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The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: A cluster randomized trial of nutritional support (food rations) to reduce TB-incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India

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The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: A cluster randomized trial of nutritional support (food rations) to reduce TB-incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India

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Abstract

Introduction: India has the largest burden of cases and deaths related to TB. Undernutrition is the leading risk factor accounting for TB incidence, while severe undernutrition is a common risk factor for TB mortality in patients with TB in India. The impact of nutritional supplementation on TB incidence is unknown, while few underpowered studies have assessed its impact on TB mortality. We designed an open-label, field based cluster randomised trial to assess the impact of nutritional supplementation (with food rations) on TB-incidence in a group at higher risk of TB infection and disease, viz. household contacts (HHC) of patients with microbiologically confirmed pulmonary tuberculosis (PTB) in Jharkhand, a state with a high prevalence of undernutrition.

Methods and Analysis: We shall enroll 2800 adult patients with PTB of the national TB program, across 28 treatment units in 4 districts; and their approximately 11,200 eligible contacts. The sample size has 80% power to detect the primary outcome of 50% reduction in incidence of active TB in HHC over 2 years of follow-up. Patients and HHC in both the arms will undergo nutritional assessment and counseling. Patients will receive monthly food rations (supplying 1200 calories and 52 proteins) and multivitamins along with anti-tubercular treatment. The HHC in the intervention arm will receive food rations (supplying 750 calories and 23 g proteins) and multivitamins while HHC in control arm will be on usual diet. The secondary outcomes in HHC will include effects on nutritional status, non-TB infections. Secondary outcomes in patients are effects on TB mortality, adherence, adverse effects, nutritional and performance status. Sub-studies will examine micronutrient status and effects on dietary intake, body composition, muscle strength and immune function.

Ethics and dissemination: The Institutional Ethics Committee of ICMR-NIRT, Chennai approved the study (289/NIRT-IEC/2018. The results will be disseminated in publications and presentations.

Trial registration number: Clinical Trial Registry of India (CTRI/2019/08/020490).

Strengths and Limitations of the study

- The RATIONS study is the first trial addressing undernutrition to reduce TB incidence in communities with high prevalence of poverty, undernutrition and low prevalence of HIV infection.
- It is the largest trial to evaluate the impact of nutritional support on TB mortality in a programme-based cohort of patients with pulmonary tuberculosis and a high prevalence of undernutrition.
- The follow-up period of two years will ensure detection of most cases of incident TB in household contacts and recurrence of TB in index cases.
- The quantum of food rations per participant is fixed and meets only part of the daily dietary requirements.
- Food sharing in the families in the control arm and extra food consumption from other sources can't be ruled out

Introduction

Tuberculosis (TB) is a global public health problem leading to significant morbidity and mortality, especially in low and middle income countries. An estimated 10 million people developed TB and 1.2 million (HIV-negative) people succumbed to it in 2019.[1] India was the major contributor to the global TB burden with an estimated 2.6 million new cases (27% of global) and 0. 4 million (35% of global) TB-deaths in HIV-negative people in 2019.[1]

The United Nations Sustainable Development Goals-3 (SDG-3) has a target for ending the TB epidemic by 2030 and aims to reduce TB-incidence and TB-deaths by 80% and 90% of the 2015 levels respectively.[2] As per the National Strategic Plan (2017-25), the Revised National Tuberculosis Control Program (RNTCP) (renamed as National Tuberculosis Elimination Program, NTEP) in India has set an ambitious target of achieving the 2030 SDG milestone by 2025, five years ahead of the global target.[3]

The End TB strategy will require a mix of biomedical, public health and social interventions to achieve these goals.[2] The strategy requires acceleration of the current decline of 1.5% to 10-17% per year.[4] The present biomedical approach to TB prevention based on vaccination and TB preventive treatment (TPT) has its limitations. The efficacy of BCG vaccine is limited to prevention of severe forms of childhood TB.[5] The TPT with isoniazid in countries like India currently covers only select groups of contacts like under-six children and people living with HIV (PLHIV).[6] WHO recently made a conditional recommendation of offering TPT to all house-hold contacts (HHC).[7] However, there are considerable logistical and technical challenges in countries with a high burden of latent TB infection (LTBI).[8]

Rationale for the trial:

The End TB strategy recognizes the need for new tools, interventions and strategies to address the problem of TB-incidence and adverse outcomes.[2] Globally an estimated 1.7 billion people or 23% of the population have LTBI which remains latent in 90% in presence of innate and cell mediated immunity.[9] Risk factors like HIV, undernutrition, uncontrolled diabetes, smoking and alcohol impair immunity, leading to active TB, and act as drivers of the TB epidemic. Undernutrition is the leading cause of impaired immunity globally,[10] with a consistent inverse exponential relationship between nutritional status measured by body mass index (BMI) and TB-incidence.[11] According to the global TB report 2020, undernutrition is a

leading risk factor accounting for 2.2 million cases (19%), more than HIV and diabetes (accounting for 0.76 and 0.35 million cases respectively).[1] Undernutrition is also a consistent risk factor for TB-mortality, regardless of HIV infection, and drug-susceptibility.[12] Its prevalence was as high as 23% in women and 19% in men (BMI<18.5 kg/m^2) in the most recent National Family Health Survey (NFHS-4) in India.[13] It is higher in the poor, rural residents and those belonging to the scheduled castes and tribes, who also suffer a high burden of TB disease.[13,14] The WHO has estimated that 0.6 million cases of TB in India are attributable to undernutrition,[1] while other studies indicate that this estimate may be higher.[15] A majority of Indian patients with active TB have severe levels of undernutrition (macronutrient and micronutrient) which are associated with 2-4 fold higher risk of mortality.[16]

A single unit increase in BMI could reduce TB-incidence by 14%,[11] a modeling study has shown that TB-incidence and mortality could decline by 40-71% with nutritional interventions.[17] There is no randomized controlled trial on the effect of nutritional supplementation on TB-incidence. The studies on the impact of nutritional supplementation on TB mortality have been limited, small and underpowered.[18]

The RATIONS study is a cluster randomized trial to assess the impact of nutritional supplementation on TB-incidence among HHC of patients with microbiologically confirmed pulmonary tuberculosis (PTB), living in a community with a high prevalence of undernutrition. They are a group at higher risk of TB infection and disease,[19] with a prevalence of 10-60 fold higher than in the general population.[20] TB-incidence was 4.8% in the HHC and 21.4% in child contacts in a previous study from Peru.[21] Food insecurity and undernutrition are strong and modifiable risk factors of TB in the HHC.[22, 23]

OBJECTIVES (Table-1):

Primary objective: To evaluate the effect of household nutritional supplementation in reducing TB-incidence among HHC of patients with microbiologically confirmed PTB.

Secondary objectives in HHC: To evaluate the effect of nutritional supplementation on anthropometric indicators, and non-TB infectious morbidity and mortality.

Secondary outcomes in index cases: To evaluate the effect of nutritional supplementation on adherence to treatment, mortality, frequency of adverse effects due to treatment,

performance status of patients as measured by the Eastern Cooperative Oncology Group (ECOG),[24] and relapse of microbiologically confirmed TB on follow-up.

Sub-studies: Six sub-studies have been planned in a subset of index cases and HHC

a) Dietary intakes: To evaluate the difference in dietary intake of calories, proteins at baseline, and at the end of treatment in a subsample of the patients in both the arms.

b) Micronutrients: Vitamin A (serum retinol) and 25- hydroxyvitamin D [25(OH) D] levels in a subsample of index patient and HHC at baseline.

c) Body composition: To evaluate the difference in body composition between patients in the two arms at baseline and six months by a multifrequency bioelectric impedance analyzer (Bodystat Quadscan 4000).

d) Muscle function (grip strength) in a subsample of index cases at baseline, and end of treatment using a digital handheld dynamometer.

e) Immune function: To evaluate select aspects of immunity in index patient and their HHC before and after treatment using the lymphocyte subsets [CD4,CD8, Natural Killer (NK) cells, B lymphocytes] and kinetics of interferon γ responses (by CD4 and CD8 cells) in a fourth generation-Interferon Gamma Release Assay (IGRA) (QuantiFERON-TB Gold Plus: QFT-Plus)

f) Qualitative study in a subset of stakeholders: A qualitative study will also be conducted in a subset of the stakeholders (patients, contacts, and field staff) at the end of the intervention period to assess the perceptions and experiences of nutrition intervention.

Methods and analysis

Study design and oversight:

This is a cluster randomized open-label parallel-arm, superiority trial of nutritional supplementation in households with microbiologically confirmed patients with PTB in the state of Jharkhand, Eastern India. The study will randomise 28 Tuberculosis units (TUs) in four districts (Ranchi, East-Singhbhum, West-Singhbhum and Seraikela-Kharsawan) into control and intervention arms, each with 1400 adult PTB patients. It is supported by the India

TB Research Consortium of the Indian Council of Medical Research (ICMR) and implemented by the Yenepoya (Deemed to be University), in association with the National Institute for Research in Tuberculosis (ICMR-NIRT), and National Institute of Nutrition (ICMR-NIN). The enrolment began on the August 16, 2019.

Study setting: Under the NTEP, each district has one District TB centre and there are sub-district administrative units called TUs. The population is predominantly rural (75%) and indigenous communities classified as "scheduled tribes" (STs) who comprise 28% of the population (national-8%) and are historically disadvantaged groups with regard to social, economic and health indicators. According to NFHS-4, the prevalence of undernutrition in Jharkhand was 23.8% and 31.6% in adult men and women respectively, significantly higher than the national average.[13] A total of 44,000 TB cases were notified in the year 2017 when this trial was proposed.[25]

Eligibility criteria (Table-2)

Inclusion criteria: Adult patients (≥18 years) with microbiologically confirmed PTB (irrespective of drug sensitivity) will constitute the index cases and will be eligible to enrol in the study. The HHC will be persons who have lived in the same house (and eating from the same kitchen), for one or more nights or for frequent or extended periods during the day with the index case during the preceding three months.

Exclusion criteria: An index case with no eligible HHC and any HHC currently on treatment for TB will be excluded.

Study interventions:

Nature and quantity: The study intervention includes macronutrients and micronutrient supplementation along with nutritional counseling as per national guidelines.[26] The index patients (in both arms) and the HHC (in the intervention arm) will receive a food basket and a recommended daily allowance of vitamins and micronutrients every month, as described in **Table-3**. This will be either delivered by the study staff or may be picked up from a depot as per the participant preference.

Frequency and duration: The food basket will be provided for six months for new patients and 12 months for patients with MDR-TB (and their HHC in intervention arm). Extension of

the intervention period to 12 months, for a patient with non-MDR-TB will be considered if there is evidence of undernutrition (BMI<18.5 kg/m^2) in the index case even at the end of six months. Extension of rations to a HHC will be considered if an adult contact has a BMI < 16 kg/m^2; children (<10 years) have weight-for-age z-score <-2SD and adolescents (10-18 years) have BMI-for-age z-scores <-2SD.

Nutritional counselling and assessing adherence: The patients and the HHC will be counselled about the importance of a balanced diet for the nutritional recovery of the patient and the protection of the health status of the family. The families will be instructed about the optimal utilisation of the food rations in locally acceptable food recipes.The field staff will undertake follow-up visits to monitor weight gain (a proxy indicator for adherence) and check the empty packets of the milk powder as an indicator of consumption by the patient.

Co-interventions permitted during the trial

The patients as well as the HHC will continue to access public distribution system, supplementary feeding programs (Integrated Child Development Services Scheme, mid-day meals) as usual and additional INR 500/month as Direct Benefit Transfer availed by patients with TB in India. The eligible under-six children and those with HIV infection who have been advised by the NTEP staff to take chemoprophylaxis with isoniazid after an evaluation will continue to do so.

Risk assessment and referral

The patients will be evaluated for nutritional status, oxygen saturation, blood pressure and presence of complications at baseline and at follow-up. Patients with severe undernutrition with edema, extremely severe undernutrition (BMI<14 kg/m^2), breathlessness or low oxygen saturation (SpO_2<94) will be referred for inpatient care as per national guidelines.[26]

Randomization and intervention allocation:

This is an open label trial, the participants and field staff, are not blinded after assignment. All the TUs from the selected districts were line-listed (supplementary file) and randomized equally to both the arms by computer generated random numbers using restricted randomization by the statistician at ICMR-NIRT, Chennai. The cluster allocation was kept

confidential until the end of training of the field staff and the TUs were ready for implementation.

Enrolment of index cases and HHC

Figure-1 describes the study flow. Consecutive patients diagnosed with microbiologically confirmed PTB in selected TUs will be enrolled after due consent process, during a 6-12 month period. Information about the study will be given to the HHC during a home visit by the trial staff and enrolled after elicitation of voluntary written informed consent. The need for adherence to treatment and food rations, cooperation with study procedures, the stability of residence and the willingness to permit home visits will be discussed with the index cases and HHC during enrolment.

Baseline evaluation of index cases and HHC:

The study procedures at baseline and follow-up are denoted in **Table-4.** Demographic characteristics including gender, occupation, caste, marital status, education, socio-economic assessment with an asset score, education will be noted. Presence of self-reported risk factors such as diabetes, alcohol consumption and tobacco use, family/past history of TB will also be recorded.

Clinical examination of index cases: Weight will be measured with a digital weighing scale (SECA 803) with accuracy of 100 gm, and height using a portable stadiometer (SECA 213) with accuracy of 0.1 cm using standard procedures. Mean of two measurements of weight will be taken for calculation of BMI. Mid-upper arm circumference (MUAC) will be measured to the nearest of 0.1 cm on the non-dominant arm, if the patient is unable to stand. Presence of edema, blood pressure using a digital instrument (OMRON) and oxygen saturation using pulse oximeter will be noted. Assessment of performance status will be done using ECOG scale as described in **Table-5.**[24]

Clinical examination in contacts: This will consist of anthropometric measurements like weight, height, MUAC (if unable to stand and in under-five), presence of edema and BCG scar.

