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Implementation of the 'Removed Injectable modified Short-course regimens for EXpert Multidrug Resistant Tuberculosis' (RISE study) in Tanzania: a protocol for a mixed-methods process evaluation

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ABSTRACT

Introduction Tanzania is adapting a shortened injectable-free multidrug resistant tuberculosis (MDR-TB) regimen, comprising new drugs such as bedaquiline and delamanid and repurposed drugs such as clofazimine and linezolid. The regimen is implemented using a pragmatic prospective cohort study within the National TB and Leprosy Programme and is accompanied by a process evaluation. The process evaluation aims to unpack the implementation processes, their outcomes and the moderating factors in order to understand the clinical effectiveness of the regimen. This protocol describes the methods employed in understanding the implementation processes of the new MDR-TB regimen in 15 regions of Tanzania.

Methods This study adopts a concurrent mixed-methods design. Using multiple data collection tools, we capture information on: implementation outcomes, stakeholder response to the intervention and the influence of contextual factors. Data will be collected from the 22 health facilities categorised as dispensaries, health centres, district hospitals and referral hospitals. Health workers (n=132) and patients (n=220) will fill a structured questionnaire. For each category of health facility, we will conduct five focus group discussions and in-depth interviews (n=45) for health workers. Participant observations (n=9) and review documents (n=22) will be conducted using structured checklists. Data will be collected at two points over a period of 1 year. We will analyse quantitative data using descriptive and inferential statistical methods. Thematic analysis will be used for qualitative data.

Ethics and dissemination This study received ethical approval from National Institute of Medical research (NIMR), Ref. NIMR/HQ/R.8a/Vol.IX/3269 and from the Mbeya Medical Research and Ethics Review Committee, Ref. SZEC-2439/R.A/V.I/38. Our findings are expected to inform the wider implementation of the new MDR-TB regimen as it is rolled out countrywide. Dissemination of findings will be through publications, conferences, workshops and implementation manuals for scaling up MDR-TB treatments.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This process evaluation study uses a theory-driven approach based on implementation science frameworks designed to evaluate healthcare innovations.
⇒ The evidence to be generated in this study is comprehensive as it involves multiple steps, tools and perspectives from range of actors including intervention designers, implementers, end users and health system actors.
⇒ Using the mixed-methods design reduces the limitations of a single method and provides a comprehensive picture of the studied phenomenon by exploring lines of argument across the collected data and obtained results.
⇒ Missing data and recall bias may challenge the internal validity of the reported findings.

INTRODUCTION

Resurgence of tuberculosis (TB) and associated drug resistance (DR) was highly influenced by emergence of HIV that causes AIDS.[1–3] Clinically relevant drug resistance includes rifampicin resistant (RR) TB, multidrug resistant (MDR)-TB and extensively resistant (XDR) TB. The RR-TB or MDR-TB treatment excludes rifampicin which is the most powerful first-line anti-TB drug while XDR-TB is RR-TB or MDR-TB strains that have additional resistance to key second-line

anti-TB medicines; the fluoroquinolones and injectable agents.[4–6] WHO declared the MDR-TB epidemic as a public health emergency since 1993 and by 2019, the incidence of RR-TB/MDR-TB globally remained stable at 3.3% of newly infected and 18% of people previously treated for TB.[7 8]

Programmatic management of MDR-TB in most of the affected countries started in the first decade of 21st century. Treatment regimens and durations have been very dynamic, started with injectable based for 18–24 months then injectable shorter regimen for 9–11 months and currently injectable-free regimen for 9–18 months.[4 9] The later regimens accommodate new anti-TB medicines such as bedaquiline, delamanid or pretomanid and repurposed anti-TB medicines that include clofazimine and linezolid. Various reports in Tanzania have shown multitude of implementation barriers and bottlenecks including limited knowledge of healthcare workforce, delay in diagnosis of RR-TB/MDR-TB, patients receiving multiple episodes of TB treatment and non-difference in final treatment outcomes in patients diagnosed with new technologies.[9–11] Without addressing the implementation barriers, new technologies including new drugs might not improve the treatment outcomes and therefore WHO suggested that in resource-limited setting, adapting new second-line anti-TB regimen be implemented under pragmatic research approach.[9]

Tanzania is one of the countries that developed a pragmatic protocol and is implementing an injectable-free regimen protocol titled as 'Removed Injectable modified Short—course regimens for EXpert Multidrug Resistant Tuberculosis' (RISE study). Key changes in the MDR-TB regimen include substitution of injectable agents with bedaquiline and prioritised levofloxacin and linezolid as described elsewhere.[9 10] The RISE study is a prospective open-label cohort continuously enrolling eligible patients (patients with newly diagnosed pulmonary MDR-TB) measuring uptake (enrolment), 6-month conversion, serious adverse events treatment results at 9 months (primary end point) and relapse and death during a follow-up period of 12 months (secondary end point). On its full implementation, the project is expected to lead to improved management of DR-TB, that is, treatment success >90%, less side effects and deduced loss to follow-up.

