STATISTICAL ANALYSIS PLAN	
Protocol number:	TB041-3/1-TAN and TB041-3/1-MOZ
Protocol title:	Molbio Truenat™ TB platform combined with the Truenat TB assays for detection of tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis at primary-level diagnostic centres in Tanzania and Mozambique: a pragmatic, cluster- randomized controlled trial
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1 Introduction

This document describes the statistical analysis plan for the following project: "Molbio Truenat™ TB platform combined with the Truenat TB assays for detection of Tuberculosis and Rifampicin resistance in adults with presumptive pulmonary tuberculosis at primary-level diagnostic centres in Tanzania and Mozambique: a pragmatic, cluster- randomized controlled trial", version 4.0, date: 18 JAN 2023.

1.1 Description of the study

Tuberculosis (TB) is the infectious disease that causes the highest number of deaths worldwide. In 2017, about 1,6 million persons died of TB globally. While TB that is sensitive to commonly used medications rifampicin and isoniazid can be treated within 6 months and mostly cured, TB with resistance to these medications requires a different, longer treatment. Besides the success in treating drug sensitive TB, it is believed that 4.3 million persons living with TB are missed every year. The reasons for this are that they cannot access quality diagnostic testing that would detect their disease at a healthcare facility close enough to their home. These are the so-called "missing millions" which may die due to undiagnosed TB or are diagnosed very late resulting in severe and irreversible lung damage. Also, individuals with undiagnosed TB may spread the disease in their families and communities.

Xpert MTB/RIF, and Xpert MTB/RIF Ultra are two diagnostic platforms that are endorsed by WHO since 2011 and 2017 respectively. In contrast to the conventional microscopy that correctly diagnoses only ~50% patients, these platforms provide up to 90% and 95% correct diagnosis of TB cases and detects rifampicin resistance.

Another rapid molecular platform and assay the Molbio Truenat platform (consisting of the Trueprep DNA extraction device and the Truelab micro-PCR machine) and the Truenat MTB Plus assay for detection of *Mycobacterium tuberculosis* complex (MTBC) and Truenat MTB-RIF Dx for detection of RIF resistance was endorsed in 2020 by the WHO for TB diagnosis (collectively referred to as the Truenat TB assays). The system is designed to be operated as a point-of-care diagnostic solution in peripheral laboratories with minimal infrastructure. It takes about 25 minutes to do the DNA extraction and another 35 minutes to diagnose TB. Extracted DNA eluate from samples testing MTBC-positive can be used for RIF-resistance reflex testing. The limit of detection was determined to be 100 CFU/ml sputum sample which is similar to the widely used Xpert MTB/RIF. Despite the successful roll-out of the Xpert MTB/RIF, which is more sensitive than microscopy, across Africa TB notifications have not increased and the impact on mortality remains uncertain. Most GeneXpert machines are placed in central or district laboratories requiring sample transport from primary health care clinics (where patients are usually seen) to the laboratory. Once the sample is tested, the results are sent back to the primary health care facility and the patient will have to be called back to start treatment. There are several bottlenecks across the diagnostic TB pathway, which results in substantial attrition during the diagnostic process. Essential steps include the individual accessing care, the health care worker referring the individual for TB investigations,

the specimen being sent for TB diagnostics and the results being returned. Initiation of appropriate treatment relies on timely receipt of laboratory results and the patient returning to clinic. The proposed study aims to address some of the bottlenecks by bringing the diagnostic device closer to the patients in the primary health clinic.
The Truenat MTB Plus assay runs on the Trueprep/Truelab platform and has similar performance characteristics as the Xpert MTB/RIF run on the GeneXpert platform. The Truenat platforms/TB assays have several advantages over the GeneXpert platform making them more suitable for placement at primary health care facilities. The standalone platforms are portable and battery-operated, have no need for a computer or laptop, and operate from 2- 40°C ambient temperature. The system uses room temperature stable reagents with long shelf life.

Main goal of this study is to evaluate the effect of using Truenat platform/TB assays combined with rapid communication, in treatment initiation. We randomize 29-37 primary health care facilities in Mozambique and Tanzania, diagnosing persons with signs and symptoms suggestive of TB of the lung using either the existing diagnostic algorithm (mostly microscopy or off-site Xpert testing) or placing Truenat platform at the facility to enable Truenat MTB Plus and Truenat MTB-RIF Dx testing on site.

In a setup period (survey of study centers) before randomization, the clinics of four sites were asked to provide information about the number of TB notifications per quarter covering the period 1/2018- 6/2020. This information was used to estimate the number of examined patients (“size of a clinic”), which was used as a stratum variable in randomization process with rapid communication of results on time-to-treatment-initiation of microbiologically confirmed TB. Facilities are randomly allocated to the SOC (control), or Truenat platform/TB assays (intervention). In the context of this trial, a cluster refers to a clinic. The clinics will be randomly assigned to intervention or control arm following a restricted randomization strategy, whereby 6-8 strata of clusters will be established using the stratification variables site (clinics belong to a site) and size, and apply balance criteria for them. The number of strata per site depends on heterogeneity of the sizes of the clinics as established during the setup period and may be increased, typically 1 or 2 strata per site will be established.

Intervention

The intervention is the placement of the Truenat platform/TB assays at primary health care clinics combined with rapid communication of results and same day TB treatment initiation.

