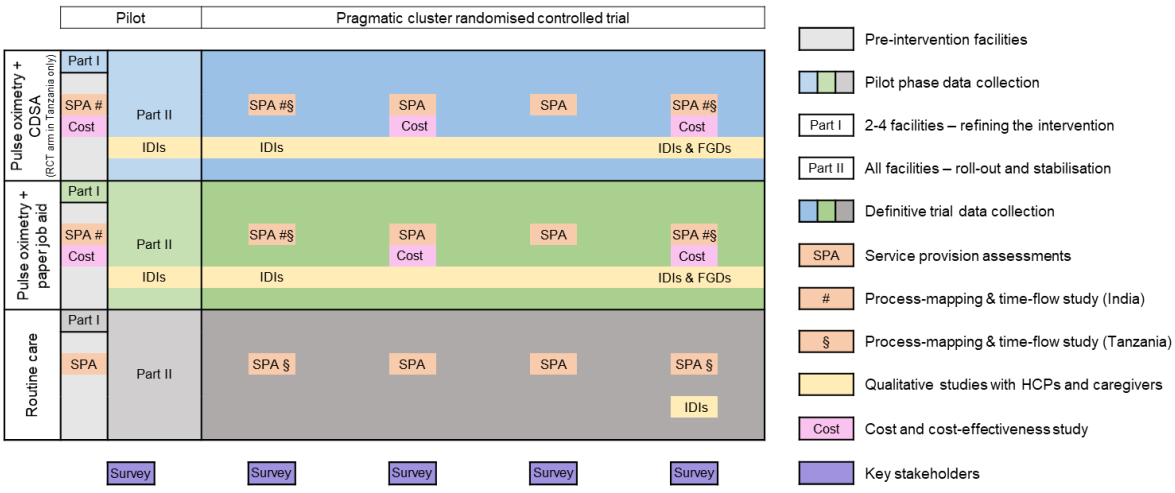


Fig. 3: Timeline of pragmatic cluster randomised control trial with pilot phase and embedded mixed methods studies. **Pre-intervention facilities**: trial dataset, SPA and process-mapping and time-flow study collected as a baseline. **Pilot Part I** – 2 to 4 facilities per arm, over 4 to 6 weeks, to refine the intervention. Trial dataset, SPA, process-mapping and time-flow, and caregiver IDIs and HCP IDIs collected. **Pilot Part II** – roll-out of the intervention to all study facilities to allow stabilisation (familiarisation with devices by HCPs) over 6 – 8 weeks prior to study start. **Definitive trial –** expected to last 12 months to capture seasonal disease burden variation and changes in implementation / impact over time. **SPAs** – cross-sectional quarterly assessments in 6 facilities per arm comprising of observations of consultations of sick children, exit interviews with caregivers, interviews with HCPs and facility

assessments. **Process-mapping and time-flow study** – during baseline, early and late implementation (intervention arms only). **Qualitative studies with caregivers and with HCPs** – during pilot phase I (IDIs only) and across the implementation period to understand change over time. In Tanzania, IDIs will also take place in the pre-intervention phase, and in the control arm. **Key stakeholders** – KIIs during baseline / pilot, early and late implementation; and quarterly surveys. **Cost and cost-effectiveness**: cost data will be collected prior to intervention and on start-up costs, and again during implementation with final data collection to capture any missing information. Abbreviations: **SPA** – service provision assessments; **IDIs** – in-depth interviews; **FGDs** – focus group discussions; **KIIs** – key informant interviews; **HCPs** – healthcare providers

This mixed methods design draws on principles of realist evaluation (focusing on processes, and mechanisms in their respective contexts leading to outcomes)[34], the MRC guidance on Process Evaluation for Complex Interventions[35], the Theoretical Framework of Acceptability of Health Care Interventions[36], and the COM-B model of behaviour change[37]. It is further informed by the project's Theory of Change (ToC, Appendix), developed in line with the approach taken by de Silva and colleagues[38] and the Centre for Theory of Change[39]. The ToC components will be tested and revised to incorporate unanticipated pathways and assumptions and provide feedback to strengthen the intervention.

5.1 Pilot phase

The pilot phase will occur over an estimated 3-month period prior to the start of the definitive pragmatic cluster RCT. It will serve to ensure the intervention package is optimised (Part I) before roll-out to all study facilities, allow for stabilisation of the intervention (Part II) and for piloting of the research instruments and processes. It will also allow certain mixed methods sub-studies to be conducted in the intervention arms prior to intervention start, to allow for comparison within the same facilities over time.

The RCT dataset collected during this pilot phase will be used for exploratory analysis of early implementation, but will not be included in the definitive RCT analysis. Mixed methods study data collected during this phase will be incorporated into the overall analysis to facilitate the understanding of the implementation processes, mechanisms and context in order to inform the development of the package for scale.

Part I – refining the intervention and piloting research processes

We will select 2 – 4 facilities per trial arm to tailor the introduction of the intervention, based on qualitative feedback from healthcare providers and caregivers (in-depth interviews, informal discussions) and key stakeholders (key informant interviews), combined with observation of the way in which pulse oximetry and CDSAs are used (from SPA observation and exit interviews, process mapping and time-flow, and training assessments conducted by PATH). These studies, further detailed in study-specific sections below, will aid understanding of implementation processes with a focus on acceptability, and barriers and facilitators to implementation to inform potential refinement of the approach to training, supervision, caregiver engagement and guidance on where to use the devices within the care process.

In addition, we will conduct a pre-intervention (baseline) assessment in a sample of study facilities in each arm, in which we will collect the RCT dataset, SPA assessments and facility-based process mapping and time-flow study to allow for comparison within the same facilities over time.

Concurrently, we will pilot the research instruments and processes and refine if necessary, including eligibility screening, participant information and consent, and data collection tools.

We estimate this phase will take 4 – 6 weeks, but will extend if more major adjustments are necessary (to intervention package, or to the protocol).

Part II – rolling-out the intervention and refining participant recruitment and follow-up procedures

Once the intervention package is refined and finalised, devices will be introduced into all the intervention facilities to enable a period of stabilisation of the intervention prior to start of the definitive trial (to allow healthcare providers to become familiarised with the intervention). The same dataset will be collected during this period, but set aside for exploratory analysis rather than included in the definitive trial analysis.

During this stabilisation phase, we will also assess rates across facilities for eligibility, recruitment, loss to follow-up and healthcare provider capacity to use pulse oximetry and CDSAs, to identify and mitigate any major challenges prior to the definitive trial start. We estimate that this phase will take 6 – 8 weeks, but will extend if adjustments are needed in order to reduce the risk of major challenges to efficiency or internal validity in the definitive trial.

5.2 Pragmatic cluster randomised controlled trial

We will conduct a pragmatic, three-arm 1:1:1 parallel group, cluster randomised controlled superiority trial in Tanzania over a 12-month period. Following the pilot in India, a decision was taken to remove one of the intervention arms, and conduct a two-arm 1:1 parallel group, cluster randomised trial in India. Cluster unit is the facility providing primary care services, with randomisation to one of the following groups:

- Pulse oximetry plus CDSA (Tanzania only)
- Pulse oximetry with paper job aid based on IMCI (or national guidelines) incorporating pulse oximetry
- Control (routine care, with refresher training)

Sick children 0 – 59 months of age will be managed by healthcare providers according to which intervention the facility they attend have been assigned (see 6.3 for further detail).

As the intervention targets healthcare provider practice, we have opted for a cluster design at the facility level to: avoid contamination that would occur if randomisation occurred at the

individual level; avoid introducing different processes within one facility; and enable evaluation of effectiveness in real-world settings.

5.3 Service provision assessment

This periodic assessment of service delivery will follow the approach of the Demographic and Health Surveys (DHS) Program Service Provision Assessment (SPA) (facility assessment, healthcare provider interview, sick child observation protocol and caregiver interview),[40–42] modified to focus on child health, pulse oximetry and CDSA use and incorporate additional quantitative and qualitative questions covering factors associated with child mortality and health-seeking behaviour, as well as patient-centred outcomes including experience of care.

We will conduct cross-sectional surveys at a stratified sample of facilities at baseline and quarterly over the following year of implementation in order to assess differences over time and with varying burden of disease in different seasons. We will also conduct the SPA at the pilot phase part I facilities to inform intervention refinement. Stratification is based on study arm, rural / urban location and facility type. On the days of the surveys, we will conduct an abbreviated facility assessment, administer a questionnaire to all providers consulting children under five, and the modified 'sick child' observation and exit interview on all eligible children attending the facility.

5.4 Facility-based process mapping and time-flow study

Prior to intervention, we will develop a basic process map defining the common steps in the care pathway of sick children in primary care facilities in each country (adapted to facility type). The map will be reviewed and refined through informal discussions with staff and non-participant observation at a sample of intervention arm facilities prior to intervention (including discussion on whether specific processes have been introduced or changed as a result of COVID-19). Time-flow data will be captured for discrete steps in the care process through observation of a sample of children attending the facility, from arrival through to consultation (including on use of the devices), to departure from the facility. Non-participant observation will focus on understanding rationale for care processes and when and why deviation from the standard pathway may occur.

This 'pre-intervention' map will then be adapted to incorporate pulse oximetry and CDSAs through discussions with staff and observations in the pilot phase part I facilities to understand the impact of the intervention on care processes (including on time) and on patient-provider interactions, and inform refinement of the intervention strategy if necessary.

After roll-out of the intervention, this will be repeated both early and late in the intervention (intervention and control arms) to understand changes in care processes and time with the refined intervention package, and adaptations that may have occurred as a result of provider preferences (or as a result of other changes to care processes external to the TIMCI project). This will generate information on whether the intervention has been normalised into care

processes over the longer-term in order to understand sustainability and inform the package for scale. Time-flow data will also be used in the cost and modelled cost-effectiveness study.

5.5 Healthcare providers' acceptability and perceptions of the intervention

We will conduct semi-structured in-depth interviews (IDIs) and possibly focus group discussions (FGDs) with a purposive sample of healthcare providers working in intervention facilities. IDIs (and informal group discussions where required) will be conducted during the pilot phase to inform intervention refinement. IDIs and possibly FGDs will be conducted over the course of the intervention to understand changes in perception of the intervention over time and reasons for early and late adoption. In Tanzania only, IDIs will also take place pre-intervention, and during the late intervention period in the control arm for comparison. Focus group discussions will be based around clinical vignettes to facilitate discussion of experiences with the devices (including usability, practicality and design) and on quality of care and acceptability of tools without causing unwanted disclosure, or bias due to self-stigmatization or self-censorship. In-depth interviews, which may include vignettes, will focus particularly on the individual experience with the introduction of the intervention and over time; the acceptability of the intervention; mechanisms, processes and contexts leading to behaviour change and identifying barriers and facilitators for intervention success.

5.6 Caregiver perceptions of the intervention and health-seeking behaviour

Semi-structured in-depth interviews (IDIs), and possibly focus group discussions (FGDs) will be conducted with a purposive sample of caregivers who have attended study facilities. IDIs and possibly FGDs will be carried out at the household and respective community level.

IDIs (and informal group discussions where required) will be carried out during the pilot phase to inform intervention refinement. IDIs, and possibly FGDs will be conducted with caregivers attending intervention facilities over the course of the implementation period to understand changes in perception of the intervention over time and behaviour change, as well as reasons for loss to follow-up among caregivers who will miss their Day 7 follow-up (Tanzania only). IDIs will also take place during early and the late intervention period and possibly in the control arm for comparison during the late intervention. The IDIs and possibly FGDs will focus on aspects of the quality of care and acceptability frameworks, as well as health-seeking behaviour and decision making, incorporating a realist approach.

Participants with a particularly interesting or divergent view in focus group discussions with health care providers or caregivers might be approached for follow-up IDIs.

Additionally, a rapid qualitative inquiry among caregivers lost to follow-up (LTFU) will be conducted. This includes IDIs with a selected caregiver who could not be reached during Day

7 follow-ups so as to understand reasons, caregivers' perceptions and challenges associated with loss to follow-up, allowing to develop context-specific solutions.

Qualitative data collection is exploratory in nature; time points in data collection are preliminary. Final time points will depend on the preliminary analysis of qualitative data and findings throughout the data collection. Therefore the studies planned may require a closer follow-up or data collection at additional time points (e.g. mid phase of the intervention).

5.7 Stakeholder perceptions and project data review

This will incorporate key-informant interviews (KIIs) with selected stakeholders at global, national, subnational and local level with perspectives on implementation, policy and research. Stakeholders will include those internal (i.e. project stakeholders; e.g. PATH) and external (i.e. non-project stakeholders, e.g. Ministry of Health, community, other organisations) to the project, either directly involved in implementation or affected by implementation. This includes, but may not be limited to: selected International Advisory Group members, Unitaid and WHO representatives, PATH headquarters staff, national policy makers, members of district health management teams, health facility managers, community leaders, national and local PATH implementation staff, and research staff. The KIIs will be conducted during the pilot phase, to understand the start of implementation, and during late intervention, to gain reflections into implementation over time to inform a package for scale. In Tanzania only, KIIs will also be conducted prior to intervention, and local key stakeholders may be included late in the control arm for comparison.

These interviews will be complemented by quarterly electronic surveys of selected project informants and a structured review of key documents including PATH project reports, (including on changes as a result of COVID-19), minutes and M&E data (e.g. on training evaluation or maintenance and replacement of devices) for each country. It will primarily focus on the processes, mechanisms and context (i.e. MRC process evaluation criteria) of implementation including adaptations made.

In each country, PATH project data, along with routine Health Management Information Systems (HMIS) data will be assessed for all facilities and administrative regions where the project is running to draw inferences on the impact of the intervention on indicators used for routine monitoring by Ministries of Health, and their potential for longer term use.

5.8 Cost and cost-effectiveness study

The economic evaluation will involve a cost and cost-effectiveness analysis using direct health system costs in which financial and economic costs will be assessed. The scope of the costing will cover only intervention costs and not research-based costs, and will include costs incurred by the health system as well as estimated direct costs paid out of pocket by the households to the health system. It is important to note that this cost methodology is not comprehensive. It does not include the indirect costs incurred by the consumer (patient) e.g. the caregiver's time

or transport costs. Rather, it focuses exclusively on the provider's direct costs, whether borne by the health system or paid out of pocket by the patient's household.

The approach that has been taken in applying this methodology has been to capture what is thought to be the "most likely" cost scenario, on average. In identifying this "most likely" cost scenario, effort will be made to supplement the analysis with a discussion about factors that influence the level of costs (e.g. the number of trainees per training, or the frequency of supervision) so as to provide a type of sensitivity analysis of the robustness of the estimates. Cost scenarios will also guide possible future programme scale up. The cost resources for each cost centre might differ between India and Tanzania. For instance, at some facilities laboratory tests or some treatments may not be available, and patients have to be referred elsewhere: we will have to take account of these differences.

Research-based costs are excluded to enable the costing to provide guidance on future replication and potential scale up of the intervention. Full and incremental costing involving an activity-based and ingredient-based approach will be used. When available, effectiveness data will be combined with the cost data and cost per DALY averted will be estimated as outlined in 8.3.3. The costing and cost-effectiveness will use a 12-month time frame and a 3% discount rate. Where applicable, discount rates will be adjusted to prevailing rates at country-level.

6 Participants, interventions, and outcomes

6.1 Study setting

Whilst the study is taking place in diverse health systems and communities in Africa and Asia, the common feature is the focus on facility-based primary care. Caregivers often attend a diverse range of facilities to meet their primary care needs. The study setting therefore includes any facilities providing primary care services, including outpatient settings within larger health centres in addition to the more traditionally-labelled primary care facilities.