The RISE study is driven by the concept of patient-centred care, and aims to measure the clinical effectiveness of the modified shorter duration injectable-free MDR-TB regimen in RR-TB/MDR-TB population and assesses the programmatic implementation feasibility in the Tanzania health system. The intervention consists of strategies to deploy the shorter injectable-free regimen for MDR-TB in selected health facilities in Tanzania. The strategies include: provision of medicines, drugs safety monitoring and management, supplies and equipment, technical backstopping (training, mentorship, maintenance of equipment, guidelines and Standard Operating Procedures (SOPs), patient support on nutrition and transport, patient education and engaging stakeholders at all levels.

The RISE regimen is being implemented and evaluated in the real-world settings in Tanzania to understand the clinical effectiveness and programmatic feasibility. A process evaluation of the implementation processes and contextual factors is important to facilitating transferability of the RISE intervention to different patients' situations and healthcare contexts. Conducting a process evaluation alongside the implementation of the RISE intervention helps to provide an insight on the context, mechanism, stakeholder reactions and perceptions about the intervention, the implementation outcomes and their moderators. Process evaluations are helpful in differentiating between intervention failure (flawed intervention concept) and implementation failure (poorly delivered intervention), the type III error.[12 13] Process evaluation helps to explain how the intervention was implemented, the mechanisms by which it achieved its effect and how the intervention interacted with the context in which it was implemented.[12 14 15] Typically, process evaluations examine the extent to which the intervention reaches the intended beneficiaries (reach), the extent the intervention is received in the implementation sites (adoption), the extent of the implementation team adherence to intervention protocol and delivery of all the intervention components (quality of delivery and fidelity of implementation), beneficiaries experiences of interacting with the intervention processes (acceptability), the extent to which an intervention is maintained over time (maintenance) and contextual factors that may influence the implementation processes, the precise form of the intervention delivered and maintenance in routine practice.[16] The variations observed in the way the same intervention is implemented in a multisite or pragmatic trial calls for the necessity of conducting process evaluations.

The aim of this protocol is to describe the implementation outcomes (reach, adoption, acceptability, fidelity and maintenance) that will be subsequently analysed and associated with moderating factors in the context of the RISE study when assessing clinical effectiveness and feasibility in Tanzania.

METHODS

Study settings

The RISE project is implemented in 22 health facilities scattered in 15 regions of Tanzania. The regions where the facilities are located include: Dar es salaam, Morogoro, Mbeya, Dodoma, Kilimanjaro, Singida, Kagera, Shinyanga, Mwanza, Geita, Mtwara, Manyara, Lindi, Tabora and Tanga. The regions carry a high share of TB burden in the country, with Dar es salaam contributing 20% of all new case notifications in the country.[17] The distribution in terms of number of facilities per region is found in table 1. To be included in the study, each site should have at least six healthcare workers dedicated to provide services to patients (two clinicians, one Direclty

Table 1 Distribution of health facilities implementing the RISE project

Serial number	Region	Number of sites	Site names
1	Dar es salaam	8	Temeke Regional Referral Hospital, Mbagala Rangi Tatu Hospital, Sinza Hospital, Mwananyamala Regional Referral Hospital, Muhimbili National Hospital, Ukonga Dispensary, Buguruni Health Centre, Kigamboni Health Centre
2	Morogoro	2	Sabasaba Health Center, Kibaoni Health Centre
3	Mbeya	1	Mbeya Regional Referral Hospital
4	Dodoma	1	Dodoma Regional Referral Hospital
5	Kilimanjaro	1	Kibong'oto Infectious Diseases Hospital
6	Singida	1	Singida Regional Referral Hospital
7	Shinyanga	1	Kahama District Hospital
8	Mwanza	1	Sengerema District Hospital
9	Geita	1	Geita Regional Referral Hospital
10	Mtwara	1	Ligula Regional Referral Hospital
11	Kagera	1	Kagera Regional Referral Hospital
12	Manyara	1	Mbulu District Hospital
13	Lindi	1	Sokoine Regional Referral Hospital
14	Tabora	1	Igunga District Hospital
15	Tanga	1	Muheza District Hospital

Observed Therapy (DOT) nurse, one pharmacist, one data clerk, one laboratory technician).

Steps to conduct the process evaluation

In line with previous process evaluation efforts,[15 18 19] we followed the following steps to develop this process evaluation study: (1) clarifying what is to be evaluated by developing a theory of change (TOC), (2) assessing resources for the evaluation and evaluability plan, (3) developing the process evaluation objectives and questions, (4) defining the study design to address the questions, (5) determining the sources of data, measurements and data collection tools, (6) developing a data gathering plan and field work (data gathering exercise), (7) defining data processing and analytical approach and (8) developing results dissemination plan as described in later paragraphs. Figure 1 provides a pictorial presentation of the process evaluation steps to be followed.