Standard of care (control)

All control clinics will have access to off-site Xpert testing. The degree to which patients and/or samples are referred for Xpert testing will vary across clinics and potentially across time dependent on availability of transport.

Study population: 28 clinics will be randomized at the four participating sites aiming to enrol approximately 28 x 150 = 4200 adults (≥ 18 years of age) with signs and symptoms suggestive of

TB. The number of clinics might be extended to a maximum of 36 dependent on recruitment rates, clinic closures (due to COVID19) and drop out of clinics due to placements of GeneXpert instruments.

Follow-up:

Individuals will be enrolled at the time they present to the clinics with symptoms suggestive of TB. All participants will be followed at the following time points:

1. Week 1 8-21 days from recruitment
2. Month 2 61-90 days from recruitment

1.2 Timing of the analysis

Primary endpoint, and treatment related, diagnosis related and morbidity related secondary endpoints will be analysed by FIND after the data collection is completed, the data has been cleaned and the database has been locked.

Direct cost and productivity related endpoints will be analysed by Johns Hopkins University, Infectious Disease Epidemiology Unit throughout the study as these endpoints are operational, and do not influence patient safety.

2 Study outcomes and statistical hypotheses

2.1 Primary endpoint

The primary outcome of the study is the absolute number and point estimate (with 95% CIs) of the proportion of participants with TB microbiological confirmation starting TB treatment within 7 days of their first visit. We evaluate the probability of the patients in the intervention arm (with Truenat) for a favourable outcome of interest compared to patients in the SOC arm as a binary outcome of success or failure.

The hypotheses of interest are:

$$H0: Number\ of\ successes\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm.$$

$$H1: Number\ of\ successes\ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

and,

$$H0: Proportion\ of\ success\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm.$$

$$H1: Proportion\ of\ success\ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of odds ratio (OR) for odds of success in the intervention arm to be different from the odds of success in the SOC arm thus leading to the definition of the following hypothesis:

$H0 : OR_{Intervention:SOC} = 1 \; vs. \; H1 : OR_{Intervention:SOC} \neq 1$

2.2 Secondary endpoints

Diagnosis related endpoints:

- Estimate of time-to-bacteriological confirmation of TB (up to 60 days) from enrolment

The endpoint of interest is a time-to-event outcome of bacteriological confirmation of TB and censored at 60 days from enrolment.

$$H0 : Time\ to\ confirmation\ TB\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1 : Time\ to\ confirmation\ TB\ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of hazard ratio (HR) for the hazards of TB confirmation in the intervention arm to be different from the SOC arm, or the instantaneous rate of TB confirmation to be different in the two arms, leading to the hypothesis:

$H0 : HR_{Intervention:SOC} = 1 \; vs. \; H1 : HR_{Intervention:SOC} \neq 1$

- Point estimate with 95% CIs of the proportion of patients treated for TB who are diagnosed up to 60 days from enrolment
  1) Microbiologically
  2) Clinically

The endpoint of interest is a binary outcome of treatment for TB “yes” or “no” at 60 days from enrolment for the patients, allowing us to calculate the proportions. This is repeated for the two categories of microbiologically and clinically enrolled subgroups.

The hypotheses of interest are:

$$H0 : Number\ of\ TB\ treatments\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm$$

$$H1 : Number\ of\ TB\ treatments\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

And,

$$H0 : Proportion\ of\ TB\ treatments\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm$$

$$H1 : Proportion\ of\ TB\ treatments\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of odds ratio (OR) for the odds of TB treatment start in the intervention arm to be different from the SOC arm leading to the hypothesis:

$H0 : OR_{Intervention:SOC} = 1 \; vs. \; H1 : OR_{Intervention:SOC} \neq 1$

Treatment/outcome related endpoints

- Absolute number and point estimate with 95% Cis of the proportion of participants with signs and symptoms of pulmonary TB starting TB treatment with microbiological confirmation within 60 days from enrolment

The endpoint of interest is a binary outcome of signs and symptoms suggestive of pulmonary TB "yes" or "no" among patients allowing us to calculate the incidents and proportions.

The hypotheses of interest are:

$H0$: $Number\ of\ pulmonary\ TB\ patients\ starting\ treatment\ in\ the\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm.$

$H1$: $Number\ of\ pulmonary\ TB\ patients\ starting\ treatment\ in\ the\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$

And,

$H0: Proportion\ of\ pulmonary\ TB\ patients\ starting\ treatment\ in\ the\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm.$

$H1$
$: Proportion\ of\ pulmonary\ TB\ patients\ starting\ treatment\ in\ the\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$

This is translated in terms of odds ratio (OR) for the odds of TB treatment start in the intervention arm to be different from the SOC arm leading to the hypothesis:

$H0: OR_{Intervention:SOC} = 1\ vs.\ H1: OR_{Intervention:SOC} \neq 1$

Absolute number and point estimate with 95% Cis of the proportion of participants with signs and symptoms of pulmonary TB starting TB treatment without microbiological confirmation within 7 and 60 days from enrolment

- Absolute number and point estimate (with 95% CIs) of the proportion of enrolled participants with signs and symptoms of pulmonary TB starting TB treatment regardless of microbiological confirmation within 7 and 60 days from enrolment

The hypothesis from the previous point is repeated here at the specific time points instead of within the interval of 60 days.