Laboratory evaluation of index cases: The results of the sputum smear microscopy, cartridge based nucleic acid amplification test (CB-NAAT) - Gene Xpert MTB/RIF test,

blood glucose and HIV tests (if available) will be retrieved from the NTEP records. Hemoglobin will be measured during the home visit using HemoCue Hb 201^{+} using standard procedures and precautions. Chest X-ray (CXR) of patients at baseline will be done wherever feasible.

Laboratory evaluation of HHC: Symptom screening for TB will be done in all HHC and CXR will be done wherever feasible as per the NTEP guidelines.[6] In case of symptoms of presumptive TB or an abnormal CXR, the HHC will be referred for sputum examination. Children with symptoms/abnormal CXR will be referred for further evaluation by sputum smear and CB-NAAT (if cough is productive) and induced sputum/gastric aspirate, if unable to produce sputum at a referral hospital.

Follow-up of index cases and HHC:

The enrolled index cases and their HHC will be followed-up for two years after the diagnosis of the index case. Jharkhand is a state with potential seasonal labor migration from rural areas. All attempts (including telephonic contact) will be made to retain follow-up in case of temporary migration with an in-person visit on their return. Participants will be termed as lost to follow-up if in-person or telephonic contact is not made for ≥2 months in the intervention period; or for ≥ 6 months in the follow-up period. All participants lost to follow-up will be approached for an end of study evaluation to ascertain information on the primary and relevant secondary outcomes.

The schedule of follow-up and assessments is described in **Table-4**. Evaluation will be done for current symptoms, any adverse effect related to treatment, adherence to treatment and rations. All HHC will be evaluated for symptoms of active TB on each visit, consumption of rations (in intervention arm), and review of non-TB infectious morbidity and mortality based on symptoms, hospitalization, or death.

Patients will undergo repeat sputum examination on follow-up as per NTEP guidelines. Contacts that develop any symptoms of active TB (PTB or EPTB) will undergo appropriate investigations.

The cases of active TB in HHC will be classified as co-prevalent or incident according to the time of diagnosis of the index case. A co-prevalent case is a HHC diagnosed with active TB (microbiologically confirmed active TB or as clinically diagnosed tuberculosis) at the

baseline, or within two month of the baseline screening and evaluation of the HHC. An incident case is a new case of TB in a HHC (microbiologically confirmed active TB or as clinically diagnosed) that was diagnosed more than two months following the initial negative screening and evaluation. The definition of microbiologically confirmed case and clinically diagnosed cases is as per **Table-6**.

Qualitative study about the nutritional intervention

We will use a phenomenological approach to generate qualitative data through the in-depth interview of TB patients and their HHC. The participants will be purposively selected till conceptual saturation and triangulation is reached, and will be interviewed using topic guides prepared in line with the study objectives. Interviews will be tape-recorded, transcribed verbatim, and translated to English. Open Code software will be used to facilitate analysis. This sub-study will be conducted at the end of the intervention period.

Criteria for discontinuation or withdrawal of study participants

Study participants will be free to withdraw at any time during the trial. Other reasons for discontinuation are non-consumption of rations, non-availability for follow-up and development of active disease (in HHC). Discontinuation may also occur if the study sponsors decide to stop or cancel the study.

Study outcomes

The primary outcome in HHC is the difference in number of incident cases of active TB (all forms) in the two arms by active case finding over a follow-up period of two years. The secondary outcomes are improvement in the nutritional indicators over six months, frequency of malaria, diarrhea, lower respiratory tract infection, hospitalization with fever of any cause, or death with fever of any cause less than 15 days in duration in both the trial arms.

The secondary outcomes in the index cases are successful treatment completion, TB related deaths, improvement in performance status, adverse effects, and recurrence of TB during two years follow-up. The ascertainment of primary outcomes of incident TB in contacts is by NTEP program staff (not part of the trial team).

Participant timeline:

The trial has a preparatory phase of three months for site selection, staff recruitment and training, and preparation of manual of procedures. The intervention phase will be six months for drug-susceptible cases and 12 months in the MDR-TB. The follow-up phase will continue for two years from the initiation of treatment.

Sample size estimation

The estimated incidence rate of PTB in the general population in India is 217/100,000 population (0.208 %).[4] The incidence rate-ratio of TB in HHC is 15.9 (IQR, 2.6-21.4) compared to the general population, translating into 4% incidence in the HHC.[19] Assuming a higher burden of TB and undernutrition in India, and recent emerging evidence of significantly higher risk of TB disease following infection in close contacts, [27] we considered TB-incidence in HHC to be 5% over the study period. We assume 50% reduction in TB-incidence at household level with intervention.[28]

Our sample size considers design effect at three levels; the TU level, the families of index cases and finally their HHC.[29] We assumed approximately 100 index cases (80-120) and their families in a cluster per annum, a correlation coefficient of 0.2 for the outcome in HHC and 0.01 between members of the same cluster,[19] and thus a design effect of 6.75. Thus a sample size of 28 clusters with 2800 patients and approximately 11,200 contacts equally distributed in both the arms would have 80% power to detect 50% reduction of TB-incidence in intervention arm with a type-1 error of 5%.

The sub-study sample sizes were estimated based on the assumptions related to the objective of the sub-study. The sample size of 250 cases (125/arm) and 250 contacts (125/arm) was based on the prevalence of multiple vitamin deficiencies in patients with PTB, [30] and the prevalence of Vitamin D deficiency in apparently healthy individuals in India.[31]

A sample size of 352 contacts (176/arm) was assumed to be needed to detect a 10% difference in mean CD4 counts in the contacts of the two arms after six months of intervention, with 90% power. This proportion is about 3% of the HHC and we will enroll a similar 3% of the index cases (50/arm) to assess determine the immune function at baseline and after intervention in them.

The sample size for the dietary intake sub-study assumes a standard deviation of 525 KCalories, over a wide range of caloric intakes.[32] Assuming a mean difference in caloric

intake between both the arms as 400 KCalories and 20% loss to follow-up, we will enroll 45 contacts and 45 patients in each arm.

Data collection, management

The data will be collected by field investigators working in close collaboration with the NTEP staff. Study data will be collected and managed using REDCap, an electronic data capture tools[33] hosted at ICMR-NIRT. The data capture will be done real time using a handheld device, will be subjected to range and logic checks and will be monitored by the project technical team. A periodic quality check will be performed for accuracy and completeness by the data management team at ICMR-NIRT, which will minimize missing data. Appropriate imputation methods will be used for missing values in the analysis if required. The final dataset will be accessible to the investigators based in Yenepoya (deemed to be University) and ICMR-NIRT and will be deposited in electronic format with the trial sponsor, ICMR, at the end of the study.

All essential trial documents, consent forms will be stored under lock and key at the recruitment site under the supervision of investigators. Electronic data will be password protected and the records will be retained for a period of five years after completion of the study.

We will constitute a data safety management board (DSMB) comprising of subject experts in clinical trials, TB and nutrition along with independent biostatistician and ethicist.

Apart from the regular monitoring by the project team, there is periodic reporting to the ICMR, to the IEC of ICMR-NIRT, the trial advisory committee and the DSMB.

Data analysis:

The primary outcome is TB incidence among contacts, expressed as events per 100,000 person-months of follow-up. Follow-up is defined as time from date of randomization until the earliest endpoint, i.e. documented TB disease or censoring (death, loss to follow-up or end of the study).

Cox proportional hazards model, accounting for varying follow-up times and clustering effect, will be used to compare the rate of progression of TB infection to disease among contacts between the arms and to assess its association with risk factors. Unadjusted and

adjusted hazard ratios along with their 95% confidence intervals will be reported. The crude effect of the intervention will be calculated using Kaplan-Meier survival plots and compared using the log rank test.

The primary analysis will be intention to treat. Per-protocol analysis will also be done. The models will be adjusted for relevant risk factors (age, smoking, diabetes, duration of exposure) during the sensitivity analysis.

The secondary outcomes of change in weight and z-scores in patients and HHC, and the performance status in patients, will be compared using unpaired and paired t-tests and Bonferroni correction for multiple comparisons. Linear mixed regression models adjusted for age, gender, TU, caste, asset score, family size, and baseline weight will be done.

The secondary outcomes of frequency of non-TB morbidities and deaths due to infections in the HHC, and the frequency of deaths, adverse effects, defaults, relapse in the index cases in the two arms will be compared using the chi-square test and Cox proportional hazards regression for time to first event.

The patients enrolled in the sub-studies will be compared in their baseline characteristics as these have been drawn by non-random sampling of patients from the main trial. The changes in dietary intake of calories and proteins, body composition parameters and lymphocyte will be assessed among index and contacts. Interactions between treatment and change in nutritional and body composition indicators will be tested using likelihood ratio tests.

The effect of subgroups will be analysed based on age, gender, caste, residence, BMI, asset score, and possession of below poverty line card, alcohol use, and family history of TB. A p value <0.05 (two-tailed) will be considered statistically significant. All data will be analysed using STATA version 16.1 (StataCorp, Texas, USA).

Interim analysis will be performed on attaining 50% of outcomes in the control arm (approximately 230 cases) with a p-value<0.0054 as statistically significant. The final analysis will be done at the end of attainment of planned sample size and completion of follow-up, considering a p-value <0.0492 as statistically significant.

Harm

The intervention involves locally consumed food items which are part of the daily diet and hence no specific adverse events are expected. Patients who have lactose intolerance will be offered alternatives. The possibility of 're-feeding syndrome' in severely undernourished patients will be prevented by training the field staff to offer a graded increase in food intake in such patients.

Ethics, participant information and consent: Ethics clearance has been obtained from Institutional Ethics Committee of ICMR-NIRT, Chennai (NIRT-IEC no: 2018020), to which all the amendments of the protocol will be communicated. Patients and their HHC who are enrolled in the study will receive a detailed 'Participant Information Sheet' in local language before administering the informed consent. A separate consent form will be used for the adult participants enrolled in the sub-study on micronutrient status and immune function. No blood specimen will be stored for any future use. A unique numerical code will be allocated to each participant for purpose of their identification and for maintaining confidentiality. Personal identifiers will be deleted in the final research database for analysis. All forms with personal identifiers will be under lock and key with the trial team.

Responsibility for ancillary care during the trial

Any index case or HHC found to have an acute illness other than TB during the follow-up visits will be facilitated by the field staff to reach the nearest government health set-up.

Patient and public involvement statement

Patients were not directly involved in the development of the research question. The components of food basket were discussed with community health workers during the preparatory phase of the trial. The training of the field staff involved interaction with TB survivors and two of the field staff in the trial are TB-survivors.

Dissemination Plan

The impact of nutritional support on TB incidence and outcomes in this trial will be of relevance to NTEP, India. The results will be disseminated through publications, conference presentations and briefs for the program managers, Jharkhand department of Health, policy makers and other stakeholders. We intend to share the published results in simple language with the participants and community leaders.

Trial status

The trial was started on 16th of August 2019 after trial registration (CTRI/2019/08/020490) and an intensive two weeks training of 56 field staff, two project consultants and one project director by State NTEP staff, nutritionist, and specialists in TB, ethicist, TB-champions, communication experts and social scientists. We have enrolled 2488 index cases and 9125 HHC in the trial as of 31st of October, 2020.

Author contributions

AB conceived the research question. AB, BR, MB, TK, BK designed the study protocol and drafted the manuscript. BW, MS, RD, AM, RRP, KR, KSS reviewed the study protocol and provided critical intellectual content. All authors carefully read and approved the final version of the manuscript.

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Competing interests statement:

The authors state that they have no competing interests to declare.

Figure 1: Study flow for the RATIONS Trial

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Table-1: Objectives of the RATIONS trial and the outcome variables

Objective	Outcome variables	Index case	HHC
Primary Objective			
Effect of household nutritional supplementation in reducing TB incidence among HHC of patients with microbiologically confirmed PTB	Difference in number of incident cases of active TB (all forms) in the two arms detected by active case finding over a follow-up period of two years after diagnosis of index case		✓
Secondary Objectives			
Effect of nutritional supplementation on anthropometric indicators over 6 months	Anthropometric indicators such as weight and Body Mass Index	✓	✓
Non-TB infectious morbidity and mortality in HHC in both the arms	Malaria, diarrhea, lower respiratory tract infection, hospitalization with fever of any cause, or death with fever of any cause <15 days in duration		✓
Adherence to anti-TB therapy	Proportion completing the therapy successfully	✓	
Mortality during treatment	Proportion of index cases who died during treatment	✓	
Adverse effects	Severe adverse effects with TB drugs	✓	
Recurrence of TB within 2 years after cure	Relapse rate of microbiologically confirmed TB	✓	
Performance status	Change in ECOG scale at 1,2 and 6 months compared to baseline	✓	
Dietary Substudy			
Evaluate the difference in dietary intake of calories and proteins	Calorie and protein intake at baseline, and end of treatment in intervention and control arms	✓	✓
Micronutrient substudy			
Assess Vitamin A and D [25(OH)D]	Level of vitamin A and D at baseline	✓	✓

levels			
Body composition substudy			
Evaluation of body composition	Estimate fat-free mass, fat mass, and other Bioimpedance analysis parameters at baseline, and 6 months after treatment	✓	✓
Substudy on grip strength			
Evaluate muscle strength using hand grip dynamometer	Grip strength at baseline and 6 months	✓	
Substudy of immune function			
Evaluate cellular immunity in patients and HHC	Lymphocyte subsets (CD4,CD8, Natural Killer cells, B lymphocytes), 4th generation Interferon Gamma Release Assay (IGRA) at baseline and end of treatment	✓	✓

HHC=household contact; PTB=pulmonary tuberculosis; MDR=multi-drug resistant tuberculosis; ECOG=eastern co-operative oncology group

Table-2: Eligibility criteria for RATIONS trial participants

Index cases	**Household contacts (HHC)**
Inclusion Criteria	
Patients ≥18 years with microbiologically confirmed pulmonary TB	Persons living in the same house, eating from same kitchen as index case for ≥ one night or for frequent or extended periods during the day during the 3 months before diagnosis in index case
Exclusion criteria	
Non eligible HHC	Current smear or GeneXpert or LPA or culture confirmed TB
Time interval between initiation of treatment and enrolment is > 14 days	Clinically diagnosed pulmonary or extra-pulmonary TB and currently on treatment

LPA = Line probe assay

Table-3: Nutritional supplementation in the RATIONS trial

	Intervention arm	**Control arm**
Index case*, quantity per person per month	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient
Household contact§, quantity per person per month	Nutritional counselling 5 kg rice 1.5kg pulses (split pigeon peas) One RDA of micronutrient per adult/adolescent HHC Half of this amount for children less than 10 years.	Nutritional counselling Usual food assistance available to eligible households through public distribution system

RDA = Recommended Dietary Allowance; * approximately 1200 Kcal of energy and 52 gm proteins per day. § approximately 750 Kcal of energy and 23 gm of proteins per day.