Step 1: developing a theory of change

Developing a TOC is a key step in conducting a process evaluation.[20–22] The TOC is 'a theory of how and why an intervention works' which can be empirically tested by measuring indicators for every expected step on the hypothesised causal pathway to impact.[21] It is developed in collaboration with stakeholders and modified throughout the intervention development and evaluation process through an 'ongoing process of reflection to explore change and how it happens'. TOC articulates the change process within interventions and describes the sequence of events linking intervention activities to their long-term outcomes. They make explicit the conditions and assumptions required to enable change and acknowledge the role of context in influencing the process.

To aid the focus of the evaluation and provide additional insight into causal mechanisms affecting outcomes

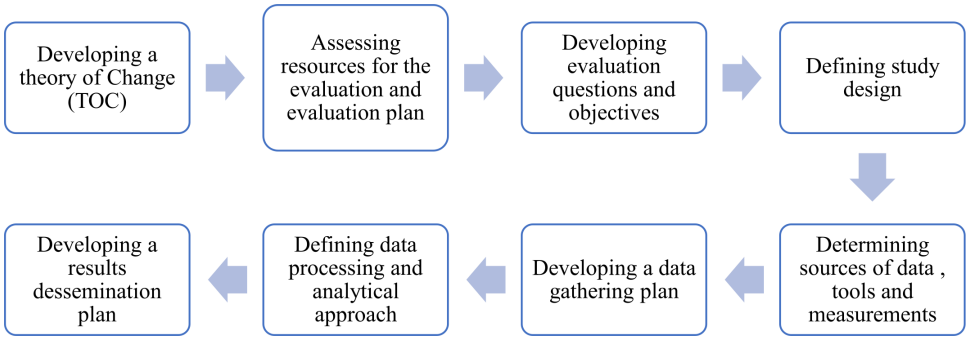

Figure 1 Process evaluation steps of the Removed Injectable modified Short-course regimens for EXpert Multidrug Resistant Tuberculosis project.

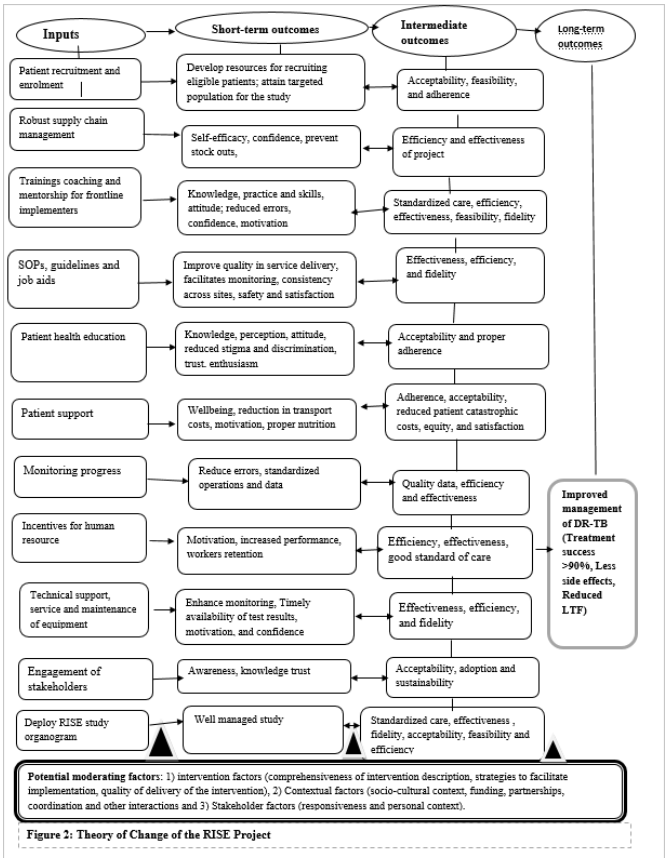

Figure 2 A schematic presentation of the inputs, short-term outcomes, intermediate outcomes and long-term outcomes of the Removed Injectable modified Short-course regimens for EXpert Multidrug Resistant Tuberculosis (RISE) project. DR-TB, drug resistant tuberculosis; LTF, loss to follow-up.