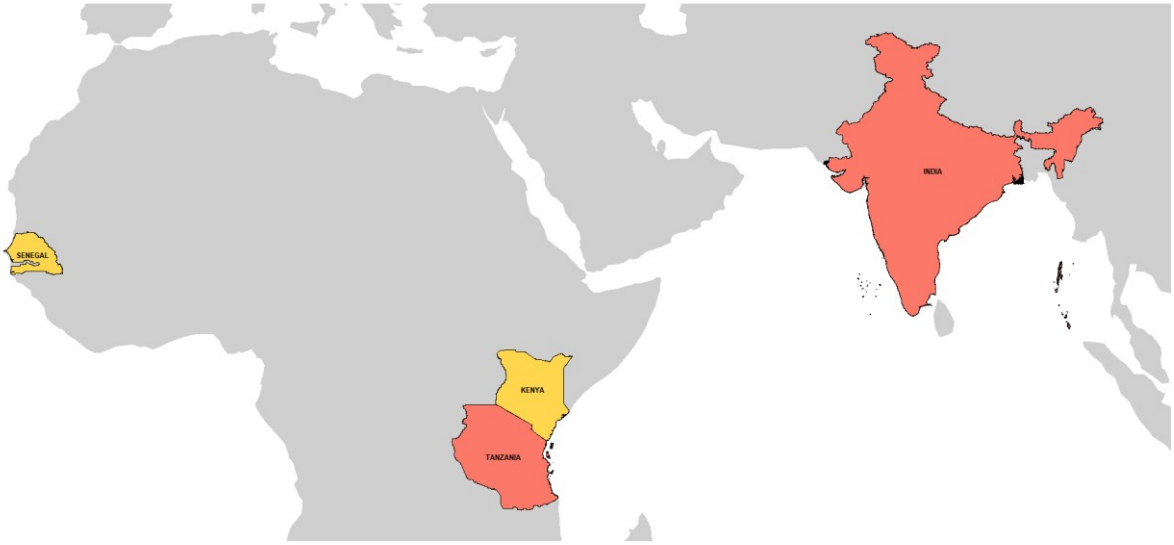


Fig. 4. Map overview of the countries involved in TIMCI. Countries conducting the pragmatic cluster RCT (India and Tanzania) are displayed in red, while countries that are involved in the longitudinal observational study (Kenyaand Senegal) are displayed in yellow.

6.1.1 India

Setting

Three districts of Uttar Pradesh (Unnao, Sitapur, and Deoria). Under-5 mortality rate 46/1000 live births[43]

Facilities

Primary healthcare centres (PHCs) and **community health centres** (CHCs)

Services

PHCs provide outpatient only consultations for 6 – 8 hours per day, Monday to Friday.

CHCs provide outpatient consultations and have capacity to admit children for observation and management in a separate part of the facility. They are open from 8am to 2pm (including 2 Saturdays per month). Emergency services are available 24 hours a day, 7 days a week.

Staffing

Both PHCs and CHCs are staffed with non-specialist doctors: PHCs usually have one doctor, while CHCs have 4 – 10 doctors, and may have MD doctors and/or a paediatrician.

Referral system

Both PHCs and CHCs have normally access to free ambulance services for referral of children for a higher-level of care, but this is subject to availability in the area.

O_2 availability

All CHCs have cylinder-based oxygen. Oxygen is occasionally available at the PHC level. The availability of a 24x7 functional oxygen cylinder at a PHC will need to be confirmed after an initial assessment. Most ambulances also have an oxygen cylinder on board.

6.1.2 Tanzania

Setting

Three councils (Sengerema District Council in Mwanza region, Tanga City Council in Tanga region and Kaliua in Tabora region)

Tanzania under-5 mortality rate: 53 / 1000 live births[44]

Facilities

Dispensaries and **health centres (HCs)**

Services

Dispensaries offer services such as immunization, family planning, antenatal care, treatment of common diseases, treatment and management of tuberculosis, and HIV/AIDS counselling among curative and preventive services. Although they provide services to outpatients, a few dispensaries may also have a ward for observation. HCs offer similar services to dispensaries with the addition of 24-hour maternity service, emergency care, and casualty admissions in some centres.

Staffing

Both dispensaries and HCs are staffed with nurses and clinical officers. HCs may also have medical doctors

Referral system

Phone numbers for key people involved in the referral processes are registered and displayed in public places, but use varies by provider. Identified transport providers, such as boda bodas (motorbikes) and taxis, are a quick mode of transport to the referral hospital.

O_2 availability

Only HCs have cylinder-based oxygen.

6.2 Eligibility criteria

6.2.1 Pragmatic cluster RCT (including pilot)

Facility inclusion:

- Consenting government-designated healthcare facilities within the selected geographical areas of each country

- Providing curative primary care services for children 0 – 59 months of age
- Oxygen available or referral mechanism in place with oxygen available at a higher level facility
- Electricity available (from any source with continuous or intermittent supply)

Facility exclusion:

- Attending to fewer than 20 sick children per month (based on the prior 12 month average)
- Already using pulse oximetry as a routine part of outpatient-based consultations of children 0 – 59 months
- Selected to be part of a major child health programmatic or research intervention during the study period likely to significantly affect the primary outcome
- Inaccessible to the study team (e.g. due to weather conditions or security issues) for significant parts of the year.

Individual child inclusion:

- Children 0 – 59 months for whom caregivers provide consent
- Consulting for an illness, or reported to be unwell when attending for a routine visit (e.g. vaccination, growth or chronic disease monitoring)

Individual child exclusion:

- Children in the immediate post-natal period or first day of life
- Attending for a consultation related to trauma only (including new and follow-up presentations for burns, injuries, wounds)
- Admitted within an inpatient part of the facility (including neonates delivered at the facility admitted with their mother)
- Enrolled in the study within the preceding 28 days at any study facility

6.2.2 Other mixed methods studies

Facilities for the remaining studies will be sampled from the pragmatic cluster RCT (including pilot and non-pilot) study facilities. A stratified sample of facilities will be selected for the SPA and process mapping and time flow study, with stratification factors including study arm (all arms for SPA, intervention arm and control arm only for process mapping and time-flow), location (rural/urban in Tanzania, district in India) and type of health facility (if applicable, regional differences may also be taken into account). Sub-samples for qualitative studies with healthcare providers and caregivers will be sampled from SPA facilities in the intervention arms to allow for triangulation of data between studies, but may also be sampled from non-SPA facilities and control arm facilities to avoid research fatigue or amplification of the Hawthorne effect.

Individual children and caregivers will be eligible for inclusion in the SPA observed consultation and exit interviews if they are eligible for the RCT and attend a study facility selected for the SPA during a period when it is being conducted (5 time points, for 3 – 10 days as outlined in 6.6.2). Caregivers will be eligible for inclusion in IDIs and FGDs if their child has been enrolled in the RCT. Individual healthcare providers will be eligible for the SPA interview if they are present on the day(s) of assessment and are involved in the care of children 0 – 59 months at that facility. Healthcare providers for IDIs and FGDs will be eligible if they provide care for children 0 – 59 months at any study facility.

Individual stakeholder eligibility: policy, implementation or research stakeholders at a national or international level with expertise in child health and / or the devices introduced; local and sub-national stakeholders either internal or external to the project, directly involved in any aspect of implementation or affected by the intervention.

6.2.3 Cost and cost-effectiveness study

Medical and non-medical personnel from study facilities and the government-designated hospitals to which they refer will be approached for costing data as described in section 6.6.3.

6.3 Interventions

The interventions included in the TIMCI project will be implemented in facilities according to allocation arm:

- **Pulse oximetry plus CDSA (Tanzania only)**
    - Pulse oximeters, with guidance (integrated into CDSA), training and mentorship as detailed below
    - Tablet-based CDSAs, with guidance, training and mentorship as detailed below
    - Refresher training on latest national / IMCI guidelines integrated with pulse oximetry and CDSA training
- **Pulse oximetry with paper job aid**: training on pulse oximetry,
    - Pulse oximeters, with guidance (pulse oximetry specific job-aid, plus adapted IMCI chartbook), training and mentorship as detailed below
    - Refresher training on latest national / IMCI guidelines integrated with pulse oximetry training
- **Control (routine care)**
    - Refresher training on latest national / IMCI guidelines

Where possible, the interventions of both pulse oximetry (and CDSA in Tanzania) will be embedded into existing monitoring, supportive supervision and device maintenance systems.

Refresher training on IMCI / national guidelines, delivered by MOHs (supported by PATH if required), is incorporated into each arm to address the issue that many practicing healthcare providers will not have received recent training, particularly on recent guideline updates. This is provided in the routine care arm to control for the effect of training as part of the introduction of pulse oximetry, alone or embedded into a CDSA.

Community engagement, further described below, will complement the facility-based intervention in all arms, to promote health-seeking behaviour and compliance with referral advice.

Pulse oximetry

UNICEF-approved handheld pulse oximeters (Acare, AH-MX)[45] will be provided, along with a package of supplies that includes a carry case, spare set of rechargeable batteries, battery charger, and six reusable probes (two each of adult, paediatric and neonatal sizes). Handheld devices were selected as they are portable, and thus better suited for point-of-care use in PHC settings, and more affordable than benchtop devices. Handheld devices are also more appropriate for children and neonates than fingertip devices, which are typically not designed for these populations.

The criteria for pulse oximetry use, agreed with the International Advisory Group and Ministries of Health of Tanzania are:

- All children under 2 months of age
- Children 2 – 59 months of age presenting with cough / difficulty breathing
- Children 2 – 59 months of age with IMCI signs of moderate / severe disease (IMCI 'yellow' or 'red' classification)

These criteria aim to identify children with the highest likelihood of having hypoxaemia whilst avoid unnecessary referrals of children with a low likelihood of having hypoxaemia and a false positive result, as well as avoiding over-burdening healthcare providers or contributing to clinic delays.

Young infants represent a small proportion of all clinic attendees[46], but with a relatively high prevalence of hypoxaemia and risk of severe disease and mortality.[1,7,16] Children with cough or difficulty breathing represent around 40 – 70% of children attending primary care. Children with WHO-defined suspected pneumonia (around 15 – 30% of clinic attendees)[7,46,47] are more likely to be hypoxaemic than those with cough / cold, but respiratory rate, one of the key differentiating signs is often not measured.[16,47,48] All children with cough / difficulty breathing are therefore chosen to avoid missing children inappropriately classified as not having suspected pneumonia.

Lastly, children presenting with signs of moderate or severe disease are included to ensure detection of children with illnesses such as sepsis, meningitis, malaria, malnutrition, diarrhoea,

anaemia that may also present with hypoxaemia.[16,17] Children with mild disease – such as diarrhoea with no evidence of dehydration, fever with no evidence of malaria, meningitis / encephalitis, or complicated measles – are very unlikely to have hypoxaemia and pulse oximetry use will therefore not be advised in this group.

In certain circumstances, there may be a deviation from these criteria for operational reasons. Such circumstances will be agreed with local decision-makers, but, for example, may include the use of pulse oximetry during a triage step in large, high volume facilities. In such circumstances, preference may be given to using pulse oximetry on all sick children. In the event that this occurs, children found to have low oxygen saturation will be triaged for immediate assessment by a clinician, who may repeat the pulse oximetry measurement if needed.

In India, the Ministry of Health and Family Welfare opted to recommend be used in the assessment in all sick children under five years of age.

Healthcare providers will be advised to use a cut-off of SpO2 <90% for referral, in line with WHO guidance. The message to refer children with other signs will be reinforced. Different SpO2 cut-offs for referral for sites at high altitude will be finalised with the IAG and MoHs, given that the normal range for SpO2 varies with altitude, but this is unlikely to affect cut-offs below 2500m.[49]

Healthcare providers will be advised to only take one measurement for children with severe or moderate disease and will be advised not to attempt to obtain a reading for more than 5 minutes (most readings are obtainable within this time).[13,50,51] However, if a child with no other sign of moderate or severe disease (i.e. IMCI 'green' category) is found to have SpO2 <90% (or altitude-specific cut-off), healthcare providers will be advised to repeat the reading. In cases of conflicting readings (i.e. one <90% and one ≥90%, or altitude-specific cut-off), a third reading will be advised as confirmatory.

As the cluster unit is the facility, and more than one level of facility is included in both India and Tanzania, there is a possibility that an intervention lower-level facility (dispensary or PHC) would routinely refer to a non-intervention higher-level facility (health centre or CHC). In this circumstance, a child could be assessed and found to be hypoxaemic with pulse oximetry in a lower-level facility and then be referred to be seen in a facility where pulse oximetry is not routinely being used. To navigate this issue, staff at all lower-level facilities who find a child to be hypoxaemic will be advised that they should refer a child directly to hospital, and only refer to the inpatient / emergency area of a higher-level primary care facility (rather than their outpatient consultation area) if oxygen is available.

The above guidance will be incorporated into the CDSA (facilities in Arm 1) and a paper-based job aid and updated IMCI chartbook (facilities in Arm 2).

Clinical Decision Support Algorithm

In addition to pulse oximetry, healthcare providers in the pulse oximeter plus Clinical Decision Support Algorithm (CDSA) will be guided throughout their medical consultations by an algorithm called ePoct+ and developed by Swiss TPH in collaboration with Unisanté/Wavemind (Lausanne, Switzerland).

Healthcare providers will used ePoct+ for the assessment, diagnosis and management of all sick children 0 – 59 months of age (i.e. only excluding those coming for routine immunisation or monitoring visits and not reported to be unwell). In case a child comes back to the facility during the same disease episode, ePoct+ can be used to manage the child in the same way as during the baseline visit, as the algorithm takes into account duration of symptoms and previous treatments provided.

MedAL-R, the front-end application developed by Unisanté/Wavemind to implement ePoct+ is available for Android tablet or PC. The application can be deployed in health facilities in a standalone mode or a multi-device mode to facilitate the collaboration of several healthcare providers and storage of information in the patient's medical records. In the context of this study, MedAL-R will be deployed on tablets. The choice of a standalone / multi-device setting will depend on discussions with the country MoHs.

The clinical algorithm will be adapted to reflect national guidelines for the management of children 0-59 months of age in primary care. An expert group will be established and consulted in each country using a Delphi method approach and / or nominal group technique to validate the clinical algorithm.

The adaptation of ePoct+ will be done using MedAL-C, the back-end software developed by Unisanté/Wavemind to manage, reference, modify and deploy the different versions of the clinical algorithm into MedAL-R. Recommendations on use of additional point of care laboratory and diagnostic test use, such as malaria or haemoglobin, will be incorporated into the algorithm if routinely available at the targeted health facilities. Before the start of the study, ePoct+ will be reviewed and validated by national key experts in child health. MedAL-C allows an interactive visualization of the clinical algorithm and therefore clinicians without any IT programming skills can modify the decision trees to release a new version of the clinical algorithm. However, the clinical algorithm will not be updated for the duration of the study, except for technical reason (patches).

Training

PATH, with input from other collaborators, will develop the pulse oximetry and CDSA curricula, adapting existing materials (such as Lifebox training materials) to IMCI context using WHO and national guidelines, specifically including examples of pneumonia and possible serious bacterial infection. Materials will be pilot tested at PATH HQ, and the next iteration will be reviewed by the technical working group in each country. The feedback from countries will be incorporated into the final English version of the pulse oximetry training materials and job aids. Materials will then be translated into local languages as applicable and back translated to

ensure accuracy. Training materials and job aids will be printed and distributed to all TIMCI health facilities in draft form for the pilot phase and pending finalization after the pilot phase.

In collaboration with respective Ministries of Health (MOHs), PATH will conduct training of healthcare providers in the use of pulse oximetry and use of CDSA. To avoid creating a parallel program and improve sustainability, PATH will work with each MOH to integrate with existing training programs. Both India and Tanzania have updated their IMCI guidelines recently to include changes in pneumonia management and offering outpatient treatment of possible serious bacterial infection in young infants when referral is not feasible. As of March 2020, the MOH in both countries is planning, but has yet to conduct, trainings in these updates. Per WHO curricula, the trainings for these updates include clinical sessions with visits to health facilities to see real life patients, which is out of the scope of the TIMCI project. To expedite the updated IMCI training process, PATH may provide financial support to ensure that these trainings are conducted in TIMCI areas. Trainings will be conducted using a "train the trainers" approach, leveraging the experience of MOH IMCI trainers. Moreover, supervisors will also be included in training sessions to equip them for their supportive supervision role.

The pulse oximetry and CDSA training sessions will be interactive, in line with adult learning principles, and with sessions that allow hands-on practice on the use of the devices. At the end of the pulse oximetry training session, a post-training written test and one observation of the use of the pulse oximetry per participant will be used to determine immediate acquisition of knowledge and skill. If incorrect answers or limited skills were observed, the trainer will reinforce the correct concepts and provide supportive guidance and encouragement to correct use of the pulse oximeter. At the end of the CDSA training session, a post-training practical test based on a set of pre-recorded cases will be used to determine immediate acquisition of knowledge and skills. Competency evaluation will be extended post-course by asking trainees to perform a certain number of consultations while using the CDSA and including a minimum number of classical IMCI conditions.

In the case of staff turnover in TIMCI facilities detected during monitoring visits, PATH in consultation with the MOH will elaborate a plan for training such new staff either at the facility or a in a group session elsewhere, depending on circumstances at the time.

Mentorship

As per training, PATH will work with each MOH to integrate pulse oximetry and CDSA use into existing supervision mechanisms where possible. Supportive supervision for CDSA may additionally include personalized feedback directly informed by data recorded in the device. Intensive mentoring / supervision will be conducted following training, and then will be gradually tapered and fully transferred to government mechanisms.