Table 4: Schedule of enrolment, assessments at baseline and follow-up in the RATIONS trial

	Investigations	Base-line	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15	M18	M21	M24
	In index cases																	
1	Informed consent	X																
2	Demography, socio-economic status, co-morbidities, household characteristics, access to PDS	X																
3	Clinical Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	Anthropometry (Height, Weight, MUAC), SpO_2 pedal edema	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	*Laboratory evaluation RBS, HIV, Hb	X																
6	Compliance to Nutritional supplement in new cases, (12 mo. in MDR-TB)	X	X	X	X	X	X	X	X	X	X	X	X	X				
7	Performance status (modified ECOG Scale)	X	X	X				X	X	X	X	X	X	X				
8	*CB NAAT	X							(in case of symptoms of recurrent disease)									
9	*CXR	X						X										
	In subsample of index cases																	
1	Dietary recall of calories, protein intake	X						X										
2	Body composition (By BIA)	X						X										
3	Micronutrient estimation(Vit. A, D)	X																
4	Hand grip strength	X						X										
5	Immunological tests (4^{th} generation IGRA, lymphocyte subsets)	X						X										
	In household contacts																	
1	Informed consent	X																
2	Baseline demography, socio-economic status, co-morbid conditions, household characteristics, Access to PDS	X																

3.	Symptom screen	X	X	X	X	X	X	X			X			X	X	X	X	X
4.	Clinical Evaluation if symptomatic	X	In case of symptoms of active TB															
5	Anthropometry (Height, Weight, Upper mid arm circumference)	X	X	X	X	X	X	X			X			X	X	X	X	X
6	Compliance to Nutritional supplement (Intervention arm); (12 mo. in MDR-TB)	X	X	X	X	X	X	X										
7.	#Review of non-TB infectious illnesses	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	Sputum smear, CBNAAT	In case of symptoms of active TB																
9	@CXR	X	In case of symptoms of active TB															
	In subsample of household contacts																	
1.	Dietary recall of calories, protein intake	X						X										
2	Body composition (By BIA)	X						X										
3	Micronutrient estimation (Vit. A, D)	X																
4	Immunological tests (4th generation IGRA, lymphocyte subsets)	X						X										

* Through public health system; #respiratory infections, diarrhea, hospitalization with fever of any cause, death due to fever < 15 days duration; @ for under-five children, symptomatic contacts.

MUAC=Mid upper arm circumference; SpO2=Oxygen saturation; RBS=Random Blood Sugar; HIV=Human immunodeficiency virus; Hb=Hemoglobin; MDR-TB=Multidrug resistant tuberculosis; ECOG=Eastern Co-operative Oncology Group; CXR=Chest X-ray; CB NAAT=Cartridge based nucleic acid amplification test; BIA=Bio Impedance Analysis; PDS=public distribution system

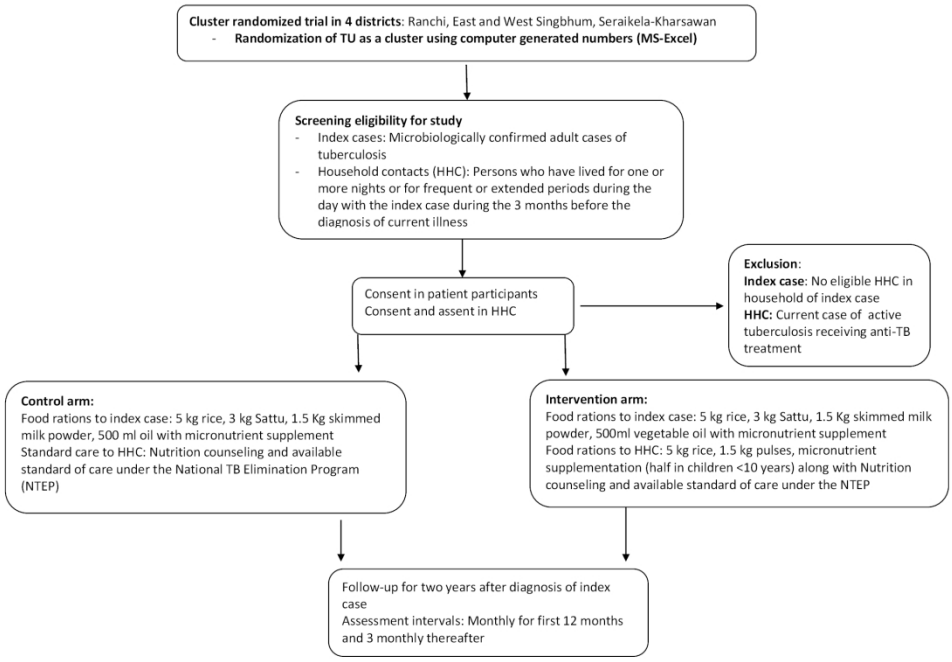
Table 5: Eastern Co-operative Oncology Group (ECOG) scale for functional assessment[24]

ECOG categories	Additional description	Score
Able to carry out normal activity without restriction	No physical restriction	0
Unable to do physically strenuous activity, but ambulatory and able to carry out light work	Able to walk around the neighbourhood, but unable to do any income-generating work	1
Ambulatory and capable of all self-care, but unable to carry out any work; up and about <50% of waking hours	Able to walk around the house and backyard	2
Capable of only limited self-care; confined to bed or chair >50% of waking hours	Able to go to the bathroom,	3
Completely disabled; cannot carry out any self-care; totally confined to bed or chair	Unable to go to the bathroom	4

Table 6: Case definitions for outcomes used in RATIONS trial [6]

Outcome	Case definition
Active tuberculosis	Any patient with microbiologically confirmed tuberculosis or clinically diagnosed TB
Microbiologically confirmed tuberculosis in adults or children	A patient who has a positive sputum smear for mycobacterium tuberculosis and/or - Sputum/gastric aspirate is positive on CB-NAAT - And/or positive on culture
Clinically diagnosed pulmonary TB	A patient who has symptoms suggestive of TB, is smear negative and/or negative on CB-NAAT, and/or who has chest X-ray is suggestive of TB, and where there is no alternative clinical diagnosis
Clinically diagnosed extrapulmonary TB	A patient who is either negative on microbiological testing and/or CB-NAAT, or where an appropriate specimen is not available, and the findings (clinical/ biochemical/ cytological/ histopathological/radiological or direct visualization procedures) are suggestive of tuberculosis, and where alternative diagnosis have been ruled out.
Clinically diagnosed pulmonary TB in children	A patient who has symptoms suggestive of active pulmonary TB (Fever, cough, weight loss or absence of weight gain), and/or a chest X-ray is suggestive of TB, and there is absence of alternative diagnosis, who is negative on CB-NAAT on gastric aspirate or induced sputum, or when bacteriological confirmation has not been possible.

CB-NAAT=Cartridge based nucleic acid amplification test



Study flow for the RATIONS Trial

279x215mm (200 x 200 DPI)

List of Tuberculosis treatment Units (TUs):

1. DTC Seraikela
2. Rajnagar
3. Chandil
4. Adityapur
5. Gamharia
6. Kharsawan
7. Icchagarh
8. Angara-Ratu
9. Bundu
10. Doranda
11. Itki
12. Mandar-Burmu
13. Ormanjhi
14. Sadar (Ranchi)
15. Jagannathpur
16. Chaibasa (Urban)
17. Chakradharpur
18. Jhinkpani
19. Chaibasa (Rural)
20. Manjhari
21. Tantnagar
22. Dalbhumgarh
23. Sadar (Jamshedpur)
24. Mushabani
25. Mango
26. Baharaghoda
27. Jugsalai
28. Potka

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 and 16 CTRI/2019/08/020490), Clinical Trials Registry of India.
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page no.6, 7
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Affiliation in submission website placeholders and protocol contribution: Pg 16
	5b	Name and contact information for the trial sponsor	Page 2, 16

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Appendix- 1
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
	6b	Explanation for choice of comparators	Page 4-6
Objectives	7	Specific objectives or hypotheses	Pages 5-6, Table 1
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pages 6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7, supplementary file
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 11

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pages 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 5-6, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pages 7-10,12, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	We are enrolling consenting patients who have been diagnosed in the National TB program
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pages 8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable as this is an open label cluster randomised trial

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pages8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 8-9, trial participants
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 7-9, Page 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 13

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 13 mentions reporting and oversight in the trial. Decision for audit lies with the trial sponsor. This is not a drug trial so audit by regulatory agency is not involved.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	We shall follow ICMJE guidelines
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix-2 (for editor only)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 15

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: A cluster randomized trial of nutritional support (food rations) to reduce TB-incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Nutrition and metabolism, Global health
Keywords:	NUTRITION & DIETETICS, Tuberculosis < INFECTIOUS DISEASES, PREVENTIVE MEDICINE, Public health < INFECTIOUS DISEASES

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The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: A cluster randomized trial of nutritional support (food rations) to reduce TB-incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India

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Abstract

Introduction: India has the largest burden of cases and deaths related to TB. Undernutrition is the leading risk factor accounting for TB incidence, while severe undernutrition is a common risk factor for TB mortality in patients with TB in India. The impact of nutritional supplementation on TB incidence is unknown, while few underpowered studies have assessed its impact on TB mortality. We designed an open-label, field based cluster randomised trial to assess the impact of nutritional supplementation (with food rations) on TB-incidence in a group at higher risk of TB infection and disease, viz. household contacts (HHC) of patients with microbiologically confirmed pulmonary tuberculosis (PTB) in Jharkhand, a state with a high prevalence of undernutrition.

Methods and Analysis: We shall enroll 2800 adult patients with PTB of the national TB program, across 28 treatment units in 4 districts; and their approximately 11,200 eligible contacts. The sample size has 80% power to detect the primary outcome of 50% reduction in incidence of active TB in HHC over 2 years of follow-up. Patients and HHC in both the arms will undergo nutritional assessment and counseling. Patients will receive monthly food rations (supplying 1200 kilocalories and 52 proteins per day) and multivitamins along with anti-tubercular treatment. The HHC in the intervention arm will receive food rations (supplying 750 kilocalories and 23 g proteins per day) and multivitamins while HHC in control arm will be on usual diet. The secondary outcomes in HHC will include effects on nutritional status, non-TB infections. Secondary outcomes in patients are effects on TB mortality, adherence, adverse effects, nutritional and performance status. Sub-studies will examine micronutrient status and effects on dietary intake, body composition, muscle strength and immune function.

Ethics and dissemination: The Institutional Ethics Committee of ICMR-NIRT, Chennai approved the study (289/NIRT-IEC/2018. The results will be disseminated in publications and presentations.

Trial registration number: Clinical Trial Registry of India (CTRI/2019/08/020490).