and in line with the recommended steps,[20] we developed the TOC during a 2-day stakeholders meeting. The stakeholders invited for developing a TOC comprised technocrats and programme officers of the National TB and Leprosy control Programme (NTLP), technocrats from the President's Office-Regional Administration and Local Government, specifically the department of health, social welfare and nutrition, representatives from non-state actors, healthcare workers who administer services to patients with TB and RISE project researchers. The TOC is displayed as a diagram in figure 2 and has elements interacting in a non-linear fashion, with indirect causal pathways and feedback loop. The key components evaluated in this process evaluation include: (1) patient recruitment and enrolment in the RISE project, (2) robust supply chain management, (3) trainings, coaching and mentorship for frontline implementers, (4) availability and use of SOPs guidelines and job aids, (5) patient health education with regard to RISE project, (6) patient support (nutritional, psychosocial and transport support), (7) monitoring of project progress (quarterly meetings, recording and reporting (R&R) tools, monthly data reviews), (8) incentives for human resources, (9) technical support, service and maintenance of equipment, (10) engagement of stakeholders and (11) deploy RISE project organogram. The current TOC is not final but is based on an initial understanding of the intervention, and is therefore subject to modification as we acquire additional information as we conduct the project itself.

Step 2: evaluability and resources availability assessment

Conducting an evaluability and resources availability assessment (ERA) is an important step in any evaluation study as it helps to explain whether the evaluation should be carried out given the available information and resources.[23 24]

We developed an evaluability and resource availability plan and implemented it. The assessment answered the following questions: (i) What is the scope of the RISE project, (ii) What are the RISE project components in relation to the developed TOC, (iii) Who are the actors in the project and their readiness and availability for process evaluation, (iv) Who are the beneficiaries of the project, (vii) Which activities are taking place in the RISE project sites, (viii) Who are the stakeholders and what are their expectations in the RISE project and (ix) What are the available resources to aid completion of the evaluation study. The completion of this step helped to supplement information in the developed TOC and in developing clear evaluation questions and data gathering plans. Online supplemental file 1 provides details on ERA assessment tool.

Step 3: process evaluation objectives

In this step, we developed the evaluation objectives informed by the TOC, ERA results and usability of the process evaluation results in the RISE project. We first defined the broad objective and thereafter stated the specific objectives.

Broad objective

The overall aim of this study is to produce evidence on the implementation feasibility and influencing factors of the RISE project in Tanzania.

Specific objectives

1. To determine the reach of the modified shorter duration injectable-free MDR-TB regimen to the target population.
2. To determine the adoption of the modified shorter duration injectable-free MDR-TB regimen by the health workers.
3. To determine the implementation fidelity of the modified shorter duration injectable-free MDR-TB regimen.
4. To determine the extent to which the modified shorter duration injectable-free MDR-TB regimen becomes part of the routine health facility practices and maintain its effectiveness.
5. To assess acceptability of modified shorter MDR-TB regimen among people diagnosed and treated for RR-TB/MDR-TB.
6. To determine the facilitators and barriers of implementation of the modified shorter duration injectable-free MDR-TB regimen.

Step 4: study design

This study employs concurrent triangulation mixed-methods design as heterogeneity in implementation outcomes is likely, due to multiple components with diverse contexts and participants, both healthcare workers and patients.[25 26] Mixed methods entail an inclusion of both quantitative and qualitative methods of data collection and analysis. In a triangulation design, quantitative and qualitative methods hold equal weight and are used to answer the research objectives by looking at complementarities and differences.[25] The term concurrent refers to the fact that quantitative and qualitative data are collected in parallel, without waiting for the findings from one strain of research to be available to inform data collection for the other strain.

Step 5: determining the sources of data and data collection tools

Data will be collected from the following types of participants and documents: patients, health workers, managers of health facilities, district-level managers and independent RISE study GCP and GLP monitors. Table 2 provides the details on the set of tools and their alignment to evaluation objectives and sources of data. In line with our mixed-methods design, the tools include: structured questionnaires, document review checklists, observation checklists, focus group discussions (FGDs) and semi-structured in-depth interviews (IDIs). We relied on the following theories and models in designing our tools; the fidelity of implementation framework,[27 28] the diffusion of innovation theory,[29 30] the theoretical framework of acceptability (TFA)[31] and framework put forward by Wierenga *et al* to guide the conduct of the process evaluation.[32]

Quantitative component

Data for the quantitative data part will be collected from a census of patients to be recruited in the study. Based on statistical power, a minimum sample size of 220 would be sufficient. Also, a consecutive sample of healthcare workers from the participating health facilities with a maximum of six participants based on the assumption that the selected facilities should have a minimum of healthcare workers, that is, a total of 132 health workers. In addition, routine health facility files and documents will be read and summarised to fit the study context. To collect quantitative data, we will use structured questionnaires (patient and healthcare worker questionnaires), document review checklists and observation checklists.