Community and caregiver engagement

PATH will build on existing relationships with local civil society organisations (CSOs) and networks active in the child health space, and relevant Ministry of Health community initiatives

(such as community healthcare provider networks), establishing new collaborations as needed. PATH will work closely with these CSOs and Ministries of Health to integrate information on the intervention, and content aimed at encouraging care seeking and following referral recommendations into their ongoing child health activities.

Additional information materials on pulse oximetry and CDSAs will be provided at intervention facilities, including multi-media materials or public health nurse talks, depending on preferences within each country.

6.4 Outcomes

6.4.1 Pilot phase

Progression to the definitive trial will be based on the following outcomes:

- 80% of healthcare providers adhering to critical steps of the pulse oximetry use guidelines (combination of WHO and manufacturer guidelines provided as part of intervention), assessed using the SPA observation in pilot facilities
- 80% of eligible children recruited
- 90% of caregivers reachable by phone on Day 7 for outcome assessment

If these outcomes are not met during the pilot phase, the research steering committee will review and advise on adjustments and progress to the definitive trial.

Furthermore, the following outcomes will be assessed in order to verify sample size assumptions:

- Attendance rate of eligible children per month attending study
- Primary outcome proportions in routine care

If a deviation from the original assumptions are substantial, sample size calculations and recruitment strategies will be reviewed and modified if necessary.

6.4.2 Pragmatic cluster RCT

Two primary outcomes will be assessed in order to improve the ability to detect a difference between intervention and control arms, given the relatively low occurrence of severe outcomes at primary care level:

- Proportion of children with a severe complication (death or secondary hospitalisation) by Day 7
    - Secondary hospitalisation refers to any delayed hospitalisation (occurring at any point greater than 24 hours after Day 0 consultation) and any hospitalisation occurring without referral. The denominator is all enrolled children

- Proportion of children admitted to hospital within 24 hours of the Day 0 primary care consultation and as a result of a referral
    - This is used as a proxy for 'appropriate referral' of children, as those with severe disease should generally be admitted to hospital. The denominator for this outcomes is also all children enrolled in the study, rather than only referred children. This is because the proportion of referred children that are admitted may be high in routine care, in the context of an inappropriately low referral rate. The aim of the intervention is therefore to increase the overall referral rate of children with severe disease. Hospital admission is chosen as the proxy of severe disease rather than using primary care classification of severe disease, as there are inadequacies in the classification of severe disease in routine practice

The trial will be interpreted as positive if either primary outcome is positive with no indication of harm from non-significant outcomes. This will be assessed separately in India and Tanzania and will also be assessed across the two countries for the sub-group of children presenting with cough or difficulty breathing.

We anticipate that we will see a greater effect on the 'appropriate referral' outcome, given that increasing detection and referral of children with severe disease is the focus of the intervention, and that morbidity and mortality among children with severe disease is highly contingent on quality of care at hospital level, which is not the focus of the intervention. Whilst hospital admission is still contingent on factors beyond the remit of the intervention (e.g. on caregiver completion of referral and hospital bed availability), it is not dependent on quality of care during hospital admission.

Secondary outcomes:

- Proportion of children with severe complication (death or secondary hospitalisation) by Day 28
- Proportion of children cured (defined as caregiver reported recovery from illness) at Day 7 follow-up
- Proportion of children referred by a primary care healthcare provider to a higher level of care (either to a hospital or to an inpatient part of a larger primary healthcare facility) at Day 0 consultation

Proportion of children who completed referral, as reported at day 7 follow-upOther outcomes of interest – hypoxaemia (in intervention arms only)

- Proportion of children with severe (SpO2 <90%), moderate (SpO2 90 – 91%) and mild hypoxaemia (SpO2 92 – 93%), adjusted for sites at high altitude
- Proportion of children with hypoxaemia (according to differing cut-offs) with severe complication
- Proportion of children with severe hypoxaemia not meeting any other clinical criteria for severe disease

- Proportion of children referred with hypoxaemia who receive oxygen at hospital

Other outcomes of interest – referral and follow-up

- Proportion of children with non-severe disease referred to a higher level of care on Day 0
- Average length of stay (in days) of children admitted to hospital
- Proportion of children attending scheduled follow-up at the same facility by Day 7
- Proportion of children presenting for unscheduled follow-up to any health facility by Day 7

Other outcomes of interest – antimicrobial prescription

- Proportion of children prescribed an antibiotic at Day 0
- Proportion of children prescribed a diagnosis-appropriate antibiotic
- Proportion of febrile children tested for malaria at Day 0
- Proportion of malaria positive children prescribed an antimalarial
- Proportion of malaria negative children prescribed an antimalarial
- Proportion of untested children prescribed an antimalarial

Sub-groups for analysis of primary and secondary outcomes:

- Age (under 2 months, 2 – 12 months, 13 – 59 months)
- Sex
- Presentation with cough / difficulty breathing

Other factors for exploratory analyses

- Additional sociodemographic characteristics urban / rural location, distance from health facility, key household indicators such as maternal age and education
- Main complaint / symptom categories (including cough / difficulty breathing, fever, diarrhoea and other) and time since onset of symptoms
- Alternative hypoxaemia cut-offs
- Healthcare provider severity classification
- Facility and health system factors – type of facility, healthcare provider qualification and previous training

6.4.3 Other mixed methods studies

These studies will mostly be exploratory, particularly the qualitative studies which seek to understand perceptions, values, attitudes, and beliefs. Process evaluation criteria will be evaluated according to the MRC criteria.[35]

Service provision assessments, at baseline and each quarter during implementation, will assess: adherence to IMCI (or national guidelines) and device guidelines (only in relevant arms),

including proportion of: caregivers asked about all three danger signs; caregivers asked about all main symptoms; children with cough or difficulty breathing in whom a respiratory rate is counted for a minute and (where applicable) in whom a pulse oximetry reading is attempted, conducted correctly, obtained at first attempt or at repeated attempts; and proportion of children in whom CDSA is used and recommendations are adhered to. Furthermore, correctness of classification and treatment (as far as is possible with available information), and other indices of quality of care will be assessed. Facility and healthcare provider factors associated with health and quality of care impact and intervention uptake will be assessed.

Facility-based process maps and associated non-participant observational data will be described and compared between baseline and early and late intervention periods. Time (in minutes) will be compared (pre, early and late intervention) for total in clinic; in consultation; and on use of devices, and any other relevant single steps of the care process. Comparison will be made using mean (if parametric) or median (if non-parametric).

Qualitative enquiry with healthcare providers and caregivers will primarily focus on service provision, the participant response to the intervention and acceptability of devices, with exploration of change in perceptions, attitudes and behaviour over time. With caregivers, we will also explore experience of care and care-seeking behaviour through IDIs, as well as reasons for lost to follow-up and related perceptions and challenges.

The sub-study of stakeholder perceptions, surveys and project data review will primarily focus on the processes, mechanisms and context (i.e. process evaluation criteria with focus on fidelity, dose, reach, context and adaptation) of implementation including adaptations made.

6.4.4 Cost and cost-effectiveness study

- Full implementation cost of the intervention per focal country (cost to health system as well as direct costs paid by the household to the health system)
- Cost per child screened using pulse oximetry devices and CDSA where applicable, compared to cost per child in routine care.
- Cost per DALY averted attributed to the introduction of pulse oximetry both with and without CDSAs modelled on proportions referred to hospital on day zero or by day 7 or requiring secondary hospitalization by day 28 in each arm and the predicted outcomes in each case, using published literature supplemented where necessary by expert opinion. We will utilize data on any other severe outcomes and also use predictors of severity on children who are admitted to hospital.

6.5 Participant timeline

6.5.1 Pragmatic cluster RCT

The study flowchart is presented in Fig. 5. Research assistants will screen and recruit participants in the waiting area prior to consultation as outlined in Section 10.3. Following informed consent and enrolment, research assistants (RAs) will record participant name,

address and contact details (including personal and alternate contacts) for Day 7 and Day 28 follow-up, basic sociodemographic details, reason for attendance and care-seeking. This will be collected from the caregiver before consultation, except in critical / emergency cases who will be seen immediately by the healthcare provider. The clinical consultation will be conducted by healthcare providers who have been advised to use the devices as described above according to the facility allocation.

After the consultation, the RA will use extract information from the clinical records from the caregiver (child health card and / or referral note), and / or from clinic ledgers or medical records. Information will be extracted and recorded on the final diagnosis, oxygen saturation and results of laboratory investigations (if performed), prescribed medication with dosage, referral or follow-up advice and the usage of the pulse oximeter device and/or CDSA (if applicable). Research assistants will seek clarification from healthcare providers in cases where the diagnosis is not clear from the records.

Caregivers will be offered several options for completing follow-ups at Day 7 and Day 28. Follow-up will be conducted remotely when possible. For caregivers who can provide a phone number at the day of enrolment, Day 7 and Day 28 follow-ups will be conducted by phone. If the initial phone call fails and the phone number is valid, at least three attempts will be made on subsequent three days at different times of the day to try to reach the caregiver. If the phone number is not valid, no other call attempts will be made and alternative follow-up options will be initiated if consented for. Except during the initial phone call, follow-up can be carried out with a caregiver other than the one who gave consent at the day of enrolment if this person is able to provide information about the child. For caregivers who cannot provide a phone number at the day of enrolment, community mechanisms will be relied on to arrange a call with the caregiver through a community focal person, e.g. a community health worker (CHW) or a community leader. To this aim, CHWs and community leaders in the targeted study areas will be asked for their consent to have their phone numbers shared with RAs in order to contact caregivers without a phone for their Day 7 and Day 28 follow-ups. Independently on whether they provided a phone number or not, caregivers will be given the alternative option to consent for in-person Day 7 follow-up that will have to be conducted as soon as possible after all remote attempts failed. In-person Day 7 follow-ups could be conducted either at the caregiver's household or another specified community location.. If Day 7 follow-up has been unsuccessful, Day 28 follow-up will still be attempted. During both Day 7 and Day 28 follow-ups, a structured questionnaire will be administered to assess the primary and secondary outcomes, including details of any government or private hospital admission. In case of non-recovery, if the child is still at home, the study team will advise the family to return to the PHC clinic for a follow-up consultation.

Additionally, visit information from government-designated hospital records will be collected retrospectively for children reported to have attended hospital by the caregiver at follow-up or referred at day 0 and lost to follow-up including clinical assessment on arrival (vital signs, admitting diagnosis), admission details (duration, if oxygen was administered, intensive care

admission) and admission outcome (final diagnosis, discharge against medical advice, death). The same data will be collected for children who visit a non-hospital higher-level of care (emergency or admission unit of a primary or secondary care facility).

It is expected that some participants may present at the same or another health facility enrolled in the study during the follow-up period. These visits and the findings will be recorded on the appropriate scheduled / unscheduled visit eCRFs.

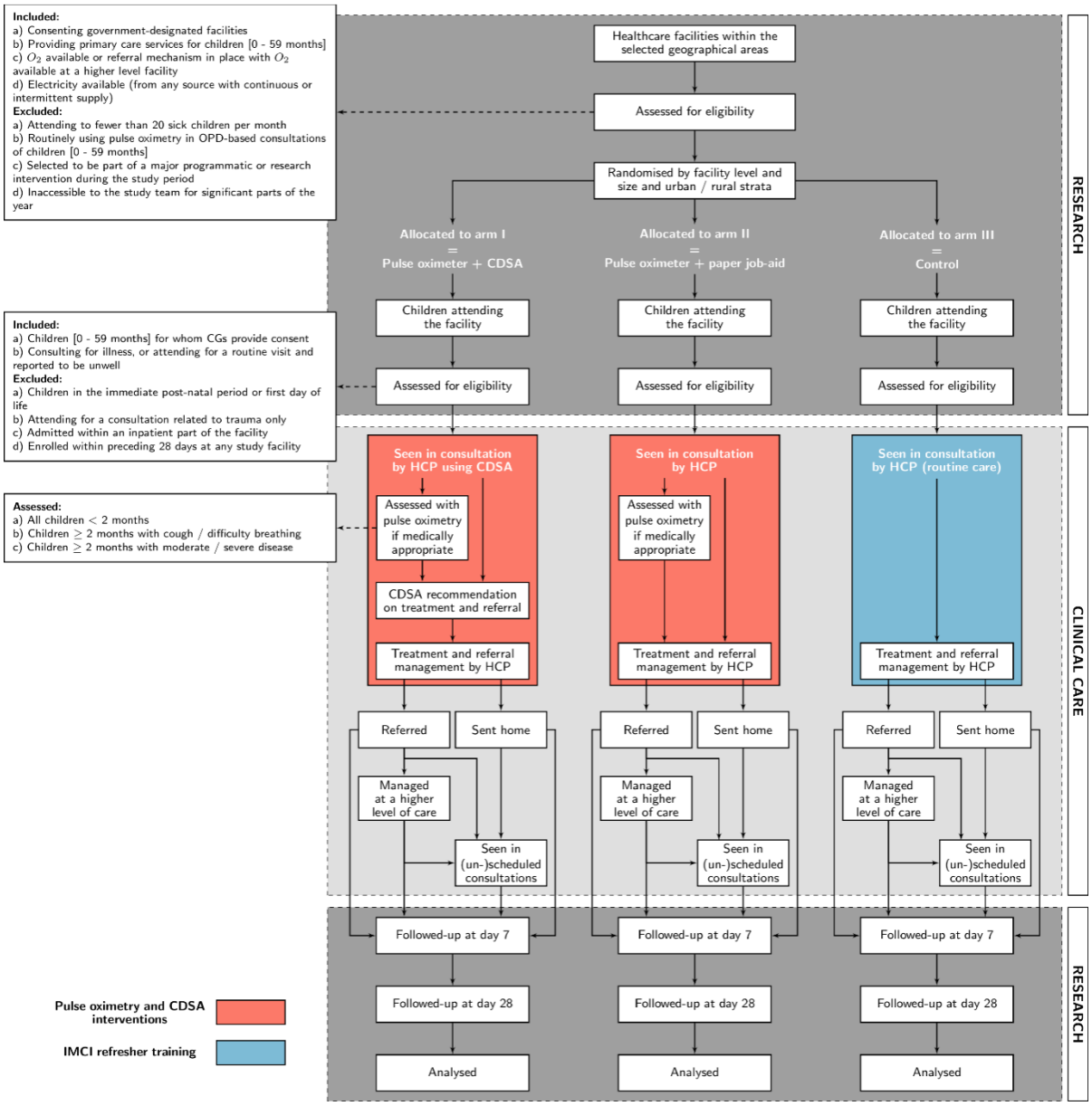


Fig. 5. Flowchart of the pragmatic cluster randomised controlled trial. CDSA = Clinical Decision Support Algorithm. CG = Caregiver. HCP = Healthcare provider. OPD = Out-patient department. Arm 1 not applicable in India.

Tab. 4. Schedule of the visits and associated CRFs for the pragmatic cluster RCT. Arm 1 not applicable in India. The different types of data collectors are represented by the following icons:

Facility-based research assistants | Research assistant rotating between different referral health facilities | Healthcare providers | Call centre-based research assistant

			Health facility baseline visit			Higher level of care visit[1],Error! Bookmark not defined.	Scheduled[2] or unscheduled visit at any study facility			Phone follow-up	
Time point / window			Day 0			Day 0-7	Day 1 -28			Day 7	Day 28 [28 - 35]
Data collection method			Prospective data collection			Review of medical records / registries	Prospective data collection			Phone interviews	Phone interviews
Randomization[3]			Arm I	Arm II	Arm III		Arm I	Arm II	Arm III		
Events		**Forms**									
Informed consent		-									
Screening		TIMCI-01									
Identification & contact information	Full identification	TIMCI-02a									
	Contact information	TIMCI-02b									
	Identification and contact information check	TIMCI-02c									
	Referral facility identification	TIMCI-02d									
	Follow-up identification check	TIMCI-02e									
Socio-demographics		TIMCI-03									
Visit info	Care seeking behaviour, transport and costs for visiting health facility reported by caregiver	TIMCI-04a									

	Visit and admission info recorded by referral facility (medical records, registries)[Error! Bookmark not defined.]	TIMCI-04b									
	Patient journey reported by caregiver at follow-up	TIMCI-04c									
Clinical presentation & medical history	Clinical presentation and medical history reported by caregiver at baseline	TIMCI-05a									
	Medical history recorded in clinical notes and / or facility registries	TIMCI-05b									
	Chief complaints and medical history recorded in CDSA	TIMCI-05c									
Basic measurements & physical exams	Basic measurements and physical exams recorded in clinical notes and / or facility registries	TIMCI-06a									
	Basic measurements and physical exams recorded in CDSA	TIMCI-06b									
Respiratory rate & pulse oximetry	Respiratory rate and pulse oximetry recorded in clinical notes and/or facility registries[Error! Bookmark not defined.]	TIMCI-07a									
	Respiratory rate and pulse oximetry recorded in CDSA[Error! Bookmark not defined.]	TIMCI-07b									
	Respiratory rate and oxygen saturation recorded at arrival by referral facility[Error! Bookmark not defined.]	TIMCI-07c									
Laboratory investigations	Laboratory investigations recorded in clinical notes	TIMCI-08a									

	and / or facility registries **Error! Bookmark not defined.**										
	Laboratory investigations recorded in CDSA**Error! Bookmark not defined.**	TIMCI-08b									
Diagnosis & care management	Diagnosis and care management in clinical notes and / or facility registries (medical records, discharge summaries)	TIMCI-09a									
	Diagnosis and care management recorded in CDSA	TIMCI-09b									
	Diagnosis and care management recorded by referral facility (medical records, discharge summaries)	TIMCI-09c									
Follow-up at Day 7		TIMCI-10									
Follow-up at Day 28		TIMCI-11									

[1] Data will be collected retrospectively for visits at facilities offering a higher level of care, including district hospitals, any study facility receiving referrals or admitting patients. [2] If appropriate for clinical management.
[3] Allocation at the level of the facility to intervention or control groups.