Strengths and Limitations of the study

- The RATIONS study is the first trial addressing undernutrition to reduce TB incidence in communities with high prevalence of poverty, undernutrition and low prevalence of HIV infection.
- It is the largest trial to evaluate the impact of nutritional support on TB mortality in a programme-based cohort of patients with pulmonary tuberculosis and a high prevalence of undernutrition.
- The follow-up period of two years will ensure detection of most cases of incident TB in household contacts and recurrence of TB in index cases.
- The quantum of food rations per participant is standardized, and in the absence of individual needs assessment, the extent to which the intervention meets individual needs is unknown. .
- Food sharing in the families in the control arm and extra food consumption from other sources can't be ruled out

Introduction

Tuberculosis (TB) is a global public health problem leading to significant morbidity and mortality, especially in low and middle income countries. An estimated 10 million people developed TB and 1.2 million (HIV-negative) people succumbed to it in 2019.[1] India was the major contributor to the global TB burden with an estimated 2.6 million new cases (27% of global) and 0. 4 million (35% of global) TB-deaths in HIV-negative people in 2019.[1]

The United Nations Sustainable Development Goals-3 (SDG-3) has a target for ending the TB epidemic by 2030 and aims to reduce TB-incidence and TB-deaths by 80% and 90% of the 2015 levels respectively.[2] As per the National Strategic Plan (2017-25), the Revised National Tuberculosis Control Program (RNTCP) (renamed as National Tuberculosis Elimination Program, NTEP) in India has set an ambitious target of achieving the 2030 SDG milestone by 2025, five years ahead of the global target.[3]

The End TB strategy will require a mix of biomedical, public health and social interventions to achieve these goals.[2] The strategy requires acceleration of the current decline of 1.5% to 10-17% per year.[4] The present biomedical approach to TB prevention based on vaccination and TB preventive treatment (TPT) has its limitations. The efficacy of BCG vaccine is limited to prevention of severe forms of childhood TB.[5] The TPT with isoniazid in countries like India currently covers only select groups of contacts like under-six children and people living with HIV (PLHIV).[6] WHO recently made a conditional recommendation of offering TPT to all house-hold contacts (HHC).[7] However, there are considerable logistical and technical challenges in countries with a high burden of latent TB infection (LTBI).[8]

Rationale for the trial:

The End TB strategy recognizes the need for new tools, interventions and strategies to address the problem of TB-incidence and adverse outcomes.[2] Globally an estimated 1.7 billion people or 23% of the population have LTBI which remains latent in 90% in presence of innate and cell mediated immunity.[9] Risk factors like HIV, undernutrition, uncontrolled diabetes, smoking and alcohol impair immunity, leading to active TB, and act as drivers of the TB epidemic. Undernutrition results from deficient intake or assimilation of energy and nutrients, often in association with disease-associated inflammation, and is a part of the broader spectrum of malnutrition, which includes both undernutrition, overweight and obesity

and deficiencies of micronutrients. Undernutrition in children is commonly defined by the well-accepted WHO indicators of low birth weight in newborns, underweight(low weight for age), stunting(low height for age) and wasting (low weight for height) in preschool children and by age and gender-specific cutoffs for BMI in those 6-18 years of age. In adults undernutrition is based on a low body mass index which reflects low body energy stores or chronic energy deficiency. The body mass index cut-off for underweight proposed by WHO of < 18.5 kg/m^2 for populations,[10] has also been accepted as a criterion for clinical diagnosis of malnutrition/undernutrition in a recent consensus statement.[11] In addition there have been proposals for diagnosis of undernutrition based on altered body composition, and for higher BMI cut-offs in patients undergoing significant involuntary weight loss, which require further validation.[11, 12]

Undernutrition is the leading cause of impaired immunity globally,[13] with a consistent inverse exponential relationship between nutritional status measured by body mass index (BMI) and TB-incidence.[14] According to the global TB report 2020, undernutrition is a leading risk factor accounting for 2.2 million cases (19%), more than HIV and diabetes (accounting for 0.76 and 0.35 million cases respectively).[1] Undernutrition is also a consistent risk factor for TB-mortality, regardless of HIV infection, and drug-susceptibility.[15] Its prevalence was as high as 23% in women and 19% in men (BMI<18.5 kg/m^2) in the most recent National Family Health Survey (NFHS-4) in India.[16] It is higher in the poor, rural residents and those belonging to the scheduled castes and tribes, who also suffer a high burden of TB disease.[16, 17] The WHO has estimated that 0.6 million cases of TB in India are attributable to undernutrition,[1] while other studies indicate that this estimate may be higher.[18] A majority of Indian patients with active TB have severe levels of undernutrition (macronutrient and micronutrient) which are associated with 2-4 fold higher risk of mortality.[19]

A single unit increase in BMI could reduce TB-incidence by 14%,[14] a modeling study has shown that TB-incidence and mortality could decline by 40-71% with nutritional interventions.[20] There is no randomized controlled trial on the effect of nutritional supplementation on TB-incidence. The studies on the impact of nutritional supplementation on TB mortality have been limited, small and underpowered.[21]

The RATIONS study is a cluster randomized trial to assess the impact of nutritional supplementation on TB-incidence among HHC of patients with microbiologically confirmed

pulmonary tuberculosis (PTB), living in a community with a high prevalence of undernutrition. They are a group at higher risk of TB infection and disease,[22] with a prevalence of 10-60 fold higher than in the general population.[23] TB-incidence was 4.8% in the HHC and 21.4% in child contacts in a previous study from Peru.[24] Food insecurity and undernutrition are strong and modifiable risk factors of TB in the HHC.[25, 26] The trial is being conducted in Jharkhand (meaning "Land of Forests") a state in eastern India which has the a high prevalence of undernutrition in children and adults. According to the National Family Health Survey-4 (2015-6), the state has the highest levels of underweight (47.8%), wasting (29.0%), and the second highest level of stunting(45.3%) in children under six years of age in India.[16, 27] Similarly, more than two of out of every five (41%) of adult rural women in Jharkhand had a body mass index of less than 18.5 kg/m^2, and had the highest prevalence of anemia in adult women in India(65.9%)[16, 27]

OBJECTIVES

The objectives and the outcome variables have been tabulated in table 1.

Primary objective: To evaluate the effect of household nutritional supplementation in reducing TB-incidence among HHC of patients with microbiologically confirmed PTB.

Secondary objectives in HHC: To evaluate the effect of nutritional supplementation on anthropometric indicators, and non-TB infectious morbidity and mortality.

Secondary outcomes in index cases: To evaluate the effect of nutritional supplementation on adherence to treatment, mortality, frequency of adverse effects due to treatment, performance status of patients as measured by the Eastern Cooperative Oncology Group (ECOG),[28] and relapse of microbiologically confirmed TB on follow-up.

Sub-studies: Six sub-studies have been planned in a subset of index cases and HHC

a) Dietary intakes: To evaluate the difference in dietary intake of calories, proteins at baseline, and at the end of treatment in a subsample of the patients in both the arms.

b) Micronutrients: Vitamin A (serum retinol) and 25- hydroxyvitamin D [25(OH) D] levels in a subsample of index patient and HHC at baseline.

c) Body composition: To evaluate the difference in body composition between patients in the two arms at baseline and six months by a multifrequency bioelectric impedance analyzer (Bodystat Quadscan 4000).

d) Muscle function (grip strength) in a subsample of index cases at baseline, and end of treatment using a digital handheld dynamometer.

e) Immune function: To evaluate select aspects of immunity in index patient and their HHC before and after treatment using the lymphocyte subsets [CD4,CD8, Natural Killer (NK) cells, B lymphocytes] and kinetics of interferon γ responses (by CD4 and CD8 cells) in a fourth generation-Interferon Gamma Release Assay (IGRA) (QuantiFERON-TB Gold Plus: QFT-Plus)

f) Qualitative study in a subset of stakeholders: A qualitative study will also be conducted in a subset of the stakeholders (patients, contacts, and field staff) at the end of the intervention period to assess the perceptions and experiences of nutrition intervention.

Methods and analysis

Study design and oversight:

This is a cluster randomized open-label parallel-arm, superiority trial of nutritional supplementation in households with microbiologically confirmed patients with PTB in the state of Jharkhand, Eastern India. The study will randomise 28 Tuberculosis units (TUs) in four districts (Ranchi, East-Singhbhum, West-Singhbhum and Seraikela-Kharsawan) into control and intervention arms, each with 1400 adult PTB patients. It is supported by the India TB Research Consortium of the Indian Council of Medical Research (ICMR) and implemented by the Yenepoya (Deemed to be University), in association with the National Institute for Research in Tuberculosis (ICMR-NIRT), and National Institute of Nutrition (ICMR-NIN). The enrolment began on the August 16, 2019.

Study setting: Under the NTEP, each district has one District TB centre and there are sub-district administrative units called TUs. The population is predominantly rural (75%) and indigenous communities classified as “scheduled tribes” (STs) who comprise 28% of the population (national-8%) and are historically disadvantaged groups with regard to social,

economic and health indicators. According to NFHS-4, the prevalence of undernutrition in Jharkhand was 23.8% and 31.6% in adult men and women respectively, significantly higher than the national average.[16] A total of 44,000 TB cases were notified in the year 2017 when this trial was proposed.[29]

Eligibility criteria:

The inclusion and exclusion criteria are mentioned in table 2.

Inclusion criteria: Adult patients (≥18 years) with microbiologically confirmed PTB (irrespective of drug sensitivity) will constitute the index cases and will be eligible to enrol in the study. The HHC will be persons who have lived in the same house (and eating from the same kitchen), for one or more nights or for frequent or extended periods during the day with the index case during the preceding three months.

Exclusion criteria: An index case with no eligible HHC and any HHC currently on treatment for TB will be excluded.

Study interventions:

Nature and quantity: The study intervention includes macronutrients and micronutrient supplementation along with nutritional counseling as per national guidelines.[30] The index patients (in both arms) and the HHC (in the intervention arm) will receive a food basket and a recommended daily allowance of vitamins and micronutrients every month, as described in **Table-3**. This will be either delivered by the study staff or may be picked up from a depot as per the participant preference.

Frequency and duration: The food basket will be provided for six months for new patients and 12 months for patients with MDR-TB (and their HHC in intervention arm). Extension of the intervention period to 12 months, for a patient with non-MDR-TB will be considered if there is evidence of undernutrition (BMI<18.5 kg/m^2) in the index case even at the end of six months. Extension of rations to a HHC will be considered if an adult contact has a BMI < 16 kg/m^2; children (<10 years) have weight-for-age z-score <-2SD and adolescents (10-18 years) have BMI-for-age z-scores <-2SD.

Nutritional counselling and assessing adherence: The patients and the HHC will be counselled about the importance of a balanced diet for the nutritional recovery of the patient

and the protection of the health status of the family. The families will be instructed about the optimal utilisation of the food rations in locally acceptable food recipes.The field staff will undertake follow-up visits to monitor weight gain (a proxy indicator for adherence) and check the empty packets of the milk powder as an indicator of consumption by the patient.

Co-interventions permitted during the trial

The patients as well as the HHC will continue to access public distribution system, supplementary feeding programs (Integrated Child Development Services Scheme, mid-day meals) as usual and additional INR 500/month as Direct Benefit Transfer availed by patients with TB in India. The eligible under-six children and those with HIV infection who have been advised by the NTEP staff to take chemoprophylaxis with isoniazid after an evaluation will continue to do so.

Risk assessment and referral

The patients will be evaluated for nutritional status, oxygen saturation, blood pressure and presence of complications at baseline and at follow-up. Patients with severe undernutrition with edema, extremely severe undernutrition (BMI<14 kg/m^2), breathlessness or low oxygen saturation (SpO_2<94) will be referred for inpatient care as per national guidelines.[30]

Randomization and intervention allocation:

This is an open label trial, the participants and field staff, are not blinded after assignment. All the TUs from the selected districts were line-listed (list of TUs is available in supplementary file 1) and randomized equally to both the arms by computer generated random numbers using restricted randomization by the statistician at ICMR-NIRT, Chennai. The cluster allocation was kept confidential until the end of training of the field staff and the TUs were ready for implementation.

Enrolment of index cases and HHC

Figure-1 describes the study flow. Consecutive patients diagnosed with microbiologically confirmed PTB in selected TUs will be enrolled after due consent process, during a 6-12 month period. Information about the study will be given to the HHC during a home visit by the trial staff and enrolled after elicitation of voluntary written informed consent. The need for adherence to treatment and food rations, cooperation with study procedures, the stability

of residence and the willingness to permit home visits will be discussed with the index cases and HHC during enrolment.

Baseline evaluation of index cases and HHC:

The study procedures at baseline and follow-up are denoted in **Table-4.** Demographic characteristics including gender, occupation, caste, marital status, education, socio-economic assessment with an asset score, education will be noted. Presence of self-reported risk factors such as diabetes, alcohol consumption and tobacco use, family/past history of TB will also be recorded.

Clinical examination of index cases: Weight will be measured with a digital weighing scale (SECA 803) with accuracy of 100 gm, and height using a portable stadiometer (SECA 213) with accuracy of 0.1 cm using standard procedures. Mean of two measurements of weight will be taken for calculation of BMI. Undernutrition is defined as a Body mass index < 18.5 kg/m^2 according to the underweight definition approved by the WHO.[10] Patients will further be categorized into mild underweight in case the BMI is 17.0-18.49 kg/m^2, moderate underweight if the BMI is 16.0-16.99 kg/m^2, severely underweight if the BMI is less than 16 kg/m^2 as suggested by WHO.[31] An additional category of extremely severe underweight is used to classify those with a BMI of less than or equal to 14 kg/m^2.[32] Mid-upper arm circumference (MUAC) will be measured to the nearest of 0.1 cm on the non-dominant arm, if the patient is unable to stand. Presence of edema, blood pressure using a digital instrument (OMRON) and oxygen saturation using pulse oximeter will be noted. Assessment of performance status will be done using ECOG scale as described in **Table-5.**[28]

Clinical examination in contacts: This will consist of anthropometric measurements like weight, height, MUAC (if unable to stand and in under-five), presence of edema and BCG scar.

Laboratory evaluation of index cases: The results of the sputum smear microscopy, cartridge based nucleic acid amplification test (CB-NAAT) - Gene Xpert MTB/RIF test, blood glucose and HIV tests (if available) will be retrieved from the NTEP records. Hemoglobin will be measured during the home visit using HemoCue Hb 201^+ using standard procedures and precautions. Chest X-ray (CXR) of patients at baseline will be done wherever feasible.

Laboratory evaluation of HHC: Symptom screening for TB will be done in all HHC and CXR will be done wherever feasible as per the NTEP guidelines.[6] In case of symptoms of presumptive TB or an abnormal CXR, the HHC will be referred for sputum examination. Children with symptoms/abnormal CXR will be referred for further evaluation by sputum smear and CB-NAAT (if cough is productive) and induced sputum/gastric aspirate, if unable to produce sputum at a referral hospital.