- Estimate of time to TB treatment initiation for those with microbiological confirmation and for all participants (censored at 60 days) from enrolment

The endpoint of interest is a time-to-TB-treatment-initiation for those with microbiological confirmation and censored at 60 days from enrolment.

$$H0: Time\ to\ treatment\ intitiation\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Time\ to\ treatment\ intitiation\ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of hazard ratio (HR) for the hazards of TB confirmation in the intervention arm is significantly different from the SOC arm or the instantaneous rate of TB treatment initiation after TB microbiological confirmation to be different in the two arms leading to the hypothesis:

$H0: HR_{Intervention:SOC} = 1\ vs.\ H1: HR_{Intervention:SOC} \neq 1$

- Absolute number and point estimate (with 95% CIs) of the proportion of enrolled participants with ongoing treatment (on treatment) among:
    1. Participants diagnosed with TB either clinically or with microbiological confirmation
    2. Participants clinically diagnosed with TB
    3. Participants with microbiological confirmation of TB

The endpoint of interest is a binary outcome of successful treatment outcome “yes” or “no” among patients allowing us to calculate the proportions for each of the groups described.

The hypotheses of interest are:

$$H0: Number\ of\ treatment\ successes\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Number\ of\ treatment\ successes\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

And,

$$H0: Proportion\ of\ treatment\ success\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Proportion\ of\ treatment\ success\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of odds ratio (OR) for the odds of successful treatment in the intervention arm is significantly different from the SOC arm leading to the hypothesis:

$H0: OR_{Intervention:SOC} = 1\ vs.\ H1: OR_{Intervention:SOC} \neq 1$

The number of participants with a successful treatment in described conditions will not be subject to a formal statistical hypothesis test.

<u>Morbidity related endpoints:</u>

- Prevalence of current cough, limited appetite, weakness at 60 days from enrolment

The endpoint of interest is a binary outcome of physical symptoms such as current cough, limited appetite or weakness at 60 days from enrolment "yes" or "no" among patients allowing us to calculate the proportions for each of the groups described.

$$H0: Proportion\ of\ physical\ symptoms\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Proportion\ of\ physical\ symptoms\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of odds ratio (OR) for the odds of physical symptoms in the intervention arm to be different from the SOC arm leading to the hypothesis:

$$H0: OR_{Intervention:SOC} = 1\ vs.\ H1: OR_{Intervention:SOC} \neq 1$$

Direct cost and productivity related endpoints:

- Patients' costs related to care

The endpoint of interest is a continuous outcome of patient costs related to care

$$H0: Mean\ cost\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Mean\ cost\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of a mean difference (MD), comparing the intervention arm to the SOC arm.

$H0: MD_{(int-SOC)} = 0$ vs. $H1: MD_{(int-SOC)} \neq 0$.

- Number of lost working days

The endpoint of interest is a continuous outcome.

$$H0: Mean\ lost\ working\ days\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Mean\ lost\ working\ days\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of a mean difference (MD), comparing the intervention arm to the SOC arm.

$H0: MD_{(int-SOC)} = 0$ vs. $H1: MD_{(int-SOC)} \neq 0$.

- Monthly earning

The endpoint is a continuous outcome.

$$H0: Mean\ monthly\ earning\ in\ intervention\ arm\ is\ same\ as\ in\ the\ SOC\ arm\ vs.$$

$$H1: Mean\ monthly\ earning\ \ in\ intervention\ arm\ is\ different\ from\ the\ SOC\ arm$$

This is translated in terms of a mean difference (MD), comparing the intervention arm to the SOC arm.

$H0 : MD_{(int-SOC)} = 0$ vs. $H1 : MD_{(int-SOC)} \neq 0$.

Modeled cost and cost-effectiveness endpoints:

- Unit costs of diagnosis and treatment, modified societal perspective

The endpoint will be calculated from measured costs from the patient and health system perspectives.

The primary outcome will be the sum of patient plus health system costs, expressed as unit costs (e.g., cost per test, cost per TB treatment), under the intervention and under the standard of care.

This outcome will not be subject to a formal statistical hypothesis test.

- Incremental cost-effectiveness ratio, modified societal perspective

The endpoint will be calculated from cost and effectiveness outcomes, including both patient and health system perspectives.

The primary outcome will be the incremental cost per patient treated for TB, comparing the intervention to the standard of care.

This outcome will not be subject to a formal statistical hypothesis test, however the components that make up the outcome are.

2.3 Additional Endpoints

Operational characteristics

- Truenat platform / TB assay non-determined test results rates

The endpoint of interest is a binary outcome of undetermined results among all test results allowing us to calculate the proportions for each of the groups described. There is no hypothesis testing, results are descriptive.

- Rate of Truenat platform failure

The device failure will be reported by the Molbio instrument incident log and exported data that is returned to Molbio and relayed back to the data management. There is no hypothesis testing, results are descriptive.