6.5.2 Other mixed methods studies

An overview of the timeline for participants recruited to the mixed methods studies and how they are embedded in the pragmatic cluster RCT is shown in Fig. 6. In the sub-sample of children (and their caregivers) selected as part of the SPA, two additional time-points of data collection will occur – during the consultation (observation), and after their clinical consultation (exit interview).

IDIs and FGDs with caregivers, and FGDs will take place after the day 7 follow-up phone call.

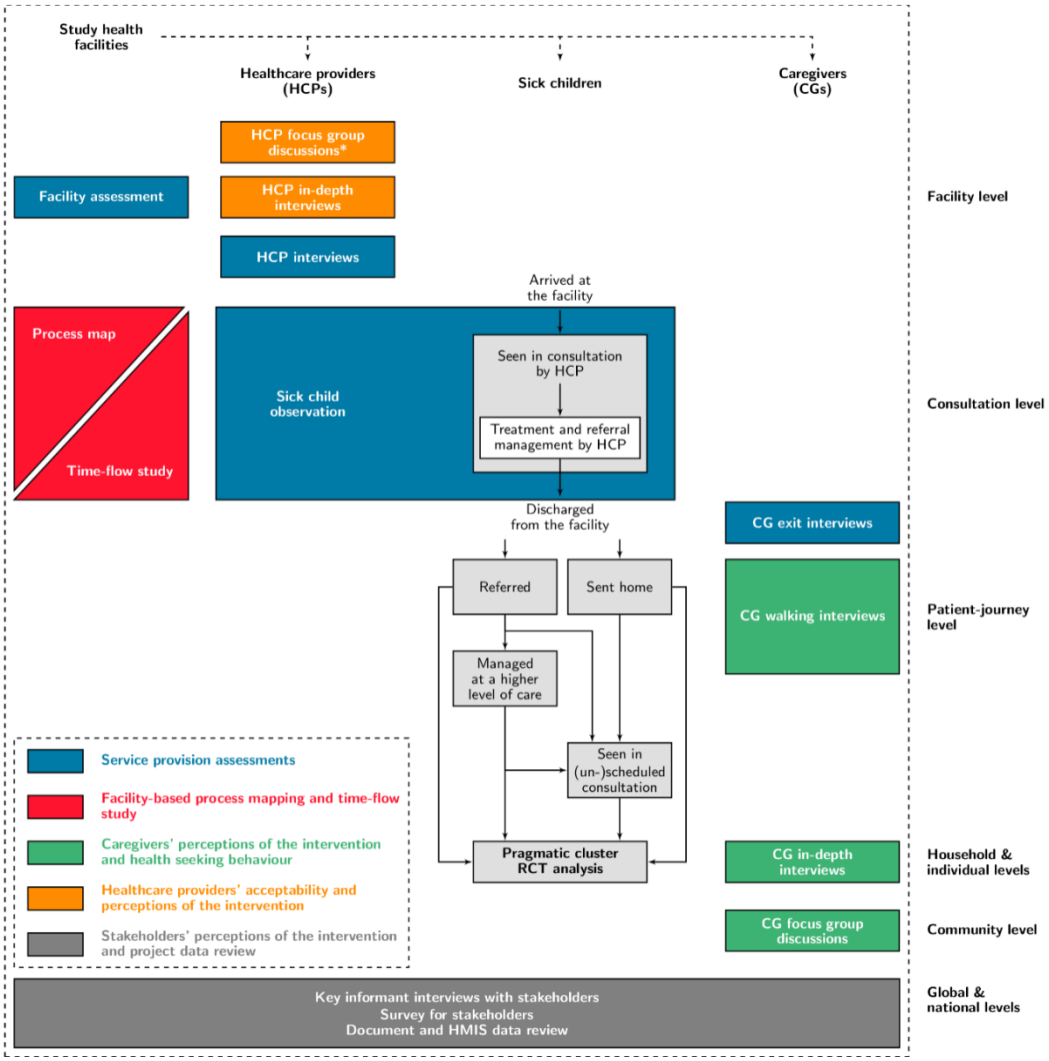


Fig. 6. Overview of the mixed methods studies and how they are embedded within the pragmatic cluster RCT. CG = Caregiver. HCP = Healthcare provider. Healthcare provider focus group discussions will group healthcare providers from different facilities.

Healthcare providers for the SPA will be invited to participate in the interview and consultation observations at the time of the first SPA assessment at that facility, after information has been provided to and assent obtained from the facility in-charge. At subsequent assessment rounds, the SPA team will meet with the in-charge and HCPs briefly, provide information on updates if required and answer any questions. Prior to participation in the interview or observation, continued consent will be checked verbally by a member of the SPA team. If the supervisor was

not involved in a previous round, they will be fully informed as per the first round, and similarly if an HCP was not previously recruited, the full written informed consent process will be adhered to.

Healthcare providers recruited for qualitative interviews or FGDs will be invited for an interview/FGD from SPA and/or non-SPA facilities. Participants with particularly interesting or divergent views might be approached from FGDs for follow-up IDIs. The final selection of stakeholders (outlined in Section 5.7) will be determined during implementation and based on implementation experience.

6.5.3 Cost and cost-effectiveness study

Facility-based medical and non-medical personnel who provide information for costing will be approached at a time convenient for them so as not to interfere with clinical or health service delivery. Information will be provided about the study and consent will be sought for personal data as outlined in 10.3.3. These providers will be approached pre-intervention and then again during intervention for data collection, though different providers may be approached in case of staff rotation.

6.6 Sample size

The estimated sample sizes for each of the studies are described below, but may be revised during the course of the study. In the case of the RCT, this is due to uncertainty of some of the assumptions (such as eligibility rate and outcome proportions in routine care, for which data reliability is a challenge). Final qualitative sample sizes will be determined based on reaching thematic saturation, i.e. when no new concepts are emerging.

The remaining sample sizes, for SPA, process mapping and time-flow study, have been chosen pragmatically and will vary according to country depending on the degree of difference in care processes between facility types and location, whilst allowing for exploratory analysis into more in-depth aspects of quality of care from baseline to intervention, between the arms, and over time within the intervention period (both due to changes in implementation uptake and seasonal variation in burden of disease).

The sample size for the pilot phase will also be pragmatically based on the degree of difference between facility types and location (and thus the potential need to understand and refine the intervention strategy according to context), but is likely to include between 2 and 4 facilities per arm per country.

6.6.1 Pragmatic cluster RCT

The sample size for the pragmatic RCT is calculated separately for each country, based on the following common assumptions:

- power of 80%

- alpha level of 0.05 per arm
- intracluster correlation coefficient (ICC) of 0.001[52]
- control arm severe complication of 1.1% (based on comparable data from a previous study in Tanzania)[30]
- control arm appropriate hospitalisation of 1.5% (based on estimates from facility staff)
- a recruitment period of 12 months

In India, Initial sample size calculation for the three arm trial was based on having the power to detect a 30% or greater decrease in severe complication and 30% or greater increase in appropriate hospitalisation for each arm compared to control with 40 cluster per arm. This assumes average recruitment of 510 children per cluster over the 12 month period, based on available DHIS2 data summaries and estimates from facility staff for 2019 indicating, with an average of 110 per CHC per month and 20 children per PHC, assuming that we recruit facilities with an average ratio CHC : PHC of 1:3. Following the decision, based on the pilot, not to introduce the CDSA, facilities were reallocated to the remaining two arms up to 60 facilities per arm.

In Tanzania, we would have the power to detect a 30% or greater decrease in severe complication and a 30% or greater increase in appropriate hospitalisation for each arm compared to control with 22 clusters per arm. This assumes average recruitment of 1680 children per cluster over the 12 month period, based on available DHIS2 data summaries and estimates from facility staff, with an average of 350 children per health centre per month and 70 children per dispensary per month assuming that we recruit facilities with an average ratio of health center : dispensary of 1:3.

Given the challenges in reliability of routine data in both countries for the assumptions on both expected eligibility rate and outcome proportions in routine care, we will assess these during the pilot phase and over the course of the study and make adjustments to the sample size calculation and recruitment strategy as necessary.

6.6.2 Mixed methods studies

We will conduct the assessment in 6 facilities per arm, stratified by location (district in India, urban/rural in Tanzania) and facility type, at 5 time points – pre-intervention (whist pilot phase I is occurring in other facilities), and each quarter over the 12 months of the RCT to capture seasonal variation in burden of disease and changes to implementation over time. We will also conduct the SPA at the pilot phase part I facilities to inform intervention refinement.

At each facility at each time point, observation and exit interview assessments will be conducted over 3 – 10 working days, in order to achieve a sample size of 10 – 30 children per facility. In smaller facilities with only one provider, the target will be a minimum of 10 observations and exit interviews, whereas in larger facilities, the target will be a minimum of 20

observations and exit interviews with at least 5 for any single provider. This would result in an estimated sample size of 600 observations per arm over the study period. Interviews will be conducted with all consenting healthcare providers responsible for the care of sick children at the study facility during the first assessment. These will only be repeated if details have changed (e.g. training updates), or for new staff not present at the first assessment. We estimate around 15 – 30 healthcare provider interviews per arm. The full facility assessment will be done at the first visit, and only variables which change over time will be recollected at subsequent visits.

We will conduct facility-based process mapping and time-flow assessments in each of the SPA facilities. One process map (and associated notes on the care process and its rationale or deviations) each will be developed per SPA facility and control arm facilities, which will be revisited and revised during early and late intervention phases to reflect changes over time, resulting in 2 to 3 maps per facility). Process maps will also be developed in the pilot facilities to inform intervention refinement. Each map will involve informal discussion with 2 – 4 healthcare providers in the facility, and non-participant observation over a period of one week, during which time-flow data will also be collected (for an estimated 10 – 30 children depending on facility size).

Final sample size for in-depth interviews (IDIs) with healthcare providers and caregivers will be determined by reaching thematic saturation, i.e. when no new concepts are emerging, while keeping the balance to document change over time; sample size estimates are provided below.

IDIs with caregivers: A purposive sample of caregivers will be selected for IDIs including those who completed referral (and arrived in the hospital within 24 hours) as well as those that did not adhere to the advice, and those that were not referred. Within these sub-categories, participants will be purposively selected with varying sociodemographic characteristics such as rural / urban location, age of caregiver/child, and education. An estimated total of 70-80 IDIs with caregivers in the intervention arms in each country throughout the entire project are expected. Approximately 10 – 12 in-depth interviews per intervention arm with caregivers will be conducted across different time points (pilot, early, mid and late intervention) within one geographical area of each country. However, if geographical variation in health-seeking behaviour and outcomes is felt to be significant, fewer time points may be selected in favour of greater geographical diversity. Caregivers from IDIs will be different from FGD participants. In Tanzania only, 10 – 15 IDIs will also take place pre-intervention, and possible late intervention in the control arm should significant changes have occurred in the health system or community aside from the intervention, for comparison. Further approximately 12-15 IDIs (i.e. 4-6 IDIs with caregivers defined as lost to follow-up (LTFU) in each geographical area (i.e. region)) will be conducted as part of a rapid qualitative inquiry.

FGDs with caregivers: If FGDs are carried out, one geographical area will be selected per country, in which a total of 12 FGDs (3 in urban and 3 in rural location and in each arm) will be conducted, each with 8 – 12 participants. These will be divided between early and late intervention. Caregivers for FGDs will be different from IDI participants. Where possible participants will be divided by age groups and gender as well as number of children.

IDIs with healthcare providers: An estimated total of approximately 70-80 IDIs in the intervention arms per country are expected, allowing to document change over time. This will include approximately 10 – 12 IDIs with healthcare providers per intervention arm at different time points (pilot, early, mid, late intervention) and by age of children they have consulted purposively selected from facilities (during later intervention also from facilities with divergent implementation) and by age of children they have consulted. Where possible, some healthcare providers will be interviewed repeatedly over time. In Tanzania only, 10 – 15 IDIs will also take place pre-intervention, and possibly also late intervention in the control arm should significant changes have occurred in the health system or community aside from the intervention, for comparison.

A total of up to 12 FGDs with healthcare providers will be conducted per country, with 6 – 8 participants per group.

Healthcare providers at SPA and non-SPA-facilities may be invited for IDIs and/or FGDs, with purposive sampling of early and late adopters at a later stage of data collection during the intervention.

KIIs with stakeholders: A total of approximately 20 key-informant interviews may be carried out, split between early and late stages of the project. This will include approximately 3-6 KIIs at global and 10-12 KIIs at national level at different time points (between pilot, early and late stages) of the project. In Tanzania only, 10 – 15 KIIs will also take place pre-intervention, and possibly also late intervention in the control arm should significant changes have occurred in the health system or community aside from the intervention, for comparison. The final selection of type and number of different types of stakeholders (outlined in Section **5.7**) will be determined during implementation, based on implementation experience.

6.6.3 Cost and cost-effectiveness study

Cost data will be collected from eight facilities per country (4 urban and 4 rural; 4 dispensaries and 4 health centres in Tanzania, and 4 PHCs and 4 CHCs in India). The senior administrative staff member at the facility will be interviewed to obtain the majority of the unit cost data, and the senior medical staff member to obtain information on time allocation of front-line staff (time seeing patients, time in supervision etc).

6.7 Recruitment

To reach the required sample size, and to ensure data collection across different seasons, it is estimated that recruitment for the definitive trial will take place over 12 months (with prior 3 month pilot phase). As we intend to validate eligibility and recruitment rate estimates in the pilot phase, we will either recruit additional facilities or slightly increase the study duration if necessary. If recruitment rates change over the study period, we will consider adding facilities if extension of the study duration is not possible.

Child and caregiver participants will be recruited for the SPA and time-flow observations on the relevant study assessment days consecutively until the sample size requirements detailed above have been met. Children and their caregivers will be enrolled to these studies at the same time as they are enrolled to the RCT. Longer assessment periods will be required for low-volume facilities. All healthcare providers providing care for children under 5 years of age and present at facilities during SPA assessments will be invited to participate in the SPA interview.

Participants for qualitative studies will be recruited as follows:

Caregivers for IDIs and possibly FGDs will be selected based on pre-defined queries (e.g. based on information from the RCT database) after Day 7 follow-up has occurred in order to identify potential participants within a selected geographical area. During the call, caregivers will be asked for their verbal assent to be contacted by a person responsible for the recruitment of participants for qualitative studies. Of those caregivers, who agreed to be contacted, a list will be generated for the recruiter with basic sociodemographic details (divided into referred and not referred for IDIs) of double the number of participants required (to allow for unreachable participants or refusals to participate) for the time point in question. The qualitative researcher will then contact participants (i.e. by phone) to arrange interviews or focus groups. If recruitment with this strategy proves challenging, individuals may be approached directly at facilities to arrange a follow-up in the community after 7 days or at the community level (i.e. by a community health worker).

A pool of caregivers defined as lost to follow-up (i.e. those not reached on Day 7 follow-up call) from a pre-defined time period will be established based on pre-defined queries (e.g. based on information from the RCT database). Caregivers will be stratified by pre-defined criteria (e.g. no phone number; invalid phone number; not able to be reached etc.) and purposively sampled. A list will be generated for the recruiter with basic socio-demographic details of double the number of participants required (to allow for unreachable participants or refusals to participate) for the time point in question. Community Health Workers (CHWs) or a person responsible for the recruitment of participants for qualitative studies will approach selected caregivers at the household level, provide a short explanation on the reason for their visit and ask for their verbal consent to participate in an IDI. If caregivers agree, the qualitative data collector or person responsible for recruitment of participants for qualitative studies will be called and an appointment scheduled.