Follow-up of index cases and HHC:

The enrolled index cases and their HHC will be followed-up for two years after the diagnosis of the index case. Jharkhand is a state with potential seasonal labor migration from rural areas. All attempts (including telephonic contact) will be made to retain follow-up in case of temporary migration with an in-person visit on their return. Participants will be termed as lost to follow-up if in-person or telephonic contact is not made for ≥2 months in the intervention period; or for ≥ 6 months in the follow-up period. All participants lost to follow-up will be approached for an end of study evaluation to ascertain information on the primary and relevant secondary outcomes.

The schedule of follow-up and assessments is described in **Table-4**. Evaluation will be done for current symptoms, any adverse effect related to treatment, adherence to treatment and rations. All HHC will be evaluated for symptoms of active TB on each visit, consumption of rations (in intervention arm), and review of non-TB infectious morbidity and mortality based on symptoms, hospitalization, or death.

Patients will undergo repeat sputum examination on follow-up as per NTEP guidelines. Contacts that develop any symptoms of active TB (PTB or EPTB) will undergo appropriate investigations.

The cases of active TB in HHC will be classified as co-prevalent or incident according to the time of diagnosis of the index case. A co-prevalent case is a HHC diagnosed with active TB (microbiologically confirmed active TB or as clinically diagnosed tuberculosis) at the baseline, or within two month of the baseline screening and evaluation of the HHC. An incident case is a new case of TB in a HHC (microbiologically confirmed active TB or as clinically diagnosed) that was diagnosed more than two months following the initial negative

screening and evaluation. The definition of microbiologically confirmed case and clinically diagnosed cases is as per **Table-6**.

Qualitative study about the nutritional intervention

We will use a phenomenological approach to generate qualitative data through the in-depth interview of TB patients and their HHC. The participants will be purposively selected till conceptual saturation and triangulation is reached, and will be interviewed using topic guides prepared in line with the study objectives. Interviews will be tape-recorded, transcribed verbatim, and translated to English. Open Code software will be used to facilitate analysis. This sub-study will be conducted at the end of the intervention period.

Discontinuation of study intervention and withdrawal of study participants

Study participants will be asked about consumption of rations and micronutrients at every visit. Rarely, they may choose to discontinue consumption of the study intervention during the intervention period, due to an unrelated illness or perceived adverse effects. The reasons for their discontinuation of study intervention will be recorded but these participants will remain in the study and undergo protocol-specified follow up procedures. However if the participants also explicitly withdraws consent for follow up and collection of additional information in addition to discontinuation of consumption of study intervention, the withdrawal of consent will be recorded, and only the data collected prior to withdrawal of consent will be used in the study. Study participants will be free to withdraw at any time during the trial. The reasons for the withdrawal will be documented which may include refusal of follow up, lost to follow up, participant request, death, or if the study sponsors decide to stop or cancel the study. Unless the participants withdraw consent for further follow up, attempts will be made to ascertain outcomes as mentioned earlier.

Study outcomes

The primary outcome in HHC is the difference in number of incident cases of active TB (all forms) in the two arms by active case finding over a follow-up period of two years. The secondary outcomes are improvement in the nutritional indicators over six months, frequency of malaria, diarrhea, lower respiratory tract infection, hospitalization with fever of any cause, or death with fever of any cause less than 15 days in duration in both the trial arms.

The secondary outcomes in the index cases are successful treatment completion, TB related deaths, improvement in performance status, adverse effects, and recurrence of TB during two years follow-up. The ascertainment of primary outcomes of incident TB in contacts is by NTEP program staff (not part of the trial team).

Participant timeline:

The trial has a preparatory phase of three months for site selection, staff recruitment and training, and preparation of manual of procedures. The intervention phase will be six months for drug-susceptible cases and 12 months in the MDR-TB. The follow-up phase will continue for two years from the initiation of treatment.

Sample size estimation

The estimated incidence rate of PTB in the general population in India is 217/100,000 population (0.208 %).[4] The incidence rate-ratio of TB in HHC is 15.9 (IQR, 2.6-21.4) compared to the general population, translating into 4% incidence in the HHC.[22] Assuming a higher burden of TB and undernutrition in India, and recent emerging evidence of significantly higher risk of TB disease following infection in close contacts, [33] we considered TB-incidence in HHC to be 5% over the study period. We assume 50% reduction in TB-incidence at household level with intervention.[34]

Our sample size considers design effect at three levels; the TU level, the families of index cases and finally their HHC.[35] We assumed approximately 100 index cases (80-120) and their families in a cluster per annum, a correlation coefficient of 0.2 for the outcome in HHC and 0.01 between members of the same cluster,[22] and thus a design effect of 6.75. Thus a sample size of 28 clusters with 2800 patients and approximately 11,200 contacts equally distributed in both the arms would have 80% power to detect 50% reduction of TB-incidence in intervention arm with a type-1 error of 5%.

The sub-study sample sizes were estimated based on the assumptions related to the objective of the sub-study. The sample size of 250 cases (125/arm) and 250 contacts (125/arm) was based on the prevalence of multiple vitamin deficiencies in patients with PTB, [36] and the prevalence of Vitamin D deficiency in apparently healthy individuals in India.[37]

A sample size of 352 contacts (176/arm) was assumed to be needed to detect a 10% difference in mean CD4 counts in the contacts of the two arms after six months of intervention, with 90% power. This proportion is about 3% of the HHC and we will enroll a similar 3% of the index cases (50/arm) to assess determine the immune function at baseline and after intervention in them.

The sample size for the dietary intake sub-study assumes a standard deviation of 525 KCalories, over a wide range of caloric intakes.[38] Assuming a mean difference in caloric intake between both the arms as 400 KCalories and 20% loss to follow-up, we will enroll 45 contacts and 45 patients in each arm.

Data collection, management

The data will be collected by field investigators working in close collaboration with the NTEP staff. Study data will be collected and managed using REDCap, an electronic data capture tools[39] hosted at ICMR-NIRT. The data capture will be done real time using a handheld device, will be subjected to range and logic checks and will be monitored by the project technical team. A periodic quality check will be performed for accuracy and completeness by the data management team at ICMR-NIRT, which will minimize missing data. Appropriate imputation methods will be used for missing values in the analysis if required. The final dataset will be accessible to the investigators based in Yenepoya (deemed to be University) and ICMR-NIRT and will be deposited in electronic format with the trial sponsor, ICMR, at the end of the study.

All essential trial documents, consent forms will be stored under lock and key at the recruitment site under the supervision of investigators. Electronic data will be password protected and the records will be retained for a period of five years after completion of the study.

We will constitute a data safety management board (DSMB) comprising of subject experts in clinical trials, TB and nutrition along with independent biostatistician and ethicist.

Apart from the regular monitoring by the project team, there is periodic reporting to the ICMR, to the IEC of ICMR-NIRT, the trial advisory committee and the DSMB.

Data analysis:

The primary outcome is TB incidence among contacts, expressed as events per 100,000 person-months of follow-up. Follow-up is defined as time from date of randomization until the earliest endpoint, i.e. documented TB disease or censoring (death, loss to follow-up or end of the study).

Cox proportional hazards model, accounting for varying follow-up times and clustering effect, will be used to compare the rate of progression of TB infection to disease among contacts between the arms and to assess its association with risk factors. Unadjusted and adjusted hazard ratios along with their 95% confidence intervals will be reported. The crude effect of the intervention will be calculated using Kaplan-Meier survival plots and compared using the log rank test.

The primary analysis will be intention to treat. Per-protocol analysis will also be done. The models will be adjusted for relevant risk factors (age, smoking, diabetes, duration of exposure) during the sensitivity analysis.

The secondary outcomes of change in weight and z-scores in patients and HHC, and the performance status in patients, will be compared using unpaired and paired t-tests and Bonferroni correction for multiple comparisons. Linear mixed regression models adjusted for age, gender, TU, caste, asset score, family size, and baseline weight will be done.

The secondary outcomes of frequency of non-TB morbidities and deaths due to infections in the HHC, and the frequency of deaths, adverse effects, defaults, relapse in the index cases in the two arms will be compared using the chi-square test and Cox proportional hazards regression for time to first event.

The patients enrolled in the sub-studies will be compared in their baseline characteristics as these have been drawn by non-random sampling of patients from the main trial. The changes in dietary intake of calories and proteins, body composition parameters and lymphocyte will be assessed among index and contacts. Interactions between treatment and change in nutritional and body composition indicators will be tested using likelihood ratio tests.

The effect of subgroups will be analysed based on age, gender, caste, residence, BMI, asset score, and possession of below poverty line card, alcohol use, and family history of TB. A p value <0.05 (two-tailed) will be considered statistically significant. All data will be analysed using STATA version 16.1 (StataCorp, Texas, USA).

Interim analysis will be performed on attaining 50% of outcomes in the control arm (approximately 230 cases) with a p-value<0.0054 as statistically significant. The final analysis will be done at the end of attainment of planned sample size and completion of follow-up, considering a p-value <0.0492 as statistically significant.

Harm

The intervention involves locally consumed food items which are part of the daily diet and hence no specific adverse events are expected. Patients who have lactose intolerance will be offered alternatives. The possibility of 're-feeding syndrome' in severely undernourished patients will be prevented by training the field staff to offer a graded increase in food intake in such patients.

Ethics, participant information and consent: Ethics clearance has been obtained from Institutional Ethics Committee of ICMR-NIRT, Chennai (NIRT-IEC no: 2018020), to which all the amendments of the protocol will be communicated. Patients and their HHC who are enrolled in the study will receive a detailed 'Participant Information Sheet' in local language before administering the informed consent. A separate consent form will be used for the adult participants enrolled in the sub-study on micronutrient status and immune function. No blood specimen will be stored for any future use. A unique numerical code will be allocated to each participant for purpose of their identification and for maintaining confidentiality. Personal identifiers will be deleted in the final research database for analysis. All forms with personal identifiers will be under lock and key with the trial team.

Responsibility for ancillary care during the trial

Any index case or HHC found to have an acute illness other than TB during the follow-up visits will be facilitated by the field staff to reach the nearest government health set-up.

Patient and public involvement statement

Patients were not directly involved in the development of the research question. The components of food basket were discussed with community health workers during the preparatory phase of the trial. The training of the field staff involved interaction with TB survivors and two of the field staff in the trial are TB-survivors.

Dissemination Plan

The impact of nutritional support on TB incidence and outcomes in this trial will be of relevance to NTEP, India. The results will be disseminated through publications, conference presentations and briefs for the program managers, Jharkhand department of Health, policy makers and other stakeholders. We intend to share the published results in simple language with the participants and community leaders.

Trial status

The trial was started on 16th of August 2019 after trial registration (CTRI/2019/08/020490) and an intensive two weeks training of 56 field staff, two project consultants and one project director by State NTEP staff, nutritionist, and specialists in TB, ethicist, TB-champions, communication experts and social scientists. We have enrolled 2488 index cases and 9125 HHC in the trial as of 31st of October, 2020.

Author contributions

AB conceived the research question. AB, MB, BV, TK, BK designed the study protocol and drafted the manuscript. BW, MS, RD, AM, RRP, KR, KSS reviewed the study protocol and provided critical intellectual content. All authors carefully read and approved the final version of the manuscript.

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Competing interests statement:

The authors state that they have no competing interests to declare.

Figure 1: Study flow for the RATIONS Trial

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Table-1: Objectives of the RATIONS trial and the outcome variables

Objective	Outcome variables	Index case	HHC
Primary Objective			
Effect of household nutritional supplementation in reducing TB incidence among HHC of patients with microbiologically confirmed PTB	Difference in number of incident cases of active TB (all forms) in the two arms detected by active case finding over a follow-up period of two years after diagnosis of index case		✓
Secondary Objectives			
Effect of nutritional supplementation on anthropometric indicators over 6 months	Anthropometric indicators such as weight and Body Mass Index	✓	✓
Non-TB infectious morbidity and mortality in HHC in both the arms	Malaria, diarrhea, lower respiratory tract infection, hospitalization with fever of any cause, or death with fever of any cause <15 days in duration		✓
Adherence to anti-TB therapy	Proportion completing the therapy successfully	✓	
Mortality during treatment	Proportion of index cases who died during treatment	✓	
Adverse effects	Severe adverse effects with TB drugs	✓	
Recurrence of TB within 2 years after cure	Relapse rate of microbiologically confirmed TB	✓	
Performance status	Change in ECOG scale at 1,2 and 6 months compared to baseline	✓	
Dietary Substudy			
Evaluate the difference in dietary intake of calories and proteins	Calorie and protein intake at baseline, and end of treatment in intervention and control arms	✓	✓
Micronutrient substudy			
Assess Vitamin A and D [25(OH)D]	Level of vitamin A and D at baseline	✓	✓

levels			
Body composition substudy			
Evaluation of body composition	Estimate fat-free mass, fat mass, and other Bioimpedance analysis parameters at baseline, and 6 months after treatment	✓	✓
Substudy on grip strength			
Evaluate muscle strength using hand grip dynamometer	Grip strength at baseline and 6 months	✓	
Substudy of immune function			
Evaluate cellular immunity in patients and HHC	Lymphocyte subsets (CD4,CD8, Natural Killer cells, B lymphocytes), 4th generation Interferon Gamma Release Assay (IGRA) at baseline and end of treatment	✓	✓

HHC=household contact; PTB=pulmonary tuberculosis; MDR=multi-drug resistant tuberculosis; ECOG=eastern co-operative oncology group

Table-2: Eligibility criteria for RATIONS trial participants

Index cases	**Household contacts (HHC)**
Inclusion Criteria	
Patients ≥18 years with microbiologically confirmed pulmonary TB	Persons living in the same house, eating from same kitchen as index case for ≥ one night or for frequent or extended periods during the day during the 3 months before diagnosis in index case
Exclusion criteria	
Non eligible HHC	Current smear or GeneXpert or LPA or culture confirmed TB
Time interval between initiation of treatment and enrolment is > 14 days	Clinically diagnosed pulmonary or extra-pulmonary TB and currently on treatment

LPA = Line probe assay

Table-3: Nutritional supplementation in the RATIONS trial

	Intervention arm	**Control arm**
Index case*, quantity per person per month	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient
Household contact§, quantity per person per month	Nutritional counselling 5 kg rice 1.5kg pulses (split pigeon peas) One RDA of micronutrient per adult/adolescent HHC Half of this amount for children less than 10 years.	Nutritional counselling Usual food assistance available to eligible households through public distribution system

RDA = Recommended Dietary Allowance; * approximately 1200 kcal of energy and 52 gm proteins per day. § approximately 750 kcal of energy and 23 gm of proteins per day.