3 Trial population and analysis datasets

3.1 Criteria for eligibility, recruitment, withdrawal and follow-up

The trial population will comprise consecutively recruited adults presenting with symptoms suggestive of pulmonary TB at primary-level facilities (clinics). Presumptive pulmonary TB patients will receive diagnostic procedures according to the random allocation assigned to the clinic. Clinics randomized to the intervention will have Truenat platforms placed in the facility and sputum samples will be investigated with the Truenat MTB Plus and the Truenat MTB-RIF DX assays. In addition, procedures will be put in place to ensure rapid communication of results and same day TB treatment initiation.

These procedures will be site specific and informed by the local context. Participants accessing clinics randomized to SOC will be investigated according to the national standard, which in most cases will be smear microscopy and/or Xpert testing.

Inclusion criteria

- Presumptive pulmonary TB patients, as defined by the national TB treatment guidelines in each country: patients with cough more than 1-2 weeks and/or fever, night sweats, blood-stained sputum (haemoptysis) significant weight loss, abnormalities on chest radiograph and who are able to provide a sputum sample
- Adults 18 years old and above (including pregnant women) who are able and willing to consent.

Exclusion criteria

- Children and adolescents <18 years of age
- Circumstances that raise doubt on free, informed consent (e.g. in a mentally impaired person or a prisoner)
- Already diagnosed with TB
- Currently receiving anti-TB therapy
- Patients with symptoms which are only attributable to extra-pulmonary TB
- Patients who are seriously ill and need to be admitted to hospital
- Enrolment into the trial at a previous visit

Withdrawal from the study

Participant may decide to withdraw from the study at any time and for any reason. The investigator may also withdraw a patient for any of the following reasons:

- Protocol deviation
- If, for any reason, the investigator concludes that continued participation in the study would not be in the participant's best interest

The investigator will also withdraw a patient upon request of the sponsor or if the study is terminated as a whole. Participants who decide to withdraw or who have been withdrawn from the study will not be replaced. No further follow-up will be conducted after the withdrawal.

Visit 1 Baseline visit

Patients presenting with symptoms suggestive of pulmonary TB to one of the study clinics will be invited to be screened for inclusion in the study. Before any study-specific screening procedures will be performed, all patients will sign and date (or thumbprint) the latest version of the ICF. Illiterate participants will be encouraged to have a witness present.

After informed consent has been obtained, the patient will receive a study number. The ICF will be labelled with the study number. A primary health care nurse or dedicated researcher staff will administer a questionnaire (V1-D1 CRF) and ask the patient about their contact details and the contact details of a trusted proxy (locator form). In addition, a random sample of 5-10% of participants per site will be invited to answer a socio-economic questionnaire about income, cost of care seeking, productivity losses, diagnostics and treatment (V1-D1-SE CRF).

Depending on the clinic, the patient will receive a diagnostic work-up according to the national algorithm (smear microscopy and/or off-site Xpert testing) or the study intervention (Truenat platform/TB assays on site). Further diagnostic investigations and TB treatment initiation will be as clinically indicated. All clinical care and further investigations will be provided within the governmental health care service. Patient details (including name, sex, age and study-ID) will be documented in a study register, which will remain at the clinic. All patients will receive a study card with their details (including name, sex, age and study number and enrolment date) to take home with them. They will be asked to show the card if they present to the clinic again.

Visit 2: Day 7

All participants will be called by telephone 7 days after enrolment (between day 8 and day 21 after enrolment). Three attempts will be made to contact a participant by phone. If these attempts are unsuccessful the trusted proxy will be contacted to find out about the participant's whereabouts and arrange for a return call by the participants or a home visit. A home visit will be conducted for those participants who cannot be reached by phone.

The questionnaire administered by phone or face-face (V2-D7 CRF) will include questions about symptoms, whether TB was diagnosed (and by what means) and treatment started and if the participant had accessed another health care provider.

Visit 3: Day 60

All participants will be called by telephone 60 days after enrolment (between day 61 and day 90 after enrolment). Three attempts will be made to contact a participant by phone. If these attempts are unsuccessful the trusted proxy will be contacted to find out about the participant's whereabouts and arrange for a return call or a home visit. A home visit will be conducted for those participants who cannot be reached by phone.

The questionnaire administered by phone or face-face (V3-D60) will include questions about symptoms, whether TB was diagnosed (and by what means) and treatment started and if the

participant had accessed another health care provider and how often.

3.2 Analysis datasets

Describe the datasets that will be used in the analysis, like the examples below.

- **Intent-to treat (ITT) population:** The ITT population will consist of all randomized participants in the groups to which they were randomly assigned.
- **Modified Intent-to Treat (MITT):** All participants in ITT population who have partial outcomes (i.e. data available for V2 or V3).
- **Per-Protocol (PP) population**: The PP population will consist of all participants who fulfil the protocol in the terms of eligibility, interventions, and outcome assessment without any major protocol deviation.
- **Per-Protocol Modified (PPM) population:** All participants in the PP population who were identified to be subjected to the protocol deviation documented in 173/CNBS/23.

4 Description of statistical methods

4.1 General approach

All analyses will be performed on the MITT and PP populations. Because there was a protocol deviation (i.e. participants with missing V2 or V3), the potential difference in the primary outcome between the two populations will be explored as described in *Section 7.0.*

All analyses (i.e. generalized linear models and proportional hazards models) will take into account the effect of the clusters using a mixed model approach, introducing a random intercept for each cluster. Details of the models for each outcome are given in the sections below.