Healthcare providers from study facilities will be invited to participate in the studies by the person responsible for the recruitment of participants for qualitative studies. A pool of healthcare providers based on pre-defined queries (e.g. with information received from the PATH training log, M&E data and through RAs at TIMCI facilities) will be established. Healthcare providers will be stratified by pre-defined criteria (e.g. cadre, age, age of children consulted, sex, years working in profession etc.) and a purposive sample of HCPs established of double the number of participants required (to allow for unreachable participants or refusals to participate) for the time point in question. The qualitative researcher will then contact

participants (i.e. by phone) to arrange for an interview appointment or possibly focus group discussion appointments.

Some of the same healthcare providers invited to participate in the FGDs and IDIs will be re-invited over time. After initial implementation, a pre-defined list of variables (e.g. from the RCT study) will be used to classify healthcare providers into early and late adopters of the intervention; and change in uptake over time. This will help to inform the focus of the qualitative inquiry over the implementation period. However if the recruitment process proves challenging due to staff rotation, clinical commitments or research fatigue, a broader range of healthcare providers will be approached from both SPA and non-SPA facilities.

Recruitment of healthcare providers in the pre-intervention / non- / pilot / early intervention phase: Where only one healthcare provider is present at the facility s/he will be invited. If more than one healthcare provider is working at the same facility a purposive selection will be made, based on a variety of sociodemographic factors to ensure a diverse sample (as outlined above).

Recruitment of healthcare providers in the mid/late intervention: Healthcare providers may be purposively selected from facilities with divergent implementation. Divergent implementation will be identified as described above. Additionally, providers may be purposively selected based on the age of children consulted.

Stakeholders will be purposively selected with a focus on a diverse sample presenting the different levels of implementation (global, national, regional and local level) as well as their level of direct involvement in the project. Stakeholder mapping will be conducted to identify potential participants internal and external to the project. All pre-selected key stakeholders will be invited by the research assistant to participate in the study. The same respondents will be invited over time. If the recruitment process proves challenging (e.g. due to staff rotation) the same principals as with healthcare providers apply. Further details are outlined in Section 5.7 of the protocols on the type of stakeholders that will be invited to participate.

7 Assignment of intervention

7.1 Allocation

7.1.1 Sequence generation

The allocation sequence will be generated by a statistician, independent from the study, for all eligible facilities per country, stratified by facility type and location (urban/rural location in Tanzania, district in India). The target number of facilities will be randomly selected from all eligible facilities and allocated to the trial arms. The remaining eligible facilities will be retained in a back-up list for later allocation (using the same procedure) should the need arise (e.g. in case of facility exclusion at study start, or in case of need to add additional clusters in the event of recalculation of sample size).

7.1.2 Allocation concealment mechanism

Given the cluster design, concealment will occur only at the stage of allocation of facilities, which will be conducted centrally and distributed to study sites.

7.1.3 Implementation

Participants will be allocated to the intervention based on the facility they attend.

7.2 Blinding

Data for outcome ascertainment will be collected by phone by a research assistant blinded to the trial arm and the facility the child attended.

8 Data collection, management and analysis

The data used within the TIMCI project are described in Tab. 5. Primary research data will be generated in study and pilot facilities through case report forms, questionnaires, interviews, focus group discussions and surveys. In addition, relevant routine data will be extracted for all intervention facilities (i.e. including those in which primary research data will not be collected). This will include individual consultation data recorded in the CDSA for clinical purposes and aggregate facility data that are reported to the national HMIS.

Tab. 5. Summary of the data used within the TIMCI project. CDSA = Clinical Decision Support Algorithm. MedAL-R is the front-end application developed by Unisanté/Wavemind (Lausanne, Switzerland) to implement ePoct+, the clinical algorithm. EDC = Electronic Data Capture. FGD = Focus Group Discussion. HMIS = Health Management Information System. IDI = In-Depth Interview. KII = Key Informant Interview. RCT = Randomized Controlled Trial. SARA = Service Availability and Readiness Assessment.

Ref	Methodology	Data collection	Tool	Data format	Data origin	Data classification	Data reuse
1.1	**Routine data**	CDSA individual consultation data	MedAL-R with ePoct+	Textual, numerical, categorical	Primary	Sensitive personal	1.2 2.5
		Aggregate facility data	National HMIS	Textual, numerical, categorical	Secondary	Non-personal	1.2 2.1 2.5
1.2	**Pragmatic cluster RCT**	Pragmatic, parallel group, cluster randomised controlled superiority trial	Electronic case report forms (EDC platform)	Textual, numerical, categorical	Primary	Sensitive personal	2.1 2.2 2.3 2.4 2.5
2.1	**Service provision assessment**	Modified demographic and health survey	Facility assessment (modified SARA questionnaire)	Textual, numerical, categorical	Primary	Non-personal	2.5
			Healthcare provider interview	Textual, numerical, categorical	Primary	Sensitive personal	2.5
			Sick child observation protocol	Textual, numerical, categorical	Primary	Sensitive personal	2.5
			Structured exit interview	Textual, numerical, categorical	Primary	Sensitive personal	2.5
2.2	**Facility-based process mapping and time-flow study**	Process map	Process map tool	Abstract	Primary	Non-personal	2.5
		Time-flow study	Time-flow tool	Textual, numerical, categorical	Primary	Sensitive personal	2.5 3.1
2.3	**Healthcare providers' acceptability and**	Semi-structured in-depth interviews	IDI tool for healthcare providers	Audio, Textual, numerical, categorical	Primary	Sensitive personal	2.5

	perceptions of the intervention	Focus group discussions	FGD tool for healthcare providers	Audio Textual, numerical, categorical	Primary	Sensitive personal	2.5
		Semi-structured in-depth interviews	IDI tool for caregivers	Multimedia (audio, drawings), Textual Numerical	Primary	Sensitive personal	2.5
2.4	**Caregivers' perceptions of the intervention and health-seeking behaviour**	Focus group discussions	FGD tool for caregivers	Multimedia (audio, video-/photo-documented), Textual, numerical, categorical	Primary	Sensitive personal	2.5
		Semi-structured in-depth interviews for rapid qualitative inquiry	IDI tool for caregivers	Multimedia (audio), Textual, Numerical	Primary	Sensitive personal	2.5
2.5	**Stakeholder's perceptions of the intervention and project data review**	Key informant interviews	KII tool	Audio Textual, numerical, categorical	Primary	Sensitive personal	2.5
		Survey for stakeholders	Online survey tool	Textual, numerical, categorical	Primary	Sensitive personal	2.5
		Project data review	Document review matrix	Textual	Secondary	Non-personal	N/A
3.1	**Cost and modelled cost-effectiveness**	Cost analysis	Medical personnel questionnaire	Textual, numerical, categorical	Primary	Sensitive personal	2.5 3.1
			Non-medical personnel questionnaire	Textual, numerical, categorical	Primary	Sensitive personal	2.5 3.1
			Hospital costs	Textual, numerical, categorical	Primary	Non-personal	2.5 3.1
		Modelled cost-effectiveness			Secondary	Non-personal	2.5

8.1 Data collection methods

Quantitative research data for the pragmatic cluster RCT and mixed-method studies will be collected using a secure third-party cloud based electronic data capture (EDC) platform that meets research / ethical standards. CDSA routine individual consultation data will be extracted from MedAL-R, a software developed by Unisanté/Wavemind (Lausanne, Switzerland) to implement the clinical algorithm (ePoct+), while HMIS aggregate facility data will be extracted from the national HMIS, following MoH approval. Qualitative data will be collected using both

EDC, audio recordings, photo documentation and video recordings (method acting), and hand-written paper notes and drawings. GPS data will be collected using a mobile device.

8.1.1 Pragmatic cluster RCT

For each participant enrolled in the pragmatic cluster RCT, data will be captured in the different study arms according to the different assessments and Case Report Forms (CRFs) described in the visit schedule displayed in Tab. 4. A description of the variables collected in each CRF are available in appendix.

Health facility visits

Quantitative research assistants will use an EDC mobile application to enter the research data of enrolled participants. The quantitative research assistant will collect from the caregiver screening information, information on care seeking behaviour, transport and costs, and clinical presentation and medical history. A number of in-depth sociodemographic and household variables will also be collected either as surrogate measures of household wealth, or known to be associated with health-seeking behaviour and / or child mortality (including maternal education). Household wealth indicators were selected from DHS and other surveys in the study countries as those which best estimate wealth index that can be directly collected from the mother / caregiver and with a reasonable time vs. reliability trade-off. Data on laboratory investigations (if performed), final diagnosis, prescribed medication, referral or follow-up advice will be extracted from clinical notes and / or facility registers and/or frompaper-based clinical information forms designed for the TIMCI (only in India, where registry information is often incomplete). Quantitative research assistants will seek clarification from healthcare providers only in cases where these variables are not clear from the records. Personally identifiable information (PII), including participant's name and date of birth, as well as caregiver's phone number and physical address, will be collected for linking data and detecting possible duplicates and carrying out the study follow-up.

In the two intervention arms, information on oxygen saturation will be collected as recorded in clinical notes and / or facility registers. Pulse oximeter device savings will be cross-checked by quantitative research assistants at the end of the consultation where possible. In the pulse oximetry plus CDSA arm, the research data of participants enrolled in the study will be linked with their CDSA consultation data.

Follow-up

Quantitative research assistants will conduct the phone follow-up interviews using an EDC mobile application. Personally identifiable information (PII) will be used for contacting caregivers. No time window applies to Day 7 follow-up. A window of +7 days applies to Day 28 phone call attempts (Day 28 to Day 35).

Data that will be collected at Day 7 follow-up will include cure status (recovery from illness as reported by the caregiver), death and hospitalization information between Day 0 and Day 7 as

reported by caregivers. The primary outcomes on the proportion of children with severe complications by Day 7 and on the proportion of children admitted to hospital within 24 hours of the Day 0 primary care consultation as a result of a referral will be assessed based on Day 7 follow-up. Hospital name, duration of hospitalization and reason for admission will be collected for children reported to have been hospitalized to facilitate the retrospective data collection at referral hospital level.

Data collected at Day 28 follow-up will include death and hospitalization information as reported by the caregiver. The secondary outcome on the proportion of children with severe complications at Day 28 will be assessed on the basis of this interview.

Higher level of care visit

Data collection will be conducted retrospectively at all government-designated and private referral facilities within the study area, including hospitals or emergency / inpatient area of larger primary or secondary care facilities (e.g., study facilities that can admit paediatric patients). A quantitative research assistant using the EDC mobile application will collect data from referral facility records, registries and discharge summaries to document hospitalization for all children reported to have been hospitalized between Day 0 and Day 7. Personally identifiable information will be collected to cross-check the identity of the patients. Arrival date and time, basic clinical information on arrival and, if admitted, admission and discharge diagnosis, and admission duration and outcome will be collected. If available, data on oxygen saturation at admission, oxygen administration and intensive care unit (ICU) admission and duration will also be recorded.

8.1.2 Routine data

CDSA individual consultation data

As part of the CDSA intervention, healthcare providers will be asked to use MedAL-R during their consultations. When they do so, they will routinely enter all data necessary for the clinical management of children 0 – 59 months of age into MedAL-R. Data used within TIMCI will cover clinical presentation (including symptoms and dangers signs), medical history (including HIV and TB status if known), all physical exams and measurements relevant for clinical assessment (including pulse oximetry), and laboratory investigations. Automated recommendations from CDSA on diagnosis and child management will also be collected, as well as healthcare provider's agreement or disagreement with these recommendations and possible additional diagnoses and treatments, which will be manually entered. A description of the variables extracted from CDSA is available with other individual data in the appendix.

HMIS aggregate facility data

HMIS data will include the total number of outpatient consultations – for all patients and for children 0 – 59 months of age (disaggregated by new and follow-up visit if possible) –, disease

burden, and any other relevant indicators if available (such as referral rate or mortality rate), disaggregated by age and sex if routinely collected with this granularity.

8.1.3 Other mixed methods studies

Some data required for the SPA (observation and caregiver exit interview) are common with the pragmatic cluster RCT data and will not be collected again. To reconstruct the full SPA dataset, SPA observation and caregiver exit interviews will be linked with the pragmatic cluster RCT as described in Section 10.4.3. The consultation observation will be conducted by a standardised clinical observer who will record information asked or provided by the healthcare provider and / or caregiver during the consultation on key aspects relating to adherence to IMCI (or national guidelines) and the use of pulse oximetry and CDSA (in applicable arms). The observer will not ask any questions directly of the caregiver, but at the end of the consultation will ask a limited number of questions of the healthcare provider to record diagnosis and management.

In line with the WHO guidance on Ethical Issues in Patient Safety Research, observers in Tanzania (deemed to have sufficient experience and expertise) will be advised to intervene in the consultation only in the event that they witness an error, or suspect an imminent error, during the consultation that is "highly likely to result in direct, severe or irreversible harm" and could be mitigated by their intervention. Should they intervene, the observer will record the intervention in the sick child observation protocol instrument. No information on individual performance will be shared with supervisors, or anyone else. However, in order to mitigate the ethical issues of non-intervention when poor performance has been observed, observers in Tanzania will provide a short supportive feedback to the individual providers if they agree to it at the end of the period of observation. This will be structured in line with supervision procedures of respective MOHs. Feedback provided will be recorded.

In India, observers will not intervene or provide feedback as they are deemed not to have sufficient experience or expertise.

The exit interview will be performed after the consultation by a non-clinical research assistant who will record responses to questions on additional sociodemographic and clinical details and experience of care. The healthcare provider interviews will collect information from healthcare providers involved in the care of children 0 – 59 months, on qualifications, in-service training and experience related to child health and pulse oximetry and experience of the working environment. The facility assessment will focus on the basic infrastructure, staffing, services, diagnostics and medicines relevant to child health, with additional information collected on pulse oximetry, records and reporting and management. At the end of the SPA assessment at the facility, the clinical observer and research assistant will note down additional (prompted) summary observations about the use of pulse oximeter and / or CDSA in the facility.

For the process mapping and time-flow study, pre-drawn, country-specific process maps will be reviewed and modified by research assistants with informal input from facility staff and

observation. Time data will be recorded using an individual follow-through (timing one child from arrival to exit) and/or area-based (waiting area timing, consultation timing, further diagnostic timing, etc.) approach. Notes based on non-participant observation will be taken by research assistants on observations within the facility (e.g. if devices are not charged, waiting rooms are crowded, the type of interactions between patients and providers, change in provision of care (e.g. new triage system introduced)) and will not include any individual patient data.

If FGDs are conducted, they will be facilitated by a moderator and have an assigned note taker (in charge of documentation). Prior to moving to the main topics of discussion, ice-breaker exercises will be used to establish trust with participants and to provide an overview of the topic for discussion (pulse oximetry with or without CDSA). The FGDs with healthcare providers (and possibly caregivers) will use clinical vignettes which will be presented and jointly discussed.

Qualitative data from IDIs, and KIIs will be collected by trained qualitative research assistants using a voice recorder, , in addition to paper-based notes and drawings. Interviews will be conducted using a semi-structured guideline interview tool, with emphasis placed on building trust and using open-ended questions with probes.

Key-informant interviews with stakeholders will either be conducted in-person or via telephone/Skype/Zoom. Interviews will be scheduled and interview questions shared in advance if wished. Surveys (using an online survey tool such as Survey Monkey) for selected stakeholders will be sent out on a regular basis (quarterly) via email. Participants will be asked to answer the questions and upload additional documents. A single reminder will be sent in case no response was received. Documents will be requested from partners on a quarterly basis; a desk-review will be conducted and data entered into a document matrix.

8.1.4 Cost and cost-effectiveness study

Cost data collection will occur in all arms as shown in Fig. 3.

Definition of costs using an activity-based approach

An activity-based approach will be explored using available cost data. Specific activities in the intervention will be allocated to different cost centres. In order to provide cost estimates that will be as managerially-, policy- and programmatically-relevant as possible, the cost analysis will adopt this approach as this separate research costs from the main programme implementation costs. The focus will be on those costs that are expected to change with the introduction of pulse oximetry and CDSAs. Costs including utilities and large equipment costs will remain the same with or without the introduction of pulse oximetry and CDSAs.

To apply the activity-based approach, we will identify specific activities that are to be costed. These will be referred to as "cost centres" (See **Tab. 6**). Cost centres are a way in which the

resources used to produce the intervention activities—and the costs of those resources—are grouped. Cost centres are defined in such a way that:

- The sum of the cost centres is comprehensive—including all the resources used to produce each and every activity of the program—and together, the entire program, and
- They are mutually exclusive—thus avoiding double counting any of the resources used to provide the program.

It is important to note that this cost methodology is not comprehensive. As described in 5.8, it does not include the indirect costs incurred by the consumer (patient) e.g. the caregiver's time or transport costs. Rather, it focuses exclusively on the provider's direct costs, whether borne by the health system or paid out of pocket by the patient's household. The cost resources for each cost centre may differ between Tanzania and India according to availability of services.