Table 4: Schedule of enrolment, assessments at baseline and follow-up in the RATIONS trial

	Investigations	Base-line	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15	M18	M21	M24
	In index cases																	
1	Informed consent	X																
2	Demography, socio-economic status, co-morbidities, household characteristics, access to PDS	X																
3	Clinical Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	Anthropometry (Height, Weight, MUAC), SpO_2 pedal edema	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	*Laboratory evaluation RBS, HIV, Hb	X																
6	Compliance to Nutritional supplement in new cases, (12 mo. in MDR-TB)	X	X	X	X	X	X	X	X	X	X	X	X	X				
7	Performance status (modified ECOG Scale)	X	X	X				X	X	X	X	X	X	X				
8	*CB NAAT	X							(in case of symptoms of recurrent disease)									
9	*CXR	X						X										
	In subsample of index cases																	
1	Dietary recall of calories, protein intake	X						X										
2	Body composition (By BIA)	X						X										
3	Micronutrient estimation(Vit. A, D)	X																
4	Hand grip strength	X						X										
5	Immunological tests (4^{th} generation IGRA, lymphocyte subsets)	X						X										
	In household contacts																	
1	Informed consent	X																
2	Baseline demography, socio-economic status, co-morbid conditions, household characteristics, Access to PDS	X																

3.	Symptom screen	X	X	X	X	X	X	X			X			X	X	X	X	X
4.	Clinical Evaluation if symptomatic	X	In case of symptoms of active TB															
5	Anthropometry (Height, Weight, Upper mid arm circumference)	X	X	X	X	X	X	X			X			X	X	X	X	X
6	Compliance to Nutritional supplement (Intervention arm); (12 mo. in MDR-TB)	X	X	X	X	X	X	X										
7.	#Review of non-TB infectious illnesses	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	Sputum smear, CBNAAT	In case of symptoms of active TB																
9	@CXR	X	In case of symptoms of active TB															
	In subsample of household contacts																	
1.	Dietary recall of calories, protein intake	X						X										
2	Body composition (By BIA)	X						X										
3	Micronutrient estimation (Vit. A, D)	X																
4	Immunological tests (4th generation IGRA, lymphocyte subsets)	X						X										

* Through public health system; #respiratory infections, diarrhea, hospitalization with fever of any cause, death due to fever < 15 days duration; @ for under-five children, symptomatic contacts.

MUAC=Mid upper arm circumference; SpO2=Oxygen saturation; RBS=Random Blood Sugar; HIV=Human immunodeficiency virus; Hb=Hemoglobin; MDR-TB=Multidrug resistant tuberculosis; ECOG=Eastern Co-operative Oncology Group; CXR=Chest X-ray; CB NAAT=Cartridge based nucleic acid amplification test; BIA=Bio Impedance Analysis; PDS=public distribution system

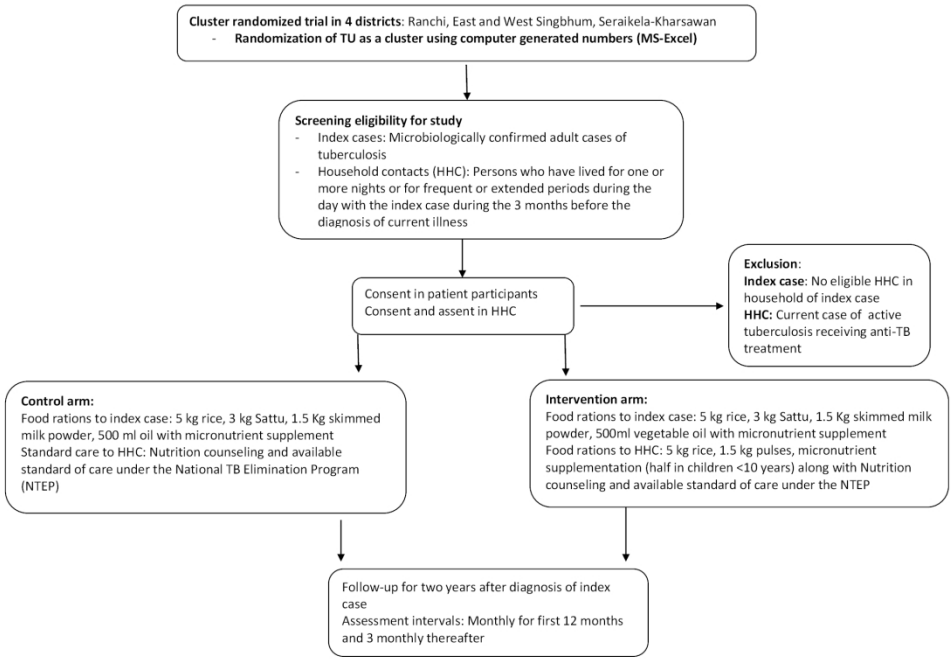
Table 5: Eastern Co-operative Oncology Group (ECOG) scale for functional assessment[24]

ECOG categories	Additional description	Score
Able to carry out normal activity without restriction	No physical restriction	0
Unable to do physically strenuous activity, but ambulatory and able to carry out light work	Able to walk around the neighbourhood, but unable to do any income-generating work	1
Ambulatory and capable of all self-care, but unable to carry out any work; up and about <50% of waking hours	Able to walk around the house and backyard	2
Capable of only limited self-care; confined to bed or chair >50% of waking hours	Able to go to the bathroom,	3
Completely disabled; cannot carry out any self-care; totally confined to bed or chair	Unable to go to the bathroom	4

Table 6: Case definitions for outcomes used in RATIONS trial [6]

Outcome	Case definition
Active tuberculosis	Any patient with microbiologically confirmed tuberculosis or clinically diagnosed TB
Microbiologically confirmed tuberculosis in adults or children	A patient who has a positive sputum smear for mycobacterium tuberculosis and/or - Sputum/gastric aspirate is positive on CB-NAAT - And/or positive on culture
Clinically diagnosed pulmonary TB	A patient who has symptoms suggestive of TB, is smear negative and/or negative on CB-NAAT, and/or who has chest X-ray is suggestive of TB, and where there is no alternative clinical diagnosis
Clinically diagnosed extrapulmonary TB	A patient who is either negative on microbiological testing and/or CB-NAAT, or where an appropriate specimen is not available, and the findings (clinical/ biochemical/ cytological/ histopathological/radiological or direct visualization procedures) are suggestive of tuberculosis, and where alternative diagnosis have been ruled out.
Clinically diagnosed pulmonary TB in children	A patient who has symptoms suggestive of active pulmonary TB (Fever, cough, weight loss or absence of weight gain), and/or a chest X-ray is suggestive of TB, and there is absence of alternative diagnosis, who is negative on CB-NAAT on gastric aspirate or induced sputum, or when bacteriological confirmation has not been possible.

CB-NAAT=Cartridge based nucleic acid amplification test



Study flow for the RATIONS Trial

279x215mm (200 x 200 DPI)

List of Tuberculosis treatment Units (TUs):

1. DTC Seraikela
2. Rajnagar
3. Chandil
4. Adityapur
5. Gamharia
6. Kharsawan
7. Icchagarh
8. Angara-Ratu
9. Bundu
10. Doranda
11. Itki
12. Mandar-Burmu
13. Ormanjhi
14. Sadar (Ranchi)
15. Jagannathpur
16. Chaibasa (Urban)
17. Chakradharpur
18. Jhinkpani
19. Chaibasa (Rural)
20. Manjhari
21. Tantnagar
22. Dalbhumgarh
23. Sadar (Jamshedpur)
24. Mushabani
25. Mango
26. Baharaghoda
27. Jugsalai
28. Potka

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 and 16 CTRI/2019/08/020490), Clinical Trials Registry of India.
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page no.6, 7
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Affiliation in submission website placeholders and protocol contribution: Pg 16
	5b	Name and contact information for the trial sponsor	Page 2, 16

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Appendix- 1
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
	6b	Explanation for choice of comparators	Page 4-6
Objectives	7	Specific objectives or hypotheses	Pages 5-6, Table 1
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pages 6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7, supplementary file
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 11

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pages 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 5-6, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pages 7-10,12, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	We are enrolling consenting patients who have been diagnosed in the National TB program
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pages 8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable as this is an open label cluster randomised trial

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pages8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 8-9, trial participants
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 7-9, Page 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 13

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 13 mentions reporting and oversight in the trial. Decision for audit lies with the trial sponsor. This is not a drug trial so audit by regulatory agency is not involved.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	We shall follow ICMJE guidelines
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix-2 (for editor only)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 15

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: A cluster randomized trial of nutritional support (food rations) to reduce TB-incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India

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Secondary Subject Heading:	Public health, Nutrition and metabolism, Global health
Keywords:	NUTRITION & DIETETICS, Tuberculosis < INFECTIOUS DISEASES, PREVENTIVE MEDICINE, Public health < INFECTIOUS DISEASES

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Abstract

Introduction: India has the largest burden of cases and deaths related to TB. Undernutrition is the leading risk factor accounting for TB incidence, while severe undernutrition is a common risk factor for TB mortality in patients with TB in India. The impact of nutritional supplementation on TB incidence is unknown, while few underpowered studies have assessed its impact on TB mortality. We designed an open-label, field based cluster randomised trial to assess the impact of nutritional supplementation (with food rations) on TB-incidence in a group at higher risk of TB infection and disease, viz. household contacts (HHC) of patients with microbiologically confirmed pulmonary tuberculosis (PTB) in Jharkhand, a state with a high prevalence of undernutrition.

Methods and Analysis: We shall enroll 2800 adult patients with PTB of the national TB program, across 28 treatment units in 4 districts; and their approximately 11,200 eligible contacts. The sample size has 80% power to detect the primary outcome of 50% reduction in incidence of active TB in HHC over 2 years of follow-up. Patients and HHC in both the arms will undergo nutritional assessment and counseling. Patients will receive monthly food rations (supplying 1200 kilocalories and 52 proteins per day) and multivitamins along with anti-tubercular treatment. The HHC in the intervention arm will receive food rations (supplying 750 kilocalories and 23 g proteins per day) and multivitamins while HHC in control arm will be on usual diet. The secondary outcomes in HHC will include effects on nutritional status, non-TB infections. Secondary outcomes in patients are effects on TB mortality, adherence, adverse effects, nutritional and performance status. Sub-studies will examine micronutrient status and effects on dietary intake, body composition, muscle strength and immune function.

Ethics and dissemination: The Institutional Ethics Committee of ICMR-NIRT, Chennai approved the study (289/NIRT-IEC/2018. The results will be disseminated in publications and presentations.

Trial registration number: Clinical Trial Registry of India (CTRI/2019/08/020490).