Patient questionnaire

An exit interview will be administered to consecutive patients exiting the health facility after receiving shorter regimen services (online supplemental file 2). The questionnaire measures experiences of the encounters related to shorter regimen processes and procedures. The questionnaire covers such aspects as sociodemographic characteristics (age, gender, marital status, occupation, when started the regimen), acceptability of shorter regimen, adherence to shorter regimen and clinic visits, satisfaction with the regimen and moderating factors. The questionnaire is composed of multiple questions, yes/no and Likert scale questions. Patients enrolled in the RISE study for a minimum of 3 months (minimum attendance of three visits) will complete the questionnaire when approached on their scheduled visits.

Health workers questionnaire

The questionnaire for health workers will capture information related to sociodemographics, general knowledge on shorter regimen, acceptability of the new regimen to health workers, fidelity of implementation, sustainability of shorter regimen processes and moderating factors (see online supplemental file 3). The questions in this tool will either be multiple choice, yes/no or Likert scale. The questionnaire will be administered to convenience sample of healthcare workers in the health facility premises. Participants will be asked for written consent and assured of anonymity and confidentiality.

Document review checklist

We will use a document review checklist to extract data from existing shorter regimen documents and other important documents for successful implementation of MDR-TB regimens (see online supplemental file 4). The documents and permanent products set to be the source of data include programme reports, day-to-day communications about the programme as documented in the files (letters, memos and meeting minutes) and programme designated MDR-TB data collection tools. The checklist will independently collect verifiable data to be triangulated with data from other tools.

Observation checklist

A structured observation checklist will be used to collect data on implementation of the MDR shorter regimen (see online supplemental file 5). This will serve as triangulation of the information obtained from the healthcare workers and patients.

Qualitative component

We will collect qualitative data in the study sites specifically on subset of participants targeted by the quantitative component. We combine FGDs, IDIs and participant observation so as to gain a comprehensive picture on the implementation of the new regimen. FGDs help to uncover collective attitudes, beliefs, views and socio-constructions of the implementers, whereas IDIs help to gain in-depth views and experiences of the individual participants. Merits of participant observation include: observation and studying of natural behaviour, closeness with the implementers, better understanding the feelings of the participants and an opportunity to learn more about the phenomenon.

Table 2 Objective, sources of data and data collection procedures

Evaluation domain	Research objective	Information to be gathered	Sources of data	Data collection tool and procedures
Reach	To determine the reach of the modified shorter duration injectable-free MDR-TB regimen to the target population	The proportion of patients enrolled in the project	Patients Routine data in health facilities	Patient survey questionnaire Document review checklist Semi-structured guides for IDIs
Adoption	To determine the adoption of the modified shorter duration injectable-free MDR-TB regimen by the health workers	Uptake of the intervention by the implementers (proportion and representativeness of individuals involved in implementing the programme)	Healthcare workers Independent project monitors Routine data in health facilities Programme reports	Healthcare workers survey questionnaire Document review Observation checklist Semi-structured guides for FGDs and IDIs
Fidelity of implementation	To determine the implementation fidelity of the modified shorter duration injectable-free MDR-TB regimen	The extent to which the implementers adhered to the original plan to implement all the essential elements of the programme; any deviations or adaptations to the original plan, and follow-up activities	Healthcare workers Independent project monitors Patients Documents	Healthcare workers survey questionnaire Document review checklist Observation checklist Semi-structured guides for FGDs and IDIs
Maintenance (sustainability)	To determine the extent to which the modified shorter duration injectable-free MDR-TB regimen becomes part of the routine health facility practices and maintain its effectiveness	Proportion of essential elements (procedures) that have been maintained over time in the course of implementing the intervention Proportion of patients who have adhered to clinic visits and medicines	Healthcare workers Independent project Patients Documents	Patient survey questionnaire Document review checklist Semi-structured guides for FGDs and IDIs
Acceptability	To assess acceptability of modified shorter MDR-TB regimen among people diagnosed and treated for RR-TB/MDR-TB	Information on affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness and self-efficacy	Patients Healthcare workers Independent project	Patient survey questionnaire Document review checklist Semi-structured guides for FGDs and IDIs
Contextual factors	To determine the facilitators and barriers of implementation of the modified shorter duration injectable-free MDR-TB regimen	Contextual facilitators Contextual barriers of the programme	Healthcare workers Independent project Patients Documents Managers	Patient survey questionnaire Document review checklist Semi structured guides for FGDs and Key Informant Interviews (KIs)

FGD, focus group discussion; IDI, in-depth interview; MDR-TB, multidrug resistant tuberculosis; RR, rifampicin resistant.

Focus group discussion

We expect to conduct a minimum of five FGDs for each of the categories of health facilities involved in this study, that is; dispensaries, health centres, district hospitals and referral hospitals. Based on literature, five FGDs are enough to achieve saturation.[33] Each FGD will have 8–12 participants with experience of implementing various components of the shorter regimen, including clinicians, nurses, laboratory personnel and pharmacists. The FGDs will be moderated by members of the project team trained in qualitative research and will be audio-recorded in Kiswahili. The exact number of FGDs will depend on saturation of information. We will conduct a repeat FGDs with the participants after preliminary findings as a form of member checking. A semi-structured instruments topic guide will be used to collect facilitate discussions (online supplemental file 6).