Tab. 6. Activity-Based Cost Centres of the TIMCI programme.

1	Training cost for staff involved in delivering the programme: - Consumable costs (including where applicable stationery, and other consumables) - Personnel costs - Overhead costs (including where applicable, rent for training venue, administrative costs, per diems and transport costs, and other overheads)
2	Delivery of intervention - Annualized[1] fixed/equipment costs (including pulse oximetry device and CDSA tablet costs) - Consumable costs (including medicines, diagnostic tests, and other consumables) - Personnel costs
5	Out of pocket costs - Any out of pocket costs paid by patients' households to the health system to access care and prescribed treatment will be collected, including resources purchased outside the facility due to unavailability in the facility. However, care not prescribed by facility healthcare professionals will not be included.

1. Since costing needs to account for both capital and recurrent costs, annualizing capital costs (i.e. calculating the annual value of a capital item) is the easiest way of combining capital and recurrent costs meaningfully. Annualizing capital cost is based on three pieces of important information: the initial purchase price of the item, its expected useful life, and a discount rate

Sources of cost data

Personnel and procurement units of the organisations involved in the TIMCI intervention especially through different local PATH offices and sampled facilities will be sourced for the cost data. Centrally available databases will be used to estimate personnel and consumable (including medicines and diagnostics) costs where available.

Start-up costs which will include training and community sensitisation costs will be collected pre facility enrolment and intervention. After facility enrolment, cost data will be collected from non-medical administrative personnel. All personnel costs for those involved in each arm of the intervention will also be collected since time in supervision, time of administrative support staff is as important as that of front-line staff seeing patients. Personnel time, and volumes of

diagnostic tests and treatments prescribed, will be obtained from the time-flow and service provision assessment studies. Data on time required for supervision and administrative tasks such as taking patient notes will be obtained from the senior medical professional at the facility, along with information on grades of personnel. Salaries of personnel according to grade will be sourced from centrally available databases which would include government salary publications for health facility workers (medical and non-medical) and complemented with salary costs sourced from health facility administrative databases where needed. Costs of consumables will also be sourced centrally where available and would for instance include cost of items on the National Essential Medicine List. Referral and hospitalization costs will be sourced from interviewing senior administrative personnel at referral health facilities.

Total programme cost and cost per child will be estimated. We will collect administrative data from appropriate levels in each country depending on organization of the specific health system, and will use time-flow data collected elsewhere in the project before and after the intervention.

The table below lists the broad areas of cost data collection for each cost centre and the respective data sources.

Tab. 7. Sources of cost data

Type of Cost		**Identification**	**Measurement**		**Valuation**	
		Categories	Costing method	Sources of data	Valuation methods	Sources of data
Recurrent	Personnel (staff)	All staff involved (field workers and managers, administrators, support staff (drivers), etc)	Percentage of time spent on different activities within TIMCI; grade of personnel	Time data collected by operational research	Gross remuneration package costs	Centrally from government databases and complemented with provider's payroll department
	Consumables	Disposable items usedper child per intervention	Quantity of consumables used per child	Medical personnel at health facility	Market prices	Centrally from government databases and complemented with provider's procurement department
	Equipment/ Capital (incurred every few years)	Pulse oximetry devices, tablets etc	Annualised cost of items	Interview, observations, and timing	Replacement prices	Provider's financial syndicate office
	Out of pocket costs	All out of pocket costs paid by patients' households to the health system for fever management	Direct fees and charges paid by households to health systems	Cost borne by households	Financial cost	Cost data collected form health system administrative records; information from interview of senior non-medical personnel

Definitions of types of costs and data to be collected

Staff time: For each activity within TIMCI, the responsible staff member involved with the activity will be identified. Secondly the time involved will be ascertained from the time-flow study and quantified. Supervision costs will similarly be estimated.

Consumables: The type and quantity of medicines, diagnostic tests and consumables used for each intervention arm will be identified. In addition, unit costs of each consumable item will be obtained (for example the cost of a box of cotton wool balls) and the size of unit (the number of cotton wool balls in each box).

Equipment: All equipment used for each activity will be identified and the price for which it was purchased. For the equipment costing, the lifespan for the equipment (usually between 3 – 5 years for smaller items including electronic tablets and pulse oximetry devices) will be obtained and annualized. Annualization will follow the cost recovery methodology where item cost, life span, and a defined interest rate is used to estimate the annual cost of an item. For equipment that is shared with other programmes, the time spent per consultation will be obtained as a percentage of total time spent using each equipment and used to calculate the cost associated with the intervention after annualization. For donated equipment, market price information will be sought.

Equipment inventories and training records will be used to collect retrospective costs. Time spent by staff on consultations with children 0 – 59 months of age will be collected from data obtained in the time-flow study. Time costs will then be determined by combining staff annual salaries obtained from government sources and/or payroll offices with time spent per intervention. Where applicable, this personnel cost will be disclosed only to the principal researcher without the identity of staff involved. Consumables used will be examined to determine the unit cost of each consumable, while equipment will be annualized to determine their unit costs.

All capital and start-up costs will be annualised using an appropriate length of life and discount rate. Out of pocket payments to health systems borne by households will be estimated to capture all health system costs. These costs might vary across different settings since there might be flat rates in one setting and a varied fee schedule in another. Hence, the cost data collection for out of pocket payments will be country specific. The cost of hospital referrals where applicable, will also be estimated from interviews with senior healthcare professionals at the hospital level.

8.2 Data management

All data management procedures will be further described in the Data Management Plan (DMP).

8.2.1 Data flow, storage and transfer

The data management system will process and combine two main data flows: the research data flow, which will be managed by a secure third-party cloud based EDC platform, and the routine consultation data flow, which will be managed by a customized Server (Unisanté/Wavemind, Lausanne, Switzerland). As illustrated in **Fig. 7**, there will be separate secured databases with restricted access rights for storing and processing CDSA consultation data that are necessary for all research operations, and (possible) linking between the different databases.

- **Study databases** – These databases will contain de-identified quantitative research data collected in study facilities. Unless specified otherwise per country requirements in the DMP, these databases will be hosted on a device owned and maintained by the country research partner.

- **CDSA consultation database** – This database will contain routine consultation data extracted from CDSA in all intervention facilities. CDSA consultation data from study facilities will be de-identified, i.e. a link will exist between these data, the pragmatic cluster RCT database and the identification database. There will be no such link for CDSA consultation data from non-study facilities, which will then be fully anonymised. Unless specified otherwise per country requirements in the DMP, this database will be hosted on a device owned and maintained by the country research partner.

- **Identification database** – This database will contain PII collected in study facilities. It will be kept under strict operating procedures, in particular it will not be shared or accessible outside of the country. The database will be used for generating follow-up call logs and random selection of a purposive sample of caregivers for qualitative studies. It will also be used for flagging possible duplicates in children enrolled in the pragmatic cluster RCT.

- **Mapping database** – This database will be used for linking data from the study databases and the identification database. Each table will be maintained confidential under strict operating procedures for the duration of the study. The mapping between databases will not be shared or accessible outside of the research institution. When all data validation and regulatory requirements have been met, the mapping database will be destroyed, so that all the study databases and CDSA consultation database are ultimately fully anonymized and independent from each other.

In addition, **qualitative study repositories** with restricted access rights will store raw (audio-recordings, notes, drawings, photos, videos, GPS coordinates and document review grids) and processed (transcribed, translated and coded) labelled qualitative material. Unless specified otherwise per country requirements in the DMP, these repositories will be hosted on a device owned and maintained by the country research partner.

A data transfer agreement will be requested from the national competent authorities for providing access to and sharing a full copy of the de-identified study databases, de-identified

consultation database and de-identified qualitative material with the core team at Swiss TPH. A subset of these database will be additionally shared with UoW as needed for the cost and cost-effectiveness study. Following approval from the national competent authorities, the copies will be stored on servers hosted in Switzerland / Canada. Data ownership will remain with the country research partner. After study termination or premature termination of the study, the de-identified databases and de-identified qualitative material will be archived by the country research partner in accordance with national laws. The shared copies will be archived for 10 years by Swiss TPH and UoW, unless otherwise stipulated by the applicable legislation. Research partners will archive study data according to the applicable national regulations. After the mandatory retention period has ended, a periodic review will check if data storage is still needed for research purposes. If not, the study data will then be deleted. All repositories, databases and related software files will be backed up by the administrator in conjunction with any updates or changes.

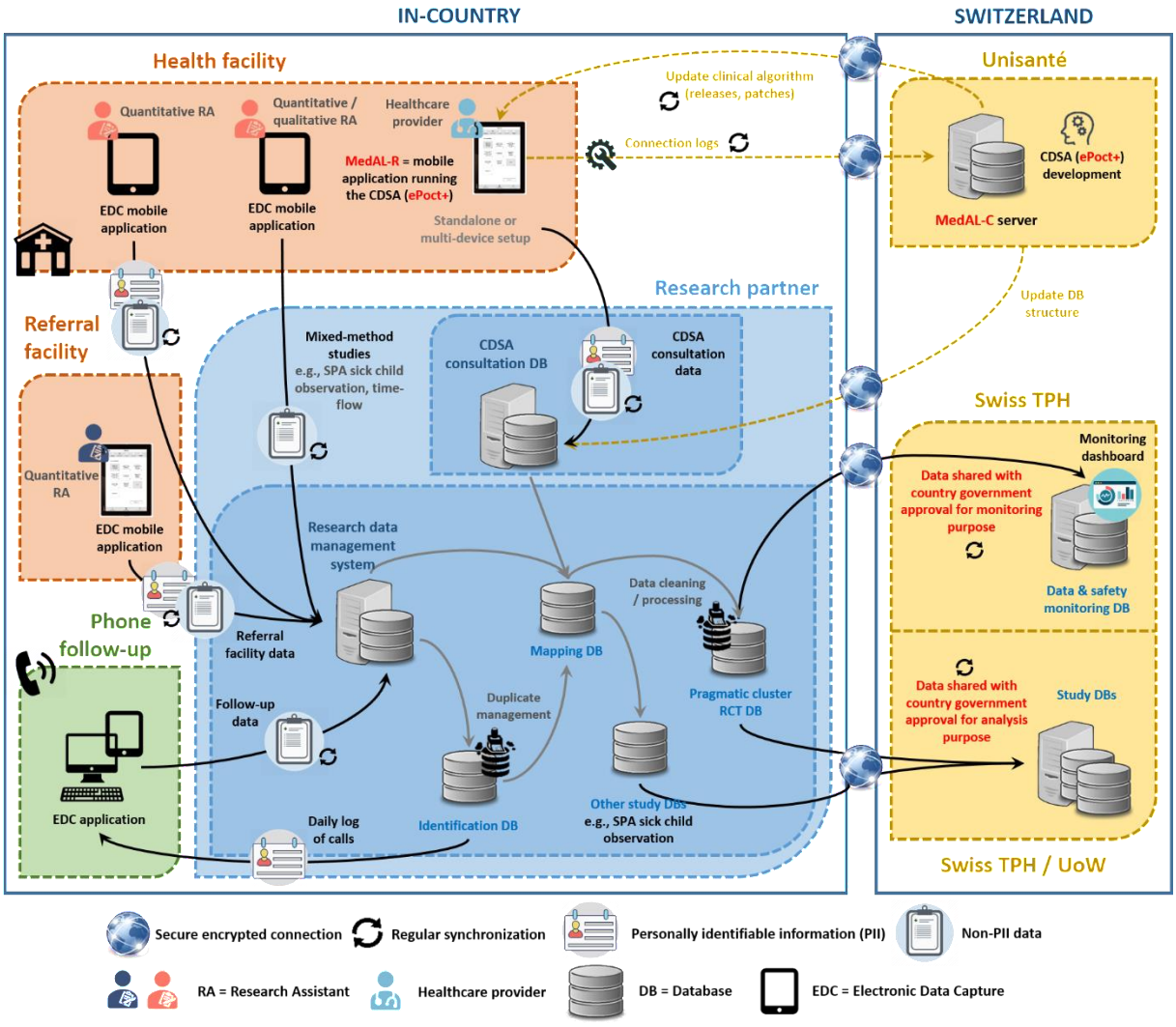


Fig. 7. Overview of the research data and consultation data flows and supporting IT architecture used within the TIMCI project. MedAL-R can receive updates directly from MedAL-C to be able to deploy patches as needed. The MedAL-C server is hosted in Switzerland and managed by the IT Unisanté team in Lausanne. This server will receive connection logs from the tablets when a network access is available.

8.2.2 Data entry, handling and validation

Quantitative research data

The EDC mobile application will perform offline validation (e.g., range and consistency) checks that immediately detect and request the correction of erroneous data entry, and prevent missing values upon compulsory data entry, guaranteeing completeness of the mandatory datasets. Standardized dictionaries such as SNOMED CT and ICD-10 will be implemented within the data collection tools (and hence available offline) in order to code clinical findings and symptoms in a consistent way. To ensure the integrity of the study-related duties and any data generated, each quantitative research assistant will log into the EDC mobile application using their secure user name and password. All passwords will be strictly personal and confidential. Electronically signed data from the mobile application will be regularly synchronized with the central server.

Procedures for cleaning and coding quantitative data will be developed by the core data manager at Swiss TPH to ensure consistency across countries. These procedures will be further described in the Data Management Plan. Data cleaning and coding activities will be supervised by the data manager in charge in each country, with possible country-specific additions. These activities will include, but will not be limited to, data de-identification, duplicate management and free text management. Data quality checks will be run on a daily basis. A follow-up log based on baseline visits and referral facility log based on Day 7 phone follow-up outputs will be generated daily. The server will certify the integrity of data by using in-built range and consistency checks to prevent errors during data manipulation.

An audit trail will be maintained for the life of the study for all quantitative research data. If a correction is required for an entry, the time and date stamps will track the person entering or updating entry and creates an electronic audit trail. There will be access control on the audit trails so that a user cannot view information about another user or site that they are not allowed to see. A synthetic visualization of the audit trail will be readily accessible by the data manager in charge in each country, so that they can check all modification to data and meta-data and who made them, as well as all successful and attempted system logins. At critical junctures of the pragmatic cluster RCT, the research database will be reviewed and cleaned per established procedures, before being locked. Consistency between the data cleaning procedures in each country will be regularly reviewed. In addition, a dashboard will be developed for facilitating the review of key indicators to trigger in-depth data review.

CDSA individual consultation data

Each patient attending an intervention facility will be given a unique identifier in the CDSA used by this facility. Each new visit at the same facility will create a new case for the patient. Similar to EDC mobile application, MedAL-R will perform offline validation checks and relies on standardized dictionaries code clinical findings and symptoms in a consistent way. MedAL-R

will allow the modification of consultation data by different healthcare providers within the health facility until the case has been closed to ensure the flexibility required by the clinical workflow. Routine consultation data from MedAL-R will be regularly synchronized with the CDSA server. Consultation data records will be electronically signed before being transferred to the central research database. A timestamp (date, time, device identifier number) will guarantee the integrity of the data associated with the electronic signature.

In non-study facilities, CDSA consultation data will be anonymised before transfer, so that no PII will leave the facility and these data can never be re-associated with the underlying individual.

Qualitative research data

Qualitative data will be voice recorded and complemented by written notes, drawings, photos and videos by a dedicated qualitative researcher. Audio-recordings, notes, drawings, photos, videos, and GPS coordinates and document review grids will be either written up in electronic files and/or directly transferred to the qualitative researcher's computer and uploaded to the central server. Electronic files will be stored on two separate password-protected devices according to country specific mechanisms (e.g. audio recording stored on a password protected computer and on an external drive in a password protected folder in locations where internet cannot be accessed; back-up on server as soon as internet is available and deleting from external drive).

Qualitative research data will be backed up at the first possible opportunity. Where connectivity to the central server is not possible, field teams will make a second back up on an encrypted external hard drive. Transcription and translations from voice recordings and hand-written notes will be entered into Word documents and translated into English and/or French. Hand-drawn process maps and health care seeking pathways will be digitalized.

8.2.3 Data privacy protection

Personally identifiable information will be maintained confidentially under strict SOPs, complying with all applicable international regulations. Study team members with access to PII will sign a confidentiality agreement prior to collecting or accessing any of the data. Each participant will be given a different unique alphanumeric identifier for each study in which he/she is associated. Voice recording files and written notes that refer to the same participant interview will be labelled using the same identifier. The IT infrastructure will provide password protected devices, laptops with encrypted hard drives, fileserver with customizable access rights, and documented and audited access right management. All transfer of data via the internet will be done via secure, encrypted connections.