Strengths and Limitations of the study

- The RATIONS study is the first trial addressing undernutrition to reduce TB incidence in communities with high prevalence of poverty, undernutrition and low prevalence of HIV infection.
- It is the largest trial to evaluate the impact of nutritional support on TB mortality in a programme-based cohort of patients with pulmonary tuberculosis and a high prevalence of undernutrition.
- The follow-up period of two years will ensure detection of most cases of incident TB in household contacts and recurrence of TB in index cases.
- The quantum of food rations per participant is standardized, and in the absence of individual needs assessment, the extent to which the intervention meets individual needs is unknown. .
- Food sharing in the families in the control arm and extra food consumption from other sources can't be ruled out

Introduction

Tuberculosis (TB) is a global public health problem leading to significant morbidity and mortality, especially in low and middle income countries. An estimated 10 million people developed TB and 1.2 million (HIV-negative) people succumbed to it in 2019.[1] India was the major contributor to the global TB burden with an estimated 2.6 million new cases (27% of global) and 0. 4 million (35% of global) TB-deaths in HIV-negative people in 2019.[1]

The United Nations Sustainable Development Goals-3 (SDG-3) has a target for ending the TB epidemic by 2030 and aims to reduce TB-incidence and TB-deaths by 80% and 90% of the 2015 levels respectively.[2] As per the National Strategic Plan (2017-25), the Revised National Tuberculosis Control Program (RNTCP) (renamed as National Tuberculosis Elimination Program, NTEP) in India has set an ambitious target of achieving the 2030 SDG milestone by 2025, five years ahead of the global target.[3]

The End TB strategy will require a mix of biomedical, public health and social interventions to achieve these goals.[2] The strategy requires acceleration of the current decline of 1.5% to 10-17% per year.[4] The present biomedical approach to TB prevention based on vaccination and TB preventive treatment (TPT) has its limitations. The efficacy of BCG vaccine is limited to prevention of severe forms of childhood TB.[5] The TPT with isoniazid in countries like India currently covers only select groups of contacts like under-six children and people living with HIV (PLHIV).[6] WHO recently made a conditional recommendation of offering TPT to all house-hold contacts (HHC).[7] However, there are considerable logistical and technical challenges in countries with a high burden of latent TB infection (LTBI).[8]

Rationale for the trial:

The End TB strategy recognizes the need for new tools, interventions and strategies to address the problem of TB-incidence and adverse outcomes.[2] Globally an estimated 1.7 billion people or 23% of the population have LTBI which remains latent in 90% in presence of innate and cell mediated immunity.[9] Risk factors like HIV, undernutrition, uncontrolled diabetes, smoking and alcohol impair immunity, leading to active TB, and act as drivers of the TB epidemic. Undernutrition results from deficient intake or assimilation of energy and nutrients, often in association with disease-associated inflammation, and is a part of the broader spectrum of malnutrition, which includes both undernutrition, overweight and obesity

and deficiencies of micronutrients. Undernutrition in children is commonly defined by the well-accepted WHO indicators of low birth weight in newborns, underweight (low weight for age), stunting (low height for age) and wasting (low weight for height) in preschool children and by age and gender-specific cutoffs for BMI in those 6-18 years of age. In adults undernutrition is based on a low body mass index which reflects low body energy stores or chronic energy deficiency. The body mass index cut-off for underweight proposed by WHO of < 18.5 kg/m^2 for populations,[10] has also been accepted as a criterion for clinical diagnosis of malnutrition/undernutrition in a recent consensus statement.[11] In addition there have been proposals for diagnosis of undernutrition based on altered body composition, and for higher BMI cut-offs in patients undergoing significant involuntary weight loss, which require further validation.[11, 12]

Undernutrition is the leading cause of impaired immunity globally,[13] with a consistent inverse exponential relationship between nutritional status measured by body mass index (BMI) and TB-incidence.[14] According to the global TB report 2020, undernutrition is a leading risk factor accounting for 2.2 million cases (19%), more than HIV and diabetes (accounting for 0.76 and 0.35 million cases respectively).[1] Undernutrition is also a consistent risk factor for TB-mortality, regardless of HIV infection, and drug-susceptibility.[15] Its prevalence was as high as 23% in women and 19% in men (BMI<18.5 kg/m^2) in the most recent National Family Health Survey (NFHS-4) in India.[16] It is higher in the poor, rural residents and those belonging to the scheduled castes and tribes, who also suffer a high burden of TB disease.[16, 17] The WHO has estimated that 0.6 million cases of TB in India are attributable to undernutrition,[1] while other studies indicate that this estimate may be higher.[18] A majority of Indian patients with active TB have severe levels of undernutrition (macronutrient and micronutrient) which are associated with 2-4 fold higher risk of mortality.[19]

A single unit increase in BMI could reduce TB-incidence by 14%,[14] a modeling study has shown that TB-incidence and mortality could decline by 40-71% with nutritional interventions.[20] There is no randomized controlled trial on the effect of nutritional supplementation on TB-incidence. The studies on the impact of nutritional supplementation on TB mortality have been limited, small and underpowered.[21]

The RATIONS study is a cluster randomized trial to assess the impact of nutritional supplementation on TB-incidence among HHC of patients with microbiologically confirmed

pulmonary tuberculosis (PTB), living in a community with a high prevalence of undernutrition. They are a group at higher risk of TB infection and disease,[22] with a prevalence of 10-60 fold higher than in the general population.[23] TB-incidence was 4.8% in the HHC and 21.4% in child contacts in a previous study from Peru.[24] Food insecurity and undernutrition are strong and modifiable risk factors of TB in the HHC.[25, 26] The trial is being conducted in Jharkhand (meaning "Land of Forests") a state in eastern India which has a high prevalence of undernutrition in children and adults. According to the National Family Health Survey-4 (2015-6), the state has the highest levels of underweight (47.8%), wasting (29.0%), and the second highest level of stunting(45.3%) in children under six years of age in India.[16, 27] Similarly, more than two of out of every five (41%) of adult rural women in Jharkhand had a body mass index of less than 18.5 kg/m^2, and had the highest prevalence of anemia in adult women in India,(65.9%), which is largely related to nutritional deficiencies of iron and folic acid. [16, 27]

OBJECTIVES

The objectives and the outcome variables have been tabulated in table 1.

Primary objective: To evaluate the effect of household nutritional supplementation in reducing TB-incidence among HHC of patients with microbiologically confirmed PTB.

Secondary objectives in HHC: To evaluate the effect of nutritional supplementation on anthropometric indicators, and non-TB infectious morbidity and mortality.

Secondary outcomes in index cases: To evaluate the effect of nutritional supplementation on adherence to treatment, mortality, frequency of adverse effects due to treatment, performance status of patients as measured by the Eastern Cooperative Oncology Group (ECOG),[28] and relapse of microbiologically confirmed TB on follow-up.

Sub-studies: Six sub-studies have been planned in a subset of index cases and HHC

a) Dietary intakes: To evaluate the difference in dietary intake of calories, proteins at baseline, and at the end of treatment in a subsample of the patients in both the arms.

b) Micronutrients: Vitamin A (serum retinol) and 25- hydroxyvitamin D [25(OH) D] levels in a subsample of index patient and HHC at baseline.

c) Body composition: To evaluate the difference in body composition between patients in the two arms at baseline and six months by a multifrequency bioelectric impedance analyzer (Bodystat Quadscan 4000).

d) Muscle function (grip strength) in a subsample of index cases at baseline, and end of treatment using a digital handheld dynamometer.

e) Immune function: To evaluate select aspects of immunity in index patient and their HHC before and after treatment using the lymphocyte subsets [CD4,CD8, Natural Killer (NK) cells, B lymphocytes] and kinetics of interferon γ responses (by CD4 and CD8 cells) in a fourth generation-Interferon Gamma Release Assay (IGRA) (QuantiFERON-TB Gold Plus: QFT-Plus)

f) Qualitative study in a subset of stakeholders: A qualitative study will also be conducted in a subset of the stakeholders (patients, contacts, and field staff) at the end of the intervention period to assess the perceptions and experiences of nutrition intervention.

Methods and analysis

Study design and oversight:

This is a cluster randomized open-label parallel-arm, superiority trial of nutritional supplementation in households with microbiologically confirmed patients with PTB in the state of Jharkhand, Eastern India. The study will randomise 28 Tuberculosis units (TUs) in four districts (Ranchi, East-Singhbhum, West-Singhbhum and Seraikela-Kharsawan) into control and intervention arms, each with 1400 adult PTB patients. It is supported by the India TB Research Consortium of the Indian Council of Medical Research (ICMR) and implemented by the Yenepoya (Deemed to be University), in association with the National Institute for Research in Tuberculosis (ICMR-NIRT), and National Institute of Nutrition (ICMR-NIN). The enrolment began on the August 16, 2019.

Study setting: Under the NTEP, each district has one District TB centre and there are sub-district administrative units called TUs. The population is predominantly rural (75%) and indigenous communities classified as “scheduled tribes” (STs) who comprise 28% of the population (national-8%) and are historically disadvantaged groups with regard to social,

economic and health indicators. According to NFHS-4, the prevalence of undernutrition in Jharkhand was 23.8% and 31.6% in adult men and women respectively, significantly higher than the national average.[16] A total of 44,000 TB cases were notified in the year 2017 when this trial was proposed.[29]

Eligibility criteria:

The inclusion and exclusion criteria are mentioned in table 2.

Inclusion criteria: Adult patients (≥18 years) with microbiologically confirmed PTB (irrespective of drug sensitivity) will constitute the index cases and will be eligible to enrol in the study. The HHC will be persons who have lived in the same house (and eating from the same kitchen), for one or more nights or for frequent or extended periods during the day with the index case during the preceding three months.

Exclusion criteria: An index case with no eligible HHC and any HHC currently on treatment for TB will be excluded.

Study interventions:

Nature and quantity: The study intervention includes macronutrients and micronutrient supplementation along with nutritional counseling as per national guidelines.[30] The index patients (in both arms) and the HHC (in the intervention arm) will receive a food basket and a recommended daily allowance of vitamins and micronutrients every month, as described in **Table-3**. This will be either delivered by the study staff or may be picked up from a depot as per the participant preference.

Frequency and duration: The food basket will be provided for six months for new patients and 12 months for patients with MDR-TB (and their HHC in intervention arm). Extension of the intervention period to 12 months, for a patient with non-MDR-TB will be considered if there is evidence of undernutrition (BMI<18.5 kg/m^2) in the index case even at the end of six months. Extension of rations to a HHC will be considered if an adult contact has a BMI < 16 kg/m^2; children (<10 years) have weight-for-age z-score <-2SD and adolescents (10-18 years) have BMI-for-age z-scores <-2SD.

Nutritional counselling and assessing adherence: The patients and the HHC will be counselled about the importance of a balanced diet for the nutritional recovery of the patient

and the protection of the health status of the family. The families will be instructed about the optimal utilisation of the food rations in locally acceptable food recipes.The field staff will undertake follow-up visits to monitor weight gain (a proxy indicator for adherence) and check the empty packets of the milk powder as an indicator of consumption by the patient.

Co-interventions permitted during the trial

The patients as well as the HHC will continue to access public distribution system, supplementary feeding programs (Integrated Child Development Services Scheme, mid-day meals) as usual and additional INR 500/month as Direct Benefit Transfer availed by patients with TB in India. The eligible under-six children and those with HIV infection who have been advised by the NTEP staff to take chemoprophylaxis with isoniazid after an evaluation will continue to do so.

Risk assessment and referral

The patients will be evaluated for nutritional status, oxygen saturation, blood pressure and presence of complications at baseline and at follow-up. Patients with severe undernutrition with edema, extremely severe undernutrition (BMI<14 kg/m^2), breathlessness or low oxygen saturation (SpO_2<94) will be referred for inpatient care as per national guidelines.[30]

Randomization and intervention allocation:

This is an open label trial, the participants and field staff, are not blinded after assignment. All the TUs from the selected districts were line-listed (list of TUs is available in supplementary file 1) and randomized equally to both the arms by computer generated random numbers using restricted randomization by the statistician at ICMR-NIRT, Chennai. The cluster allocation was kept confidential until the end of training of the field staff and the TUs were ready for implementation.

Enrolment of index cases and HHC

Figure-1 describes the study flow. Consecutive patients diagnosed with microbiologically confirmed PTB in selected TUs will be enrolled after due consent process, during a 6-12 month period. Information about the study will be given to the HHC during a home visit by the trial staff and enrolled after elicitation of voluntary written informed consent. The need for adherence to treatment and food rations, cooperation with study procedures, the stability

of residence and the willingness to permit home visits will be discussed with the index cases and HHC during enrolment.

Baseline evaluation of index cases and HHC:

The study procedures at baseline and follow-up are denoted in **Table-4.** Demographic characteristics including gender, occupation, caste, marital status, education, socio-economic assessment with an asset score, education will be noted. Presence of self-reported risk factors such as diabetes, alcohol consumption and tobacco use, family/past history of TB will also be recorded.

Clinical examination of index cases: Weight will be measured with a digital weighing scale (SECA 803) with accuracy of 100 gm, and height using a portable stadiometer (SECA 213) with accuracy of 0.1 cm using standard procedures. Mean of two measurements of weight will be taken for calculation of BMI. Undernutrition is defined as a Body mass index < 18.5 kg/m^2 according to the underweight definition approved by the WHO.[10] Patients will further be categorized into mild underweight in case the BMI is 17.0-18.49 kg/m^2, moderate underweight if the BMI is 16.0-16.99 kg/m^2, severely underweight if the BMI is less than 16 kg/m^2 as suggested by WHO.[31] An additional category of extremely severe underweight is used to classify those with a BMI of less than or equal to 14 kg/m^2.[32] Mid-upper arm circumference (MUAC) will be measured to the nearest of 0.1 cm on the non-dominant arm, if the patient is unable to stand. Presence of edema, blood pressure using a digital instrument (OMRON) and oxygen saturation using pulse oximeter will be noted. Assessment of performance status will be done using ECOG scale as described in **Table-5.**[28]

Clinical examination in contacts: This will consist of anthropometric measurements like weight, height, MUAC (if unable to stand and in under-five), presence of edema and BCG scar.

Laboratory evaluation of index cases: The results of the sputum smear microscopy, cartridge based nucleic acid amplification test (CB-NAAT) - Gene Xpert MTB/RIF test, blood glucose and HIV tests (if available) will be retrieved from the NTEP records. Hemoglobin will be measured during the home visit using HemoCue Hb 201^+ using standard procedures and precautions. Chest X-ray (CXR) of patients at baseline will be done wherever feasible.

Laboratory evaluation of HHC: Symptom screening for TB will be done in all HHC and CXR will be done wherever feasible as per the NTEP guidelines.[6] In case of symptoms of presumptive TB or an abnormal CXR, the HHC will be referred for sputum examination. Children with symptoms/abnormal CXR will be referred for further evaluation by sputum smear and CB-NAAT (if cough is productive) and induced sputum/gastric aspirate, if unable to produce sputum at a referral hospital.

Follow-up of index cases and HHC:

The enrolled index cases and their HHC will be followed-up for two years after the diagnosis of the index case. Jharkhand is a state with potential seasonal labor migration from rural areas. All attempts (including telephonic contact) will be made to retain follow-up in case of temporary migration with an in-person visit on their return. Participants will be termed as lost to follow-up if in-person or telephonic contact is not made for ≥2 months in the intervention period; or for ≥ 6 months in the follow-up period. All participants lost to follow-up will be approached for an end of study evaluation to ascertain information on the primary and relevant secondary outcomes.