In-depth interviews

In-depth interviews with healthcare workers

We will conduct at least 45 IDIs with healthcare workers. These include five interviews per selected health facility (as we expect to select nine health facilities purposively in order to elicit experiences at dispensary level, health centre level and hospital level). The individual IDI guide will largely reflect the one used to facilitate the FGDs but taking different perspectives. In the IDI guide, we will focus on the individual experiences and the perceptions on the implementation of shorter regimen (see online supplemental file 7).

In-depth interviews with study monitors

A separate IDI guide will be administered to three RISE study monitors. Given regular monitoring of the RISE project at health facilities, we expect this guide to generate information on their perspectives of implementation fidelity and other parameters related to safety monitoring of the regimen.

In-depth interviews with patients

Additionally, a third set of IDI guide will be conducted with 27 patients on acceptability of the shorter regimen. Patients will be asked on their experiences with the regimen and the way they accept it or otherwise.

Participant observations

We will conduct at least nine participant observations. that is. covering from the nine purposefully selected hospitals where FGDs and IDIs will be conducted. The observation checklist intends to capture routine operations of the RISE project namely patient screening and enrolment procedures as well as safety monitoring (see online supplemental file 8).

Step 6: data gathering procedures

Data will be collected by a few of authors together with trained research assistants and will be supported directly by the first author. All tools will be pretested and then adjusted to accommodate the knowledge acquired during the pretest. Participants in both FGDs, IDIs and participant observations will be asked for written consent and assured of anonymity and confidentiality. All FGDs and IDIs will be voice recorded, verbatim transcribed based on a more case descriptive approach on initial listening to the recorded voices and translated into English by members of the research team.

Step 7: data processing and analysis

Variables and their measures

Measure of variables (reach, adoption, acceptability, fidelity, maintenance (sustainability)) will be according to standards set by existing evidence.[28 31 34] Specifically, reach will be measured by the number of patients with MDR-TB who seek care, adoption will be measured by number of patients with MDR-TB who seek care and get appropriate doses of new regimen (use the intervention), acceptability will be measured as a multifaceted construct as per TFA constructs. Implementation fidelity will look at the providers who implement the intervention as intended with a focus on adherence to regimen procedures, coverage, content and quality of delivery. Maintenance (sustainability) will be measured by assessing the postintervention maintenance of routines of the new regimen and retention rates of the patients. Moderating factors for the implementation processes will be identified and measured accordingly.

Data management and analysis

Quantitative data will be entered into Open Clinical database and then imported into STATA statistical software V.15 for analysis. Descriptive analysis will be used to summarise data whereby continuous data will be summarised using mean and SD as well as medians and IQR. Dichotomous variables will be summarised using frequency and percentage. Fisher's exact and χ^2 test will be used to evaluate bivariate associations between categorical variables whereby t-test will be used to estimate association in numeric variables.

Thematic analysis will be used to analyse qualitative data using ATLAS.ti 8 software. Verbatim transcribed data and field notes summaries will be reviewed by two researchers (AK and DP) for completeness prior to coding. A codebook with preconceived codes informed by the study objectives, TOC and the frameworks used in this study will be developed to guide the coding of transcripts. Additionally, emergent codes will also be applied to IDI and FGD transcripts. Codes will be grouped into categories, subthemes and themes. Although we aim at thematic organisation of our findings, we will consider case descriptive analyses in order to illustrate findings and/or recommendations for easily integrating into policy guidelines.

Step 8: developing results dissemination plan

A detailed dissemination plan was developed by the team and include sharing the findings with national stakeholders. We will prepare a policy brief to enable policy makers at all levels use our research findings to change policy and practices. In addition, research findings will be shared in scientific conferences and peer-reviewed journals.

Patient and public involvement

This study involves engagement of the stakeholders (funders, policy makers, practitioners and patients) at multiple points. In the design stage of the study, particularly developing the TOC, stakeholder workshops that involved stakeholders from different levels of implementation (national, regional, district and health facility level). As the project goes into implementation, implementers and patients will be engaged in all procedures and their related practical components (commenting on the study materials and recruitment in the study). Our dissemination plan provides another important avenue for public involvement in this study.

Protocol status

This protocol is under implementation. Following securing the ethical clearance and permissions from relevant authorities, between June and November 2020, early field engagement began in December 2020 to assess evaluability and develop the TOC. The first round of data collection is underway. We expect to have completed all two rounds of data collection by December 2021. Data analysis will not have begun at the time of submission of this manuscript.