All quantitative data collection instruments will be stored in closed, locked file cabinets with restricted access. The EDC platform will be encrypted and password protected. All study databases will be safeguarded against unauthorized access by established security procedures. A double coding procedure will ensure that participant re-identification is not feasible. The

name of the facility of enrolment, geographic information and some elements of dates related to facility visits will also be de-identified. To further prevent re-identification of individuals (patients, caregivers and healthcare providers), where appropriate, data will be de-identified so that their level of granularity that does not allow indirect identification of an individual. In addition, the data imported from another study datasets will be processed (e.g., aggregated data, categorization of numeric values) so that a unique combination of facility and individual characteristics does not allow indirect identification of an individual.

Voice recordings, photos and videos, as well as GPS mapping, will be deleted from the devices after transcription, translation and digitalization. Transcriptions and translations of audio data, typed-up field notes will be stored on the central database in password protected folders accessible only to authorized qualitative researchers. Hand-written notes and drawings will be stored in locked filing cabinets in an area with restricted access. During the coding process qualitative data uploaded into the coding software will be manually de-identified (i.e. replacing names, locations, other personal identifiers) ensuring that only de-identified interview material is stored in the programme.

8.2.4 Data quality assurance and control

Quality assurance activities across all studies will be more intense during study start-up to ensure quality data practices are instituted from the start of the trial. Further details will be given in the DMP and SOPs.

All research assistants will be trained to provide information and seek written consent using the information and consent form. Separate trainings will cover all aspects of quantitative data collection and all aspects of qualitative data collection. A competency assessment using scenarios will be done before commencing field work.

Data reconciliation between the different visits of the same child will be one of the most crucial data quality activity in the pragmatic cluster RCT. Specific procedures will be developed for this purpose. To identify repeat visits of children that may re-attend the study facility where they enrolled or any other study facility during the follow-up period, participants will be given a study card (or sticker) with a unique ID number. Retrospective search for data at referral level will be restricted to facilities within the geographical area where the study is running and will be targeted to include only children reported to have attended hospital by the caregiver at follow-up and referred children lost to follow-up. The name of the referral facility will be requested during the follow-up call. If available, it should further restrict the scope of the search and the probability of negative matches when cross-checking the participant identity. Children who re-attend any study facility more than 28 days after their previous enrolment will be enrolled for the new disease episode and given a new ID number. If available, the old ID number will be recorded to facilitate linking of the different disease episodes. Data to be potentially reconciled will be flagged by automated cross-check of a set of personal identifiers. Given that

personal identifiers may not be identically recorded at each visit, fuzzy matching methods will be used to calculate a score of similarity between records and likelihood that they relate to the same child. Reconciliation of records with high similarity scores will be manually validated.

The validity of quantitative data will be ensured through data definitions and field restrictions in the electronic systems. Acceptable error rates in critical quantitative data will be established during the pilot phase and documented in the DMP. Pre-defined automated high-frequency checks will be performed including checks of completeness and indicators of other irregularities such as completion time. Reports will be shared with individual quantitative research assistants and their supervisors. In addition to reviewing automatically generated reports for their supervisees, supervisors will perform random accuracy checks of research data compared to available source data. In the pragmatic cluster RCT, quantitative research assistants responsible for the Day 7 call will be audited through random checks of phone logs and repeat phone calls. After confirmation that the study databases contain all expected data, an internal review will check their accuracy and quality. Once all the required data quality assurance and control have been completed and passed, the study databases will be "locked".

During the pilot phase, qualitative tools will be translated and back translated, and tested using cognitive interviewing to ensure questions asked are understood as intended and felt to be appropriate. Regular quality checks of transcriptions and translations will be conducted by the qualitative researcher in each country.

8.3 Statistical methods

Statistical methods will be described in detail in the Statistical Analysis Plan (SAP).

An interim analysis is planned to be conducted three months after the start of the study to assess recruitment rate, follow-up and sample size assumptions. The Data Monitoring Committee will review the results and make recommendations to the research steering committee as to whether:

- the sample size calculation should be adjusted based on estimated values in the control groups;
- the primary outcome measures should be revised due to a high number of missing values;
- the study should be terminated prematurely due to inability to achieve its objectives.

As comparisons between arms and hypothesis testing will not be performed, no adjustements to the final analysis are necessary.

We will conduct all analyses described below per country, in addition to a pooled cross-country analysis. Quantitative analyses will be conducted using Stata (or alternative statistical analysis software, depending on investigator for certain country-specific or sub-study specific analyses).

8.3.1 Pragmatic cluster RCT

Analyses will follow CONSORT guidelines and intention-to-treat principles, including all participants as randomized. A flowchart will describe the inclusion and follow-up of participants by study arm.

Baseline characteristics will be described by study arm with summary statistics such as median and interquartile range or number and percentage; no formal testing between arms will be performed. Outcomes will be described by arm using summary statistics. The two primary outcomes, the proportion of children with a severe complication and the proportion of children appropriately hospitalized, will be assessed using a random effects logistic regression models with the cluster included as a random effect. Results will be reported with odds ratios, risk differences and 95% confidence intervals (CI). Binary secondary outcomes will be evaluated in the same way. Continuous secondary outcomes will be assessed using random effects linear regression models, reporting adjusted mean differences between arms with 95% CIs.

All models will be adjusted for randomization stratification factors and any baseline variables found to be randomly imbalanced across arms. Assessment for imbalances between baseline variables will be by visual inspection only; there will be no formal testing of baseline characteristics across randomized groups.[53,54]

For the analysis of the primary endpoints, we will use a hierarchical fallback procedure, which is a closed test procedure using a weighted Bonferroni.[55,56] This method recycles unspent significant levels to test subsequent hypotheses with a pre-specified hypothesis sequence.[57] This uses alpha propagation making it more powerful that the Bonferroni method.

The primary outcomes will be evaluated according to hierarchy of importance as follows:

H_1: There is no difference between the experimental arm and control arm with respect to severe complications by day 7

H_2: There is no difference between the experimental arm and control arm with respect to hospital admissions within 1 day of the primary consultation

First, we would test the null hypothesis H_{12} which is that neither H_1 nor H_2 are significant. We would reject the null hypothesis of H_{12} if either $p1 \leq \alpha 1$ or $p2 \leq \alpha 2$ where α is equally distributed between the endpoints i.e. $\alpha 1 = 0.025$ and $\alpha 2 = 0.025$.

If we fail to reject the null hypothesis H_{12} then we will stop and this point and conclude that the study is negative as neither of the co-primary outcomes were significant. If we reject the null hypothesis H_{12} then we would go on to test H_1 and H_2. If $p2 \leq \alpha 2$ then we reject H_2 and test H_1 as $p1 \leq \alpha$. If $p2 > \alpha 2$ then we do not reject H_2 and test H_1 as $p1 \leq \alpha 1$.

All outcomes will be evaluated regardless of the outcome of the first evaluation. For each intervention arm, the overall trial will be interpreted as positive if either primary outcome is

positive compared to control. This will be assessed separately in India and Tanzania and will also be assessed across the two countries.

Missing data on key endpoints is to be expected due to the pragmatic nature of the study. If substantial data are missing (e.g. >10%), a set of sensitivity analyses shall be carried out where missing data are handled following different approaches such as, best/worst case scenario, complete cases, simple imputation or multiple imputation with chained equations (71, 72). The impact of each method on the primary outcomes results will be taken into account when interpreting the final analysis results. Further information on missing data handling will be detailed in the SAP.

We will conduct planned subgroup analysis of the primary outcomes to assess effect modifiers, specifically age, sex, clinical presentation (particularly cough / difficulty breathing) and diagnosis (particularly severity classification) and healthcare provider decision-making (particularly referral and antimicrobial prescription). Effect modification will be assessed by incorporating an interaction between trial arm and the variable in the model, acknowledging that power will be low. Planned sensitivity analysis will be conducted including only the first disease episode of each child during the study period (as some children may attend the facility on more than one occasion over the 12-month period). Further exploratory analysis will be detailed in the SAP.

8.3.2 Other mixed methods studies

Quantitative

Descriptive analysis will be conducted of the data obtained from the SPA studies by country, facility type and location and child and healthcare provider characteristics. Indices of adherence to key practices will be described and compared between arms and time points (pre-intervention and the 4 post intervention time points). Time-flow data will also be compared between pre-intervention and each of the post-intervention periods and between facilities of different RCT arms. Effect modifiers will be explored.

Relevant aggregated data from routine HMIS will be used to monitor trends over time in all facilities and administrative regions where the project is running. This will be compared with routine CDSA data and study data to identify indicators for longer term monitoring of the intervention.

Descriptive analysis will be conducted of the quantitative data (e.g. socio-demographic questions) collected as part of the qualitative studies.

Machine learning methods will be used to identify prognostic features associated with outcomes.

Qualitative analyses

Quality assurance steps for transcription and translation will be built into the process.

Qualitative data will be transcribed verbatim using modified transcription rules by Kallmeyer and Schütze[58] verbatim and translated into English (and/or French. A random sample of transcripts and translations will be quality checked by listening to audio-recordings and back translations and measures taken accordingly. After familiarization with all interviews/FGDs, an experienced qualitative researcher will code the transcripts using a qualitative coding software. A random sample of a total of 10-15% of the qualitative interviews will be coded using the framework analysis by Gale et al.[59] following an inductive and deductive approach; in-vivo codes will be created where applicable. The final draft code tree will be exported, codings deleted and the same interviews coded by a second and independent qualitative researcher for inter-rater reliability check. The Kappa-Cohen value will be calculated. Differences in coding will be discussed and a joint solution developed. A Kappa-Cohen value above 80% will allow using the code tree after minor adaptations based on joint agreements by the two coders and for final coding. The finalized code tree will be used to code the entire material. Finally, each code and each sub-code with its coded material will be exported into excel tables. A team of qualitative researchers will review the tables and jointly analyse the data identifying patterns, similarities, and differences as well as change over time. Secondary analysis of data from all study countries may be conducted jointly and findings compared across countries.

Document review

The document review data will be entered into a grid with predefined categories in line with process evaluation criteria. Data will be triangulated against qualitative and quantitative data collected.

Process evaluation

The process evaluation will draw on data from the various sub-studies to describe the context, implementation process and mechanisms of impact as outlined in **Fig 8**.

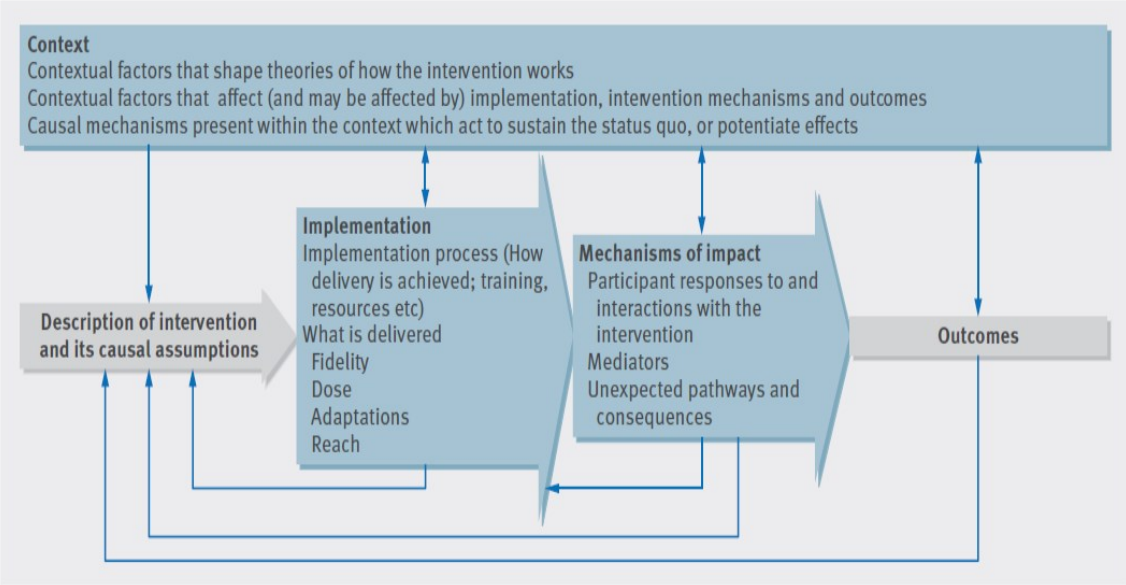


Fig 8. Overview of MRC process evaluation of complex interventions (Image credit Moore et al)[35]

8.3.3 Cost and cost-effectiveness study

When all the cost components have been collected, the data will be aggregated or collated in Excel. Once the summary is completed, a cost profile of the programme activities will be derived and after the total costs of the programme have been calculated, the unit costs will then be derived (i.e. total costs divided by the sample size). These profiles are useful in highlighting major cost components (and thus identifying potential areas where improvements in efficiency may have significant impact on costs). For this evaluation, analysis will focus on full costing and incremental costing approach. Total, average and incremental costs per year will be estimated. Costs associated with increasing the oxygen saturation referral threshold will be estimated based on the additional proportion of children meeting referral criteria.

When available, effectiveness data will be combined with the cost data and cost per DALY averted will be estimated. Effectiveness will be modelled using the information on severe outcomes such as mortality, and secondary hospitalization, adjusting as far as possible the level of severity of illness of the child at presentation.

At primary care facilities, these will include measurements (when taken by healthcare providers) such as anthropometry, respiratory rate, temperature and routine investigations where available (e.g. haemoglobin, CRP), and oxygen saturation (post-intervention/in intervention arms). We will also use diagnosis and severity classification recorded by primary care providers.

At hospital level, we will also utilize the same measurement data, and other vital sign data (such as a paediatric early warning score if recorded), decision to admit, intensive care and / or ventilation, provisional and final diagnosis, admission outcome (discharge, death, left against medical advice) and length of hospital stay. We will then use these indicators, along with mortality from phone call follow-up data by Day 28, to predict probability of mortality based on available literature. The DALY calculation will be based primarily on probability of mortality

over a relatively short horizon (to be determined based on a review of literature, likely between three and six months to reflect the time windows used in post hospital discharge mortality studies). The types of illnesses considered do not typically lead to long-term disability, and the duration of illness is too short to have a big impact on DALY calculations. We will not use age weights: we will use GBD (2017) DALYs, [60] and we will not use country-specific disutility data, both since we are unsure these exist for all the countries, and they render cross-country comparisons more difficult.

Sensitivity analysis

As not all data will be available precisely, we will explore possible assumptions using sensitivity analysis which will assess how the estimates would react to percentages changes in the value of the assumptions. It can help the reviewer to determine which parameters are the key drivers of a model's results. Guidelines and standard textbook recommend that economic evaluations should include sensitivity analysis.[61] We will undertake one-way sensitivity analysis of key parameters using the major outcome and cost parameters. Typically, such analyses are more sensitive to the assumptions about outcomes, and for this we have to rely on the best judgement of the epidemiologists.

9 Monitoring

All studies will be conducted in accordance with the protocol and international and applicable national regulatory requirements. The pragmatic cluster RCT will be monitored in accordance with ICH Good Clinical Practice in addition to the aforementioned requirements. Independent trial monitoring will be conducted by the Clinical Operations Unit within the Department of Medicine at Swiss TPH (separate unit from lead investigators). The Clinical Operations Unit will be responsible for setting up and carrying out the monitoring of trial conduct using a risk-based approach, combining on-site, remote and centralised monitoring.

On-site monitoring will be done for a random selection of sites and can be triggered in addition for sites appearing to be breaching. Screening data, consent, recruitment rates and missing data on primary and important secondary endpoints will be reviewed remotely. Findings of remote monitoring may influence on-site monitoring.

For the pragmatic cluster RCT, an independent data monitoring committee (DMC) will be established, comprising of a Chair, Biostatistician and Clinician with relevant experience. The DMC will meet after three months from the study start to review and evaluate the interim analysis results. In addition, regular reviews will be conducted throughout the course of the study as described and agreed in the DMC charter. The DMC will provide the research steering committee with recommendations after blinded and unblinded reviews of relevant data on trial progress and safety, and any issues identified by monitors.

9.1 Harms

We will collect data on death and secondary hospitalisations as part of the primary outcome. Given the low-risk nature of the intervention, the pragmatic nature of the trial, and that deaths and hospitalisations are, unfortunately, expected in this population, the DMC will review summarised rates of adverse events will be summarized by intervention and control arms and included in a report for the DMC to review. If a considerate difference (of >30%) is found, we will conduct a more in-depth evaluation (through analysis of clinical data, and collection of additional case note data from hospitals if required) of whether deaths or secondary hospitalisations are attributable to the intervention will be conducted.

9.2 Auditing

Internal or external auditing will be triggered in case of concerns about trial conduct.