For all statistical tests, alpha will be set to 0.05 for rejecting the null hypothesis. Since multiple comparisons will be performed, p-values will be adjusted using Benjamini-Hochberg method.

The proportion of observations with missing values will be summarised for all outcome variables. Missing and invalid data will not be imputed. Baseline measures will be reported for individuals with missing data on an outcome of interest, including those who withdraw or are lost to follow-up. For each analysis, the baseline measures (demographic and laboratory data) will be compared between participants with complete and incomplete data using T-Tests or Chi^2 tests, for continuous or categorical variables respectively.

4.2 Analysis of the primary outcome

The analysis for comparing the counts between the control and the intervention arms will be done using a GLMM (*lme4* package, *lmer* function in R) with Poisson distribution using log link function, where a cluster will be specified as a random factor (i.e. random intercept) and recruitment time by

clinic will be specified as a random effect nested within each cluster (i.e. random intercept and random slope).

The analysis for comparing the proportions between the control and the intervention arms will be done using a GLMM (*lme4* package, *lmer* function in R) with binomial distribution using logit link function, where a cluster will be specified as a random factor (i.e. random intercept).

The models will be adjusted for gender, age, HIV status, country, and asset index that is described below. In case of necessity, the models may be adjusted for the setting (i.e. urban, rural, peri-rural nesting the clusters), and site.

ORs will be estimated by calculating the exponent of the fixed-effect (i.e. arm) coefficients that are extracted from the models described above. 95% confidence intervals will be calculated using Wald method.

4.3 Analysis of the secondary outcomes

Diagnosis, treatment, and morbidity related endpoints

The analysis of the binary outcomes will be performed in the same way as the analysis of primary outcomes using GLMMs with Poisson or binomial distributions, for count or proportion data respectively.

Time-to-event analyses will be performed using mixed-effect Cox proportional hazards (PH) regression models (*coxme* package, *coxme* function in R). Kaplan Meier curves will be used to graphically represent the data. The possibility of non-proportional hazards will be assessed using Schoenfeld individual test and its graphical representation.

In case of non-proportional hazards, we will consider to split the time, use an interaction term, use a complementary log-log generalized linear model, or a combination of these approaches. If non-proportional hazard is caused by a confounder, we may set that variable as a strata.

As for primary outcome, the models will be adjusted for gender, age, HIV status, country, and asset index that is described below. In case of necessity, the models may be adjusted for the setting (i.e. urban, rural, peri-rural nesting the clusters), and site.

Direct cost and productivity, modelled cost, and cost effectiveness related endpoints:

MSeveral of these endpoints are not estimated using standard statistical analyses, but rather reflect descriptive analyses or model-based analyses that are not purely statistical in nature.

- Patients' costs related to care

Patient costs will be estimated as the mean cost per patient interviewed. These costs will include direct and indirect costs incurred because of TB diagnosis. Direct costs will include all medical (including consultation fees and any out-of- pocket payment for medicines, X-rays, and diagnostics) and non-medical expenses (including travel costs of participants and caregivers,

food costs incurred while in hospital, money spent buying any special foods). Indirect costs will be estimated as the opportunity cost of time spent seeking care (from the time of symptom onset to the time of treatment initiation), plus any lost productivity due to illness. Additional information from the scientific literature will be used to estimate costs that are not directly estimated (e.g., hospitalization costs, costs of TB treatment).

The total cost for each patient will be estimated as the sum of direct and indirect costs, and the mean cost will be taken as the sum of these total costs, divided by the number of patients.

- Number of lost working days

We will use patient interviews to record the self-reported number of working days lost due to TB illness in both arms. This will be directly estimated; no additional statistical methods will be used. 95% confidence intervals will be calculated assuming a Poisson distribution.

- Monthly earnings

To estimate loss in income, we will record the number of missed working days or missed working hours owing to TB illness, from the time of symptom onset to the time of treatment initiation. This number of days/hours will be multiplied by the average daily/hourly wage of employed laborers in each country to estimate the monthly earnings lost as a result of seeking care. If the patient does not have formal employment but works informally, e.g., as an agricultural worker, we will use their self-reported reduction in productivity (as a percentage of total productivity) over the course of the past year. This number will be multiplied by the average agricultural wage/earnings in each country and reported on a monthly basis. We will then calculate the mean monthly earnings lost as the sum of lost income (as described above), divided by the number of participants from which those data are obtained.

- Unit costs of diagnosis and treatment, modified societal perspective

We will estimate the health system cost per participant tested for TB on-site via the novel Molbio Truenat MTB/RIF platform versus the hub-and-spoke standard of care, predominantly off-site testing with Xpert MTB/RIF (Cepheid, Inc., Sunnyvale, CA, USA). These include cost for equipment, staffing, consumables, training, communication, and monitoring and evaluation. We will estimate ranges for health service delivery costs using trial expense reports, facility assessments, and project staff interviews. We will refer to existing scientific literature, information from facility assessments, expense reports, and project staff interviews to estimate the health system cost per patient treated.