Ethics and dissemination

This process evaluation study that this protocol describes is conducted in the framework of the RISE project which was granted ethical approvals from the National Institute of Medical research (NIMR) in November 2019 (Ref. NIMR/HQ/R.8a/Vol.IX/3269) and from the Mbeya Medical Research and Ethics Review Committee in October 2019 (Ref. SZEC-2439/R.A/V.I/38). Written informed consent will be sought from all study participants. No individually identifiable information will be presented in publications resulting from this study.

We will disseminate the findings from this work through manuscripts in peer-reviewed journals, at scientific conferences and in short reports distributed to stakeholders and study participants.

DISCUSSION

Implementation of this protocol serves as a system lens during adaption of the new MDR-TB regimen and is one of the innovative strategies to identify challenges and bottlenecks that have shown to persistently hinder access of evidence-based products in resource-limited settings.[35] The lack of process evaluations in pragmatic studies might contribute to false claims of failure of an otherwise effective intervention like the shorter MDR-TB regimen under the RISE project. Once implemented, this protocol will highlight and provide guidance on pertinent factors that may trigger implementation success or failure of the RISE project. Furthermore, the protocol serves as an indicator of generating scientific evidence when deploying interventions in real-life settings using mixed-methods evaluation design to provide a comprehensive picture of implementation realities and their effects on the programme effectiveness.

When proven clinically efficacious, the shorter MDR-TB regimen will be scaled up as a standard of care for patients with MDR-TB in Tanzania. Findings from the proposed process evaluation might provide more insights on how to scale up and explain gains in terms of patient outcomes as well as health system outcomes in the course of scaling up to different settings. Existing evidence attest on the need to identify key components that are linked with programme outcomes for the purpose of understanding how these components are implemented.[15 32 36] In developing our TOC, we identified key programme components that contribute to the programme outcomes by drawing the mechanisms and causal loops.

There will be two points of data collection, early and late during implementation. This will help to address barriers and bottlenecks identified in early stage and measure the implementation outcomes later in the stage of the RISE project implementation. These timepoints would justify variations of outcomes and guide adoption and sustainability strategies of the processes.

Likewise, the protocol includes understanding the perspectives of patients, healthcare providers and project monitors on the implementation processes of the injectable-free MDR-TB regimen. This would help to uncover the acceptability of the regimen and ensure implementation feasibility. The supply side processes may impede success of the project, especially if the healthcare workers lack knowledge, skills, motivation and satisfaction. The demand side processes and the effects of the drugs in the patient's body (positive and adverse effects) has contribution to the acceptability of the regimen and sustenance in routine care.

This protocol was developed amid the challenges of COVID-19 pandemic. COVID-19 has challenged the health systems including underutilisation of health services that subsequently observed a decrease in TB case notifications in Tanzania and elsewhere.[8] Also, implementation of the RISE project was adjusted whereby meetings and training were conducted through web-based platforms. Additional waves of COVID-19 might affect the implementation of this project. The use of mixed-methods approach as well as multiple tools of collecting data will enable the development of recommendations to improve future implementation of the RISE study and other implementation studies of similar nature by identifying trends, challenges and potential solutions to implementation challenges amid contextual influences as well as design issues if they exist. We must also acknowledge the limitations that this study may be prone to missing data as well as recall bias as collection of data will take place some months after start of the RISE project. Furthermore, the study is implemented in one country, where there is an existing TB programme which might influence how the new regimens are accommodated, hence users of the findings from this study should think how their settings differ.