10 Ethics and dissemination

10.1 Research ethics approval

Following two independent scientific merit reviews, the protocol will be submitted to all relevant research ethics committees / institutional review boards in each country. Receipts of submission to each local ethical review board will be submitted with the master protocols to the WHO Research Ethics Review Committee (ERC).

For India, this includes a) the National Health Ministry, Uttar Pradesh (NHM-UP), b) the Institutional Ethics Committee (IEC) of KGMU and c) the Health Ministry's Screening Committee (HMSC) of the Indian Council of Medical Research (ICMR)

For Tanzania, this includes a) the National Health Research Ethics Committee (NIMR), b) the Ifakara Health Institute IRB (IHI-IRB) (c) the Medical Research Coordinating Committee (MRCC), and (d) Commission of Science and Technology (COSTECH).

Regulatory status of the intervention

Pulse oximetry

The pulse oximetry device selected for the TIMCI project is the Acare AH-MX device. This was selected as it is available through the UNICEF catalogue, which infers a level of quality and device appropriateness. The competitive procurement process established by UNICEF incorporates pulse oximetry specifications developed through a collaborative process involving global and national level experts. Devices in the catalogue have regulatory approval from a stringent regulatory authority (SRA) such as the United States Food and Drug Administration (US FDA) or Conformité Européenne (CE) mark.

Country level regulatory approval will vary. It is possible that the devices will have approval in some of the countries. If the device does not have pre-existing regulatory approval in a project country, the project team will work with the MOH to receive a waiver to use the device for the study purposes. If appropriate, the study team will continue to work with the manufacturer and MOH in each country to receive a permanent regulatory approval to facilitate scale of that device.

Clinical Decision Support Algorithm

The regulatory classification of clinical decision support software is currently subject to debate at the US FDA, depending on how and in what context the software is used. In this study, the CDSA is intended to provide decision support for the diagnosis and treatment of childhood illness. It will collate and analyse patient-specific information to suggest possible diagnoses and recommend treatment plans or diagnostic tests to healthcare providers (HCPs). These suggestions and recommendations will be evidence-based and will support the decision-making of the HCP when considering treatment options or diagnostic tests for a patient. The HCP may then use this information to make a decision about the care of the patient, along with

other information and factors of which he/she is aware. In addition, the CDSA presents a low risk profile since it will supports the implementation of and strengthen the adherence to standard clinical guidelines. These functions do not meet the definition of a medical device per country regulatory authorities and the CDSA is therefore regarded as a non-regulated device.

10.2 Protocol amendments

Any important protocol modifications will be submitted to relevant research ethics committees, trial registries and study sites including participants where appropriate.

10.3 Consent or assent

10.3.1 Pragmatic cluster RCT

Information and consent procedures will be conducted in accordance with national regulatory and ethical requirements (for example on the criteria applied to determine capacity of a caregiver to provide consent). Prior to study start, information and consent mechanisms and content will be reviewed and refined with community advisory boards and piloted with participants and modified if necessary to ensure they are appropriate.

As the intervention is at the facility level, approvals from relevant authorities will be sought before engaging with facility management and staff prior to study start.

Informed consent from caregivers will be sought for the collection of data and follow-up of individual children in the pragmatic cluster randomised controlled trial. Information will be provided in the waiting area of facilities in accordance with country-specific mechanisms, which may include written, pictorial, video or spoken information. Potentially eligible children will be identified at registration (based on age) during working hours and will be screened by a research assistant in the waiting area for eligibility. Consecutive caregivers of eligible children will be provided with more detailed information on the study and provided with an opportunity to ask questions. Written informed consent will be obtained for those that agree to participate. In the case of an illiterate caregiver, an impartial witness will be asked to sign on their behalf, along with a thumbprint of the caregiver. Caregivers will be informed that they can withdraw at any point up to study completion (and anonymization) and that non-participation or withdrawal will not affect their care in any way. If the clinical condition of the child requires immediate treatment, this will supersede the written consent process, which will be conducted once the child is stabilized, and if this is still not possible, they will not be included in the study.

10.3.2 Other mixed methods studies

Additional consent from caregivers, healthcare providers and stakeholders will be sought for the embedded mixed methods studies. For the SPA, this will be conducted at the health facility as per the pragmatic cluster RCT.

The person responsible for the recruitment for qualitative studies (possibly with the help of an assistant such as a community health worker) will invite caregivers for participation providing

verbal information and asking for verbal consent. Prior to the start of the IDI or FGD participants will receive written information and asked to provide written consent. For method acting FGDs, explicit consent will be sought for photo- and video-recording. Participants will have the option to take part in the FGD but withhold consent for video-/photo-recording. In this instance, the respective participants will be kept out of shot.

For healthcare providers written information will be provided and written consent sought. No information on individual decisions to accept or decline participation will be shared, neither with supervisors nor with health authorities. For key stakeholders, written information will be provided and verbal consent sought prior to an interview via telephone; or written consent if an interview is conducted person-by-person. Stakeholders participating in the online survey will receive information on the survey in an email and need to provide consent by ticking a box in the survey prior to proceeding with the questions.

10.3.3 Cost and cost-effectiveness study

We will obtain consent from healthcare providers (including medical and non-medical personnel) participating in the costing study. An information sheet on the study will be provided prior to data collection, discussed with target providers from sampled health facility before written consent is obtained. Data relevant to the costing study collected as part of other studies will be extracted and provided as anonymised, summary data for the purposes of the costing study.

10.4 Confidentiality

Participant identifiable data will only be collected for the purpose of study conduct (participant follow-up, duplicate checking, and qualitative analysis) and will be destroyed in accordance with standard operating procedures.

10.4.1 Pragmatic cluster RCT

Study and participant data will be handled confidentially and will only be accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. All personnel who have access to data forms will be asked to sign confidentiality agreements. We will make sure consent forms make provision for future sharing of data.

A unique identifier number will be assigned to each participant (including healthcare providers) and facilities.

10.4.2 Other mixed methods studies

Qualitative data will be audio recorded using an encrypted device after which it will be transcribed and translated verbatim (personal identifiers not removed) in each country with staff signing a confidentiality clause. During walking interviews audio-recordings will only be

done during the bilateral interview between the caregiver and data collector (but e.g. switched off when the caregiver has a conversation with a third person). Hand-written notes of relevant conversations and observations will be taken in addition. Audio data will be fully de-identified when uploaded to and read through in the qualitative coding programme and according to SOPs including use of pseudonyms. Audio files will be destroyed after quality checking of transcription and translation has been completed. GPS tracking data of the walking interviews, as well as photos and videos of the method acting FGDs will be additionally analysed. Audio tracks from videos will be removed after transcription has been conducted and replaced by transcripts and/or sub-titles. Only the qualitative data collectors facilitating the FGD and the authorised qualitative researchers (including qualitative researchers in country, in other TIMCI countries, and the Swiss TPH lead social scientist) will view the non-de-identified acting method videos/photos for the purpose of primary analysis, after signing a confidentiality agreement and agreeing with the Code of Conduct. All raw qualitative material will be destroyed after validation of the final database of consolidated qualitative material. Further information on data management can be found in Section 8.2.

10.4.3 Linking between pragmatic cluster RCT and mixed methods studies

Data collected during the mixed-method studies will be linked with a subset of data collected during the pragmatic cluster RCT. The privacy protection of enrolled participants will be ensured following a multiple coding procedure: each participant will be given a different unique alphanumeric identifier for each study in which he/she is associated. These identifiers will be linked with the RCT identifier by the clinical management system. This means that the knowledge of both codes and their mutual link is needed to access the full dataset about a participant. The link between two study identifiers will be maintained confidential information under strict operating procedures (in a central, secured database with restricted access rights) for the duration of the study. In particular, this information will not be shared or accessible outside of the research institution. When all data validation and regulatory requirements have been met, the link between study identifiers will be destroyed, so that all study databases are ultimately fully independents.

10.4.4 Cost and cost-effectiveness study

Confidentiality of personnel cost of staff participating in the study will be ensured by protecting the identity of staff whose grade level will be collected as part of the study. Information on staff salaries collected will be stored in a restricted cabinet with only access to the principal investigator. All data collected will be stored in a research server with other intervention data with limited access. We will assign unique identifiers to health facilities and maintain a link between facility name and identifier stored in the research server. However, for the analyses which will be performed in Waterloo, Canada, only de-identified data will be used.

10.5 Risk and benefits to participants

No major risks are foreseen given the low risk nature of the intervention. The only potential risk envisaged is the time involved in participation in the study, which will be clearly outlined during the informed consent process. The potential risk of delaying care of sick children as a result of recruitment to the study will be mitigated by training of research assistants and sensitization of healthcare providers to ensure that they are aware that no research activity should take priority over clinical care. Scenarios in which they should not attempt to recruit participants will be provided during training to ensure this is clearly understood.

No participants will receive incentives, but participants in qualitative mixed methods studies may receive a small reimbursement (monetary/non-monetary) for their time (e.g. to compensate for travel costs or lost time) and according to country specific standards.

In order to avoid the risk of diverting healthcare providers from clinical duties, all data collection from healthcare providers will be scheduled at appropriate times. For the SPA interviews, this will be at a less busy time of the day (e.g. towards the end of the day) or just after the end of their shift. IDIs and FGDs will take place after hours or at weekends unless express (generic, not participant-specific) permission is provided to conduct during working times without clinical duties.

Whilst there are no direct benefits to participants, this study could benefit them and their community in future as a result of the understanding generated by this study.

10.6 Access to data

Access to study data will be governed by a data sharing agreement between each country research partner, Swiss TPH, UoW and PATH, in accordance with country-specific regulations. The final, anonymised datasets will be made available on an open access data sharing platform after the end of the study, in order to promote transparency and facilitate global cooperation in child health research.

10.7 Dissemination policy

The protocol will be published after all ethical approvals have been received.

Findings from the study will be shared through community engagement mechanisms described in Section 6.3. Findings will also be shared with the healthcare providers at facilities involved in the study, and supervisors / other stakeholders within district health management teams. Advocacy work through various mechanisms at national and international level based on the findings of the study will be conducted as part of Output 4 of the TIMCI project.

Globally, the project is collaborating closely with technical partners, UN agencies, and the WHO to refine research plans and ensure evidence generation is directly applicable to national and global scale-up. A key output of the TIMCI project is focused on advocacy and policy adoption. Policy and guideline landscapes have been conducted in each country and these are informing

advocacy strategies that are under development. The goal of these advocacy strategies is to work with the governments to incorporate learnings from these studies into routine practice. Pulse oximeters are currently available at a wide range of prices and PATH is planning to provide technical assistance to the governments to support procurement of appropriate devices for scale-up. Other activities to support scale-up focus on clinical guidelines, HCW training curricula, procurement guidance, financing plans, and annual budgets.

Results will be shared with the wider scientific community through presentations at national and international conferences, and through open-access peer-reviewed journal publications.

Tab. 8. Multi-method intervention evaluation overview

	Sub-study title	Objectives	Design	Tools
Impact of intervention on QoC (health outcomes, key practices)	Pragmatic cluster randomised controlled trial (India & Tanzania)	Large-scale evaluation of impact of pulse oximetry and CDSAs on health outcomes (death, hospitalisations, cure rate) and healthcare provider practice (antimicrobial prescriptions, referral decisions)	3-arm parallel cluster RCT comparing: • Pulse ox + CDSA (Tanzania only) • Pulse ox + paper job aid • Routine care (refresher training)	D0 – clinical/sociodemographic data at facility
				D7 – primary outcome
				D28 – secondary outcome
	Longitudinal observational study (Kenya, Senegal)	To evaluate impact of pulse oximetry / CDSAs on quality of care (referral, antimicrobial prescriptions with exploratory assessment of outcomes	Quasi-experimental pre-post: • 3 mo baseline • 1 year intervention (early/late) • 3 mo comparison Q1 and Q5	**D0 – clinical/sociodemographic data at facility**
				D7 - outcome / health-seeking
	Service provision assessments	To evaluate the effect of the intervention on adherence to IMCI guidelines, including the correct classification and management of children under five years & to evaluate health system factors associated with impact	Periodic assessment (in each phase) using Service Provision Assessment methodology – i.e. collecting data at facilities for (1-5) days per facility per quarter	Facility assessment
				HCP interview
				Sick child observation
				Exit interview
Evaluation of implementation (incorporating process evaluation, acceptability framework, realist approach)	Facility-based process mapping and time-flow study	To understand change in care processes including time taken for consultation and use of devices	Baseline and intervention process mapping with group discussion at sample of facilities, with observation and timing of key steps	Process map
				Time-flow study
	Healthcare provider perceptions of the intervention	To understand acceptability, usability of devices by HCPs and gain insight on perceived facilitators and barriers to successful implementation	Qualitative work with HCPs from a sample of facilities in pilot, early and late intervention	IDIs
				FGDs
	Caregiver perceptions of the intervention and health-seeking behaviour	To understand knowledge, attitudes and behaviour (i.e. experience of care, care seeking pathways, perception of devices, adherence to advice (in last consultation), child health literacy) related to the health care received	Community follow-up of individual caregivers, purposively selected (e.g. referred / unreferred, adverse / non-adverse outcomes) during intervention period	IDIs, Case Studies
		To explore knowledge, attitudes, values, beliefs related to the devices, experiences with clinical care with a focus on aspects of quality of care (i.e. people-centred outcomes, provision of care and experience of care).	FGD of purposively selected caregivers (urban / rural, type of facility, location) grouped by age/sex; During pilot, early and late intervention phases	FGDs
	Stakeholder perceptions	To understand health care provision in the non-intervention arm; and specifically intervention mechanisms / decision-making, identification of facilitators and barriers to implementation, best practices, inform package for scale	Baseline & late intervention	KIIs with govt & project stakeholders
	Project data review		Late intervention	Desk review incl. project data e.g. on devices, training

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12 Appendix

12.1 Informed consent forms appended to the protocol

- 01 TIMCI ICF RCT V0.3.3, 19Nov2020
- 02 TIMCI ICF RCT CG SPA V0.2.2 19Nov2020
- 03 TIMCI ICF RCT CG TF V0.2.2, 19Nov2020
- 04 TIMCI ICF RCT CG Walking Interview V0.2.3, 19Nov2020
- 05.1 TIMCI ICF CG IDI intervention V0.2.3 19Nov2020
- 05.2 TIMCI ICF CG IDI non-intervention V0.2.3 19Nov2020
- 06 TIMCI ICF CG FGD v0.2.2, 19Nov2020
- 07 TIMCI ICF CG method acting v0.2.2, 19Nov2020
- 08 TIMCI ICF RCT HCP SPA V0.2.2, 19Nov2020
- 09.1 TIMCI ICF RCT HCP IDI V0.2.3, 19Nov2020
- 09.2 TIMCI ICF RCT HCP IDI pre-intervention V0.2.3, 19Nov2020
- 10 TIMCI ICF RCT HCP FGD V0.2.3, 19Nov2020
- 11 TIMCI ICF SH KII V0.2.3, 19Nov2020
- 12 TIMCI ICF SH survey V0.2.3, 19Nov2020
- 13 TIMCI ICF RCT costing V0.3, 19Nov2020

12.2 Study instruments appended to the protocol

- 01-TIMCI RCT CRF description v1.5 clean, 29May20
- 02-TIMCI RCT SPA Exit Interview instrument v1.4 clean, 29May20
- 03-TIMCI RCT SPA Facility Assessment instrument v1.4 clean, 29May20
- 04-TIMCI RCT SPA HealthCare Provider Interview v1.4 clean, 29May20
- 05-TIMCI RCT SPA Sick Child Observation instrument v1.5 clean, 24Nov20
- 06-TIMCI RCT process map timeflow tool v3.0, 29May20
- 07-TIMCI caregiver walking interview v4.0
- 08-TIMCI caregiver FGD v5.0, 19Nov20
- 09.1-TIMCI stakeholder KII v5.0, 19Nov20
- 09.2-TIMCI stakeholder KII v3.0_TZ, 19Nov20
- 10-TIMCI document review matrix v3.0
- 11-TIMCI stakeholder survey v4.0
- 12.1-TIMCI HCP IDI v5.0, 19Nov20
- 12.2- TIMCI HCP IDI v3.0_TZ, 19Nov20
- 13-TIMCI HCP FGD v5.0
- 14.1-TIMCI caregiver IDI v5.0, 19Nov20
- 14.2 TIMCI caregiver IDI v3.0_TZ, 19Nov20
- 15-TIMCI non-medical personnel questionnaire 08.06.20
- 16-TIMCI medical personnel questionnaire 08.10.20
- 17-TIMCI hospital costs 09.06.20
- 18-Training Comm sensitization costs TIMCI 09.06.20

12.3 Budget and collaboration appended to the protocol

12.4 TIMCI Preliminary Theory of Change