Our modified societal perspective will include both health system costs (outlined in the paragraph above) and patient costs (as outlined earlier). Health system costs and patient costs will be summed on an individual basis to generate an estimate of the per-patient cost of diagnosis and treatment. This value will be estimated as a mean across all participants providing these data. Health system costs will be divided by the total number of participants at each site. We will report this outcome both by site and by country.Incremental cost-effectiveness ratio, modified societal perspective

This quantity will be estimated as the incremental cost of the intervention (cost of intervention minus cost of standard of care), divided by the incremental effectiveness (i.e., incremental number of people diagnosed and treated in the intervention versus the standard of care). As above, a modified societal perspective will be used for both costs and effectiveness. The cost component of this equation will be estimated as described in the "unit costs" section above; the effectiveness component will be estimated as described for the primary outcome above. We will estimate uncertainty in this quantity using a simulation approach, where we draw independent simulations from the distribution of the primary outcome as inferred from the 95% confidence interval of the primary effectiveness outcome, as well as from the distribution of unit costs based on the empiric distribution of unit costs from our measurements above. We will report 95% uncertainty intervals as the outcomes falling within the smallest area covering 95% of the simulated costs and effectiveness values, plotted on a cost-effectiveness plane. We will perform these analyses separately by country.

BIA and ECEA of TB diagnostic tools.

Benefit incidence analysis (BIA) will be applied to assess the distribution of benefits of novel Molbio Truenat MTB/RIF platform (Int 1) compared to the hub-and-spoke standard of care (Int 0) and the centralized approach (Int 2). To conduct the analysis, data on health service utilization and unit costs for each strategy, categorized by socio-economic groups, will be estimated. Health service utilization rate will be estimated from the trial and expressed as the number and proportion of TB detected and started on treatment across each strategy and stratified by quintile (i.e., which indicates the extent to which the investments made in each diagnostic are allocated equitably, not considering only point of diagnosis, but also returning for test results, treatment initiation and any other needed follow up). The cost incurred by the public sector providers will be derived from the data gathered on unit cost of each diagnostic strategy. Regarding the SES status, a simplified asset indices adopted from standardized Equity Tool (https://www.equitytool.org/) is used to collect data on asset ownership (i.e., presence of a refrigerator, a mobile phone, a television, electricity, type of toilet, water supply, cooking fuel, and materials of the wall and floor) of study participants and a standardized scoring of these questions will be used to assign a wealth quintile for each respondents. Then health service utilization rate will then be multiplied by the unit costs of each diagnostic Intervention. The benefits of each diagnostic strategy utilization will be aggregated and expressed in monetary terms. Concentration curves and indexes will be computed to illustrate the extent of inequality in the distribution of health spending across quintile.

Extended cost-effectiveness analysis

Extended cost-effectiveness analysis will be used to estimate the additional financial protection offered by each diagnostic strategy (i.e., factoring benefit of early diagnosis, treatment initiation and productivity/income losses). Based on the results of the cost and cost-effectiveness analysis, it is important to check or observe variations in a decrease in out-of-pocket expenses (OOP) and indirect costs across the diagnostic strategies at a descriptive level. Once evaluated, the financial risk protection (FRP) benefits brought by each diagnostic intervention to households were measured based on the reduction in out-of-pocket expenditure (OOP) on average and across quintiles. First, the total OOP (i.e., both direct and indirect costs) for novel Molbio Truenat MTB/RIF platform, the hub-and-spoke standard of care and the centralized approach will be estimated.

Second, the total private expenditure averted will be estimated as the difference between the total OOP under each strategy from the base-case.

4.4 Analysis of missing data patterns

Additional exploratory analyses will be performed to investigate any pattern in missing data. If the outcomes will be missing at random or missing completely at random the above longitudinal data models or clustered data models considering the mixed effect regression under maximum likelihood estimation will be appropriate. Missing at random can be tested by regression the binary outcome of missing or not, with independent variables as the other covariates in the model. If this binary outcome of missingness is associated with the outcome of interest in the model framework, we expect to have the Missing Not at Random in our outcome data. In case it is dependent on other covariates but not the outcome of interest, we are likely to have Missing at Random. In the event of patterns for missing data being not random, the results of the regression will be reported and a detailed plan will be developed to assess the association between the missingness and each covariate. Depending on the results of the analyses, sources of bias will be determined and documented.

5 Baseline descriptive statistics

Descriptive statistics tables will be generated to summarize the characteristics of the participants in the PP, PPM, MITT and ITT populations. The number of participants included and excluded will be reported, overall and for each arm within the hierarchy of each cluster and site.

Among the included participants, outcomes of interest as described above as well as covariates such as sex, age (continuous and categorical as age groups defined as: 18-30, 31-40, 41-50, >50), HIV status, site (i.e. 4 different institutions), country setting (Urban, Rural, Peri-rural), RIF resistance, asset index and the variables that are used for determining the asset index will be summarized.

The summary of measurements and descriptive statistics will also be presented for the overall PP population and at the cluster level (i.e. clinic-based characteristics) for clinics in each of the study arms. The outcomes of interest are, number of patients (size of the unit), number of individuals tested positive, and number of individuals who started treatment, number of patients with presumptive TB seen, number of patients by enrolment period, number of staff at the clinic, time to TB diagnosis, time to TB treatment.

Results will be reported in both absolute numbers (e.g. number of subjects in a group) and the proportion, or summarized by mean, median, standard deviation, minimum, maximum and quartiles. Differences in the groups of Intervention and SOC will be tested by Chi^2 Test or Fisher exact test for categorical outcomes, and Kruskal-Wallis test, t- test, ANOVA or Wilcoxon signed rank test for continuous data depending on whether parametric or non-parametric tests are appropriate for the observed data.