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Contributors AK: conceptualisation, preparing the manuscript draft, developing the methodology. JL: conceptualisation, critically reviewing the methodology (quantitative part). DP and PJS: conceptualisation, critically reviewing the methodology (qualitative part). CG, HM, WN, IL, RK, LM, JJ, NAK, BM, EM, SGM and NEN: conceptualisation, critically reviewing the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1 De Cock KM, Soro B, Coulibaly IM, *et al*. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA* 1992;268:1581–7.
2 Kwan CK, Ernst JD. Hiv and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev* 2011;24:351–76.
3 Teweldemedhin M, Asres N, Gebreyesus H, *et al*. Tuberculosis-Human immunodeficiency virus (HIV) co-infection in Ethiopia: a systematic review and meta-analysis. *BMC Infect Dis* 2018;18:676.
4 Falzon D, Jaramillo E, Schünemann HJ. Who guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respiratory Soc* 2011.
5 Lange C, Chesov D, Heyckendorf J. Drug-resistant tuberculosis: an update on disease burden, diagnosis and treatment. *Respirology. Wiley Online Library* 2018;23:656–73.
6 Prasad R, Gupta N, Banka A. Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis: principles of management. *Lung India* 2018;35:78–81.
7 Organization WH. *Global tuberculosis report 2013*. World Health Organization, 2013.
8 Organization WH. *Global tuberculosis report 2020: executive summary*. World Health Organization, 2020.
9 Mpagama SG, Heysell SK, Ndusilo ND, *et al*. Diagnosis and interim treatment outcomes from the first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One* 2013;8:e62034.
10 Mpagama SG, Ezekiel MJ, Mbelele PM, *et al*. Gridlock from diagnosis to treatment of multidrug resistant tuberculosis (MDR-TB) in Tanzania: patients' perspectives from a focus group discussion. *BMC Public Health* 2020;20:1667.
11 Mkopi A, Range N, Lwilla F, *et al*. Adherence to tuberculosis therapy among patients receiving home-based directly observed treatment: evidence from the United Republic of Tanzania. *PLoS One* 2012;7:e51828.
12 Moore G, Audrey S, Barker M, *et al*. Process evaluation in complex public health intervention studies: the need for guidance. *J Epidemiol Community Health* 2014;68:101–2.
13 Decker P, Durand R, Mayfield CO, *et al*. Predicting implementation failure in organization change. *J Organ Cult Commun Confl* 2012;16:29.
14 Grant A, Treweek S, Dreischulte T, *et al*. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. *Trials* 2013;14:15.
15 Moore GF, Audrey S, Barker M, *et al*. Process evaluation of complex interventions: medical Research Council guidance. *BMJ* 2015;350:h1258.
16 Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health* 1999;89:1322–7.
17 TB Prevalence in Tanzania. National Tuberculosis & Leprosy Programme [Internet]. Available: https://ntlp.go.tz/tuberculosis/tb-prevalence/ [Accessed 28 Feb 2021].
18 Sharma S, Adetoro OO, Vidler M. A process evaluation plan for assessing a complex community-based maternal health intervention in Ogun state, Nigeria. BMC health Serv Res. *BioMed Central* 2017;17:1–10.
19 Craig P, Cooper C, Gunnell D, *et al*. Using natural experiments to evaluate population health interventions: new medical Research Council guidance. J Epidemiol community health. *BMJ Publishing Group Ltd* 2012;66:1182–6.
20 Maini R, Mounier-Jack S, Borghi J. How to and how not to develop a theory of change to evaluate a complex intervention: reflections on an experience in the Democratic Republic of Congo. *BMJ Glob Health* 2018;3:e000617.
21 De Silva MJ, Breuer E, Lee L, *et al*. Theory of change: a theory-driven approach to enhance the Medical Research Council's framework for complex interventions. *Trials* 2014;15:1–13.
22 Breuer E, Lee L, De Silva M, *et al*. Using theory of change to design and evaluate public health interventions: a systematic review. *Implement Sci* 2016;11:63.
23 Craig P, Campbell M. Evaluability assessment: a systematic approach to deciding whether and how to evaluate programmes and policies. *What Works Scotland* 2015.
24 Wholey JS. Evaluability assessment. In: *Handb Pract program Eval*. . Jossey-Bass San Francisco, 2004: 2. 33–62.
25 Creswell JW, Clark VLP. *Designing and conducting mixed methods research*. Sage publications, 2017.
26 Timans R, Wouters P, Heilbron J. Mixed methods research: what it is and what it could be. *Theory Soc* 2019;48:193–216.
27 Carroll C, Patterson M, Wood S, *et al*. A conceptual framework for implementation fidelity. *Implement Sci* 2007;2:40.
28 Pérez D, Van der Stuyft P, Zabala MdelC, *et al*. A modified theoretical framework to assess implementation fidelity of adaptive public health interventions. *Implementation Sci* 2015;11:91.
29 Rogers EM. *Diffusion of innovations*. 5th edn. Free Press, 2003.
30 Sing DL. On the Diffusion of Innovations: How New Ideas Spread [Internet], 2016. Available: https://leif.me/on-the-diffusion-of-innovations-how-new-ideas-spread/ [Accessed 02 Feb 2021].
31 Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res* 2017;17:88 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5267473/
32 Wierenga D, Engbers LH, Van Empelen P, *et al*. What is actually measured in process evaluations for worksite health promotion programs: a systematic review. *BMC Public Health* 2013;13:1190.
33 Hennink MM, Kaiser BN, Weber MB. What influences saturation? estimating sample sizes in focus group research. *Qual Health Res* 2019;29:1483–96.
34 Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. *Am J Public Health* 2013;103:e38–46.
35 Theobald S, Brandes N, Gyapong M, *et al*. Implementation research: new imperatives and opportunities in global health. *Lancet* 2018;392:2214–28.
36 Durlak JA, DuPre EP. Implementation matters: a review of research on the influence of implementation on program outcomes and the factors affecting implementation. *Am J Community Psychol* 2008;41:327–50.