6 Additional sub-group analyses

All primary and secondary endpoints will be evaluated separately by sex and gender (if the information is available), HIV status, site, country, asset index, and age categories (as given in *Section 5*).

7 Exploratory analyses

Protocol Deviation
A proportion of participants were contacted outside of their contact window. 808 participants were affected concerning the V2, and 40 participants were affected concerning the V3. For participants where V2 was not done, V3 was also not done.
Since the data was collected retrospectively, a bias might have occurred since the participants may not recall exactly their status of treatment during the actual Day 7 and Day 60. To overcome this bias,

1) A list with IDs of all affected participants was formed by the data manager (15/03/2023 data extract) and reported to national IRB ref: 173/CNBS/23 , and this is defined as the MPP population,
2) The data that was entered retrospectively was crosschecked with the TB, treatment registry at the clinic (~50 registries) to make sure the treatment initiation data was not misrecorded,
3) Descriptive statistics will be performed to describe the number and the percentage of the effected participants (V2, V3, and both) in both arms in the PPM population,
4) Descriptive statistics will be performed to describe the number and the percentage of the effected participants for the treatment outcome at day 7. Chi^2 test will be performed to assess the statistical significance of the difference between the PP and PPM populations. In case of statistical significance, all the models in the study will be adjusted for the deviation (TRUE/FALSE).
5) A survival analysis will be performed on PP (i.e. participants without the protocol deviation) and in PPM population on time to treatment initiation to explore the possibility of bias.

Other measures can be taken depending on the distribution of the outcome related data

8 Sample size

For the purpose of sample size estimation, a matched design is considered which is known to have a similar power in the range of number of clusters per treatment arm similar to this study (~15). Sample size calculations were based on 972 scenarios using the following ranges of assumptions:

- TB prevalence: 12%, 16%, 20%
- Sensitivity for intervention group: 89%
- Sensitivity for control group: 70%, 75%, 80%
- Diagnostic LTFU intervention arm: 2%
- Diagnostic LTFU control arm: 5%, 10%

- Pre-treatment LTFU intervention arm: 8%, 10%, 12%
- Pre-treatment LTFU control arm: 16%, 20%, 24%[1]
- Cluster size CS 100, 125, 150, 200 (cluster sizes are regarded as average values of a distribution of cluster sizes).
- Within pair coefficient variation CV_m: 0.25 according recommendation in case of missing information given in[32]
- Alpha-level α = 0.05
- Power: 80% (β = 0.2)

From the prevalence, sensitivity and LTFUs in the diagnostics the proportions p of treated patients is derived ($p = prev \cdot sens \cdot (1 - LTFU_{diag}) \cdot (1 - LTFU_{pre-ther})$ for each of intervention and control arm (→ p_i, p_c).

The number of cluster pairs N_{cp} is calculated according to the following formula [Hayes RJ, Moulton LH 2017]:

$$N_{cp} = A + \left(z_{\alpha/2} + z_{\beta}\right)^2 \frac{p_i(1-p_i)/CS + p_c(1-p_c)/CS + {CV_m}^2({p_i}^2 + {p_c}^2)}{(p_i - p_c)^2}$$

whereby the result is rounded up to the next whole number, with A=2, z = quantile of normal distribution.

The following scenarios have been selected according to feasibility and mid-range choice of the ranges presented above are shown in the tabulation below. Colours vary with cluster size and prevalence. The finally selected scenario is described below in red.

Cluster size	Prevalence	Sensitivity control	diagn. LTFU control (diagn. LTFU for intervention: 0.02)	pre-trt. LTFU intervention	pre-trt. LTFU control	success proportion intervention	success proportion control	number of cluster pairs	Number of clusters	Number of patients
100	16%	70%	10%	10%	20%	13%	8%	14	28	2800
100	12%	70%	10%	8%	20%	10%	6%	15	30	3000
100	12%	70%	10%	10%	20%	9%	6%	17	34	3400
100	12%	70%	10%	12%	20%	9%	6%	18	36	3600
150	**12%**	**70%**	**10%**	**10%**	**20%**	**9%**	**6%**	**13**	**26**	**3900**

150	16%	70%	5%	10%	20%	13%	9%	14	28	4200
150	16%	70%	10%	10%	20%	13%	8%	12	24	3600
200	12%	70%	10%	10%	20%	9%	6%	12	24	4800
200	16%	70%	5%	10%	20%	13%	9%	13	26	5200
200	16%	75%	10%	10%	20%	13%	9%	14	28	5600

Applying an alpha-level of 0.05, a power of 80%, 12% prevalence, diagnostic LTFU-rates of 10% (control), 10% (pre-treatment intervention), 20% (pre-treatment control), a cluster size of 150 and a within-pair coefficient of variation (default value 0.25), the results bring a total of 13 cluster pairs (3900 patients). In order to address uncertainty, 1 additional cluster pair will be added, bringing the total to 14 cluster-pairs (28 clinics, 4200 patients) to be included in the trial. If based on what will be observed in the initial setup period, smaller than average cluster sizes are expected, more sites will need to be included in the trial in order to match the total sample size.

Randomisation process

Taking into account the strata, a restricted randomisation approach [Hayes RJ, Moulton LH (2017): Cluster Randomized Trials, 2nd Ed, Chapter 6, Chapman & Hall/CRC Press] will be applied to achieve balance between the treatment arms. Among all possible distributions of clusters within strata, those, which are balanced due to specific stratification variables, will be used. This stratification will be by site and size of clinic. In addition, the same or similar number of clusters (max. difference=1) should be allocated to each treatment arm within each stratum. The number of strata per site will depend on heterogeneity of the sizes of the clinics as established during setup period. Typically, one or two strata per site will be established. A total of 6-8 strata are expected but might be increased dependent on the results of the setup period. All possible allocations will be established, whereby balance criteria covering a pre-specified variability of the stratification variables within a stratum will be applied. The size of the clinic (number of TB patients within a 2-month period) should not differ more than 20%. The allocations will be checked for validity, especially whether the clusters are spread independently among the allocations. If this is not the case, the balance criteria will be chosen less restrictive. If the number of allocations exceeds 10000, a subsample is drawn. Finally, one of the allocations will be chosen randomly.

Bias reduction

The objective of the trial is to assess Truenat platform in clinical care. The use of Truenat does not allow blinding of clinicians and participants in this trial. The trial-related procedures will be embedded into the routine practice at the primary-level facility. Data analysts will be blinded to intervention allocation.

Randomisation takes place on a cluster level rather than for the individual patients to avoid contamination between the arms within a health facility. Since clinics will be relatively far apart, contamination is unlikely.

Due to the result availability on the same day as the testing in the intervention clinics, the recruitment rate in intervention clinics may be faster than the control clinics. To minimize the

potential bias resulting from this, we will monitor the recruitment rate (i.e. percentage of interviewed participants/target enrolment by arm) continuously. If the difference between the control and the intervention arms exceeds 5% we will investigate enrolment within individual clinics to determine if the recruitment in one or a few clinics constitutes the main cause of difference. If this is the case, the sponsor will contact the clinic to determine the source of bias. Any identified biases that are not related to participant safety will be documented in a note to file.

We will contact participants for the seven and 60-day outcomes by telephone to investigate whether more diagnostics available at the level of the primary health care facility (without the need to refer samples) result in more microbiologically confirmed cases and more rapid treatment initiation. Losses to follow- up pre-diagnosis and during treatment are among the endpoints of the trial. There is a chance that contacting the participants after seven and 60 days may influence their treatment seeking behaviour in the control arm and reduce loss to follow-up. By keeping contact with trial participants to a minimum, (i.e. three time points), we hope to limit the impact on treatment seeking behaviour.

9 Statistical software

The analysis will be performed using the R statistical language (version 4.2.2 or higher).The scripts used for the entire analysis and the generation of the results will be provided to allow the reproducibility of the results.

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11 Change History

Document version	Section reference	Change from	Change to	Document date
1.0		N/A	First issuance of document	13-MAY-2022
2. 0	Section 2		Point estimates of proportions have been changed to point estimates of numbers and proportions for all relevant outcomes.	12-JUL-2022
2.0	Section 4		Methodology of analysis revised. Among minor changes, Bayesian framework statement has been removed as this may not be the approach that will be chosen necessarily.	12-JUL-2022
3.0	2		Statistical hypotheses have been revised to include the comparison of absolute numbers of patients in relevant outcomes.	31-OCT-2022
3.0	4		The analysis strategy has been revised to include a GLMM with Poisson distribution to analyse the frequencies containing the absolute number of patients.	31-OCT-2022
3.0	8		Monitoring of enrolment by arm	31-OCT-2022

Document version	Section reference	Change from	Change to	Document date
			throughout the study has been added to the strategies to minimize bias.	
3.0	Entire document		180 days follow-up has been removed from all outcomes and analyses.	31-OCT-2022
3.0	4		Analysis of missing data patterns has been revised to allow more flexibility and adapted plan in case of non-random missing data patterns	31-OCT-2022
3.0	4		P-value adjustment has been added	31-OCT-2022
3.0	2		The outcome related to the number of deaths has been removed since the cause of death independent of the disease cannot be distinguished from death due to TB.	31-OCT-2022
4.0	2		The wording of the outcomes has been revised to match the amended protocol.	03-APR-2023
4.0	4.2		Model parameters have been defined for the analysis of the primary outcome	17-MAY-2023
4.0	4.3		Model parameters have been defined for diagnosis and treatment related outcomes. Analysis methodology has	17-MAY-2023

Document version	Section reference	Change from	Change to	Document date
			been described for cost related endpoints.	
4.0	5		Items to be described are refined	17-MAY-2023
4.0	6		Subgroups are defined for the analysis	17-MAY-2023
4.0	4.3		Cost effectiveness analysis methodology was entered and revised	20-JUN-2023
4.0	3.2		MITT population defined	27-JUN-2023
4.0	4.1		The populations concerned by the analysis have been specified	27-JUN-2023
4.0	7		The description of the protocol deviation and related analysis methodology has been entered.	27-JUN-2023
5.0	2.1, 4.2		For the analysis of the count data, the wording “per month” has been removed.	11-JUL-2023