The schedule of follow-up and assessments is described in **Table-4**. Evaluation will be done for current symptoms, any adverse effect related to treatment, adherence to treatment and rations. All HHC will be evaluated for symptoms of active TB on each visit, consumption of rations (in intervention arm), and review of non-TB infectious morbidity and mortality based on symptoms, hospitalization, or death.

Patients will undergo repeat sputum examination on follow-up as per NTEP guidelines. Contacts that develop any symptoms of active TB (PTB or EPTB) will undergo appropriate investigations.

The cases of active TB in HHC will be classified as co-prevalent or incident according to the time of diagnosis of the index case. A co-prevalent case is a HHC diagnosed with active TB (microbiologically confirmed active TB or as clinically diagnosed tuberculosis) at the baseline, or within two month of the baseline screening and evaluation of the HHC. An incident case is a new case of TB in a HHC (microbiologically confirmed active TB or as clinically diagnosed) that was diagnosed more than two months following the initial negative

screening and evaluation. The definition of microbiologically confirmed case and clinically diagnosed cases is as per **Table-6**.

Qualitative study about the nutritional intervention

We will use a phenomenological approach to generate qualitative data through the in-depth interview of TB patients and their HHC. The participants will be purposively selected till conceptual saturation and triangulation is reached, and will be interviewed using topic guides prepared in line with the study objectives. Interviews will be tape-recorded, transcribed verbatim, and translated to English. Open Code software will be used to facilitate analysis. This sub-study will be conducted at the end of the intervention period.

Discontinuation of study intervention and withdrawal of study participants

Study participants will be asked about consumption of rations and micronutrients at every visit. Rarely, they may choose to discontinue consumption of the study intervention during the intervention period, due to an unrelated illness or perceived adverse effects. The reasons for their discontinuation of study intervention will be recorded but these participants will remain in the study and undergo protocol-specified follow up procedures. However if the participants also explicitly withdraws consent for follow up and collection of additional information in addition to discontinuation of consumption of study intervention, the withdrawal of consent will be recorded, and only the data collected prior to withdrawal of consent will be used in the study. Study participants will be free to withdraw at any time during the trial. The reasons for the withdrawal will be documented which may include refusal of follow up, lost to follow up, participant request, death, or if the study sponsors decide to stop or cancel the study. Unless the participants withdraw consent for further follow up, attempts will be made to ascertain outcomes as mentioned earlier.

Study outcomes

The primary outcome in HHC is the difference in number of incident cases of active TB (all forms) in the two arms by active case finding over a follow-up period of two years. The secondary outcomes are improvement in the nutritional indicators over six months, frequency of malaria, diarrhea, lower respiratory tract infection, hospitalization with fever of any cause, or death with fever of any cause less than 15 days in duration in both the trial arms.

The secondary outcomes in the index cases are successful treatment completion, TB related deaths, improvement in performance status, adverse effects, and recurrence of TB during two years follow-up. The ascertainment of primary outcomes of incident TB in contacts is by NTEP program staff (not part of the trial team).

Participant timeline:

The trial has a preparatory phase of three months for site selection, staff recruitment and training, and preparation of manual of procedures. The intervention phase will be six months for drug-susceptible cases and 12 months in the MDR-TB. The follow-up phase will continue for two years from the initiation of treatment.

Sample size estimation

The estimated incidence rate of PTB in the general population in India is 217/100,000 population (0.208 %).[4] The incidence rate-ratio of TB in HHC is 15.9 (IQR, 2.6-21.4) compared to the general population, translating into 4% incidence in the HHC.[22] Assuming a higher burden of TB and undernutrition in India, and recent emerging evidence of significantly higher risk of TB disease following infection in close contacts, [33] we considered TB-incidence in HHC to be 5% over the study period. We assume 50% reduction in TB-incidence at household level with intervention.[34]

Our sample size considers design effect at three levels; the TU level, the families of index cases and finally their HHC.[35] We assumed approximately 100 index cases (80-120) and their families in a cluster per annum, a correlation coefficient of 0.2 for the outcome in HHC and 0.01 between members of the same cluster,[22] and thus a design effect of 6.75. Thus a sample size of 28 clusters with 2800 patients and approximately 11,200 contacts equally distributed in both the arms would have 80% power to detect 50% reduction of TB-incidence in intervention arm with a type-1 error of 5%.

The sub-study sample sizes were estimated based on the assumptions related to the objective of the sub-study. The sample size of 250 cases (125/arm) and 250 contacts (125/arm) was based on the prevalence of multiple vitamin deficiencies in patients with PTB, [36] and the prevalence of Vitamin D deficiency in apparently healthy individuals in India.[37]

A sample size of 352 contacts (176/arm) was assumed to be needed to detect a 10% difference in mean CD4 counts in the contacts of the two arms after six months of intervention, with 90% power. This proportion is about 3% of the HHC and we will enroll a similar 3% of the index cases (50/arm) to assess determine the immune function at baseline and after intervention in them.

The sample size for the dietary intake sub-study assumes a standard deviation of 525 KCalories, over a wide range of caloric intakes.[38] Assuming a mean difference in caloric intake between both the arms as 400 KCalories and 20% loss to follow-up, we will enroll 45 contacts and 45 patients in each arm.

Data collection, management

The data will be collected by field investigators working in close collaboration with the NTEP staff. Study data will be collected and managed using REDCap, an electronic data capture tools[39] hosted at ICMR-NIRT. The data capture will be done real time using a handheld device, will be subjected to range and logic checks and will be monitored by the project technical team. A periodic quality check will be performed for accuracy and completeness by the data management team at ICMR-NIRT, which will minimize missing data. Appropriate imputation methods will be used for missing values in the analysis if required. The final dataset will be accessible to the investigators based in Yenepoya (deemed to be University) and ICMR-NIRT and will be deposited in electronic format with the trial sponsor, ICMR, at the end of the study.

All essential trial documents, consent forms will be stored under lock and key at the recruitment site under the supervision of investigators. Electronic data will be password protected and the records will be retained for a period of five years after completion of the study.

We will constitute a data safety management board (DSMB) comprising of subject experts in clinical trials, TB and nutrition along with independent biostatistician and ethicist.

Apart from the regular monitoring by the project team, there is periodic reporting to the ICMR, to the IEC of ICMR-NIRT, the trial advisory committee and the DSMB.

Data analysis:

The primary outcome is TB incidence among contacts, expressed as events per 100,000 person-months of follow-up. Follow-up is defined as time from date of randomization until the earliest endpoint, i.e. documented TB disease or censoring (death, loss to follow-up or end of the study).

Cox proportional hazards model, accounting for varying follow-up times and clustering effect, will be used to compare the rate of progression of TB infection to disease among contacts between the arms and to assess its association with risk factors. Unadjusted and adjusted hazard ratios along with their 95% confidence intervals will be reported. The crude effect of the intervention will be calculated using Kaplan-Meier survival plots and compared using the log rank test.

The primary analysis will be intention to treat. Per-protocol analysis will also be done. The models will be adjusted for relevant risk factors (age, smoking, diabetes, duration of exposure) during the sensitivity analysis.

The secondary outcomes of change in weight and z-scores in patients and HHC, and the performance status in patients, will be compared using unpaired and paired t-tests and Bonferroni correction for multiple comparisons. Linear mixed regression models adjusted for age, gender, TU, caste, asset score, family size, and baseline weight will be done.

The secondary outcomes of frequency of non-TB morbidities and deaths due to infections in the HHC, and the frequency of deaths, adverse effects, defaults, relapse in the index cases in the two arms will be compared using the chi-square test and Cox proportional hazards regression for time to first event.

The patients enrolled in the sub-studies will be compared in their baseline characteristics as these have been drawn by non-random sampling of patients from the main trial. The changes in dietary intake of calories and proteins, body composition parameters and lymphocyte will be assessed among index and contacts. Interactions between treatment and change in nutritional and body composition indicators will be tested using likelihood ratio tests.

The effect of subgroups will be analysed based on age, gender, caste, residence, BMI, asset score, and possession of below poverty line card, alcohol use, and family history of TB. A p value <0.05 (two-tailed) will be considered statistically significant. All data will be analysed using STATA version 16.1 (StataCorp, Texas, USA).

Interim analysis will be performed on attaining 50% of outcomes in the control arm (approximately 230 cases) with a p-value<0.0054 as statistically significant. The final analysis will be done at the end of attainment of planned sample size and completion of follow-up, considering a p-value <0.0492 as statistically significant.

Harm

The intervention involves locally consumed food items which are part of the daily diet and hence no specific adverse events are expected. Patients who have lactose intolerance will be offered alternatives. The possibility of 're-feeding syndrome' in severely undernourished patients will be prevented by training the field staff to offer a graded increase in food intake in such patients.

Ethics, participant information and consent: Ethics clearance has been obtained from Institutional Ethics Committee of ICMR-NIRT, Chennai (NIRT-IEC no: 2018020), to which all the amendments of the protocol will be communicated. Patients and their HHC who are enrolled in the study will receive a detailed 'Participant Information Sheet' in local language before administering the informed consent. A separate consent form will be used for the adult participants enrolled in the sub-study on micronutrient status and immune function. No blood specimen will be stored for any future use. A unique numerical code will be allocated to each participant for purpose of their identification and for maintaining confidentiality. Personal identifiers will be deleted in the final research database for analysis. All forms with personal identifiers will be under lock and key with the trial team.

Responsibility for ancillary care during the trial

Any index case or HHC found to have an acute illness other than TB during the follow-up visits will be facilitated by the field staff to reach the nearest government health set-up.

Patient and public involvement statement

Patients were not directly involved in the development of the research question. The components of food basket were discussed with community health workers during the preparatory phase of the trial. The training of the field staff involved interaction with TB survivors and two of the field staff in the trial are TB-survivors.

Dissemination Plan

The impact of nutritional support on TB incidence and outcomes in this trial will be of relevance to NTEP, India. The results will be disseminated through publications, conference presentations and briefs for the program managers, Jharkhand department of Health, policy makers and other stakeholders. We intend to share the published results in simple language with the participants and community leaders.

Trial status

The trial was started on 16th of August 2019 after trial registration (CTRI/2019/08/020490) and an intensive two weeks training of 56 field staff, two project consultants and one project director by State NTEP staff, nutritionist, and specialists in TB, ethicist, TB-champions, communication experts and social scientists. We have enrolled 2488 index cases and 9125 HHC in the trial as of 31st of October, 2020.

Author contributions

AB conceived the research question. AB, MB, BV, TK, BK designed the study protocol and drafted the manuscript. BW, MS, RD, AM, RRP, KR, KSS reviewed the study protocol and provided critical intellectual content. All authors carefully read and approved the final version of the manuscript.

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Competing interests statement:

The authors state that they have no competing interests to declare.

Figure 1: Study flow for the RATIONS Trial

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Table-1: Objectives of the RATIONS trial and the outcome variables

Objective	Outcome variables	Index case	HHC
Primary Objective			
Effect of household nutritional supplementation in reducing TB incidence among HHC of patients with microbiologically confirmed PTB	Difference in number of incident cases of active TB (all forms) in the two arms detected by active case finding over a follow-up period of two years after diagnosis of index case		✓
Secondary Objectives			
Effect of nutritional supplementation on anthropometric indicators over 6 months	Anthropometric indicators such as weight and Body Mass Index	✓	✓
Non-TB infectious morbidity and mortality in HHC in both the arms	Malaria, diarrhea, lower respiratory tract infection, hospitalization with fever of any cause, or death with fever of any cause <15 days in duration		✓
Adherence to anti-TB therapy	Proportion completing the therapy successfully	✓	
Mortality during treatment	Proportion of index cases who died during treatment	✓	
Adverse effects	Severe adverse effects with TB drugs	✓	
Recurrence of TB within 2 years after cure	Relapse rate of microbiologically confirmed TB	✓	
Performance status	Change in ECOG scale at 1,2 and 6 months compared to baseline	✓	
Dietary Substudy			
Evaluate the difference in dietary intake of calories and proteins	Calorie and protein intake at baseline, and end of treatment in intervention and control arms	✓	✓
Micronutrient substudy			
Assess Vitamin A and D [25(OH)D]	Level of vitamin A and D at baseline	✓	✓

levels			
Body composition substudy			
Evaluation of body composition	Estimate fat-free mass, fat mass, and other Bioimpedance analysis parameters at baseline, and 6 months after treatment	✓	✓
Substudy on grip strength			
Evaluate muscle strength using hand grip dynamometer	Grip strength at baseline and 6 months	✓	
Substudy of immune function			
Evaluate cellular immunity in patients and HHC	Lymphocyte subsets (CD4,CD8, Natural Killer cells, B lymphocytes), 4th generation Interferon Gamma Release Assay (IGRA) at baseline and end of treatment	✓	✓

HHC=household contact; PTB=pulmonary tuberculosis; MDR=multi-drug resistant tuberculosis; ECOG=eastern co-operative oncology group

Table-2: Eligibility criteria for RATIONS trial participants

Index cases	**Household contacts (HHC)**
Inclusion Criteria	
Patients ≥18 years with microbiologically confirmed pulmonary TB	Persons living in the same house, eating from same kitchen as index case for ≥ one night or for frequent or extended periods during the day during the 3 months before diagnosis in index case
Exclusion criteria	
Non eligible HHC	Current smear or GeneXpert or LPA or culture confirmed TB
Time interval between initiation of treatment and enrolment is > 14 days	Clinically diagnosed pulmonary or extra-pulmonary TB and currently on treatment

LPA = Line probe assay

Table-3: Nutritional supplementation in the RATIONS trial

	Intervention arm	**Control arm**
Index case*, quantity per person per month	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient
Household contact§, quantity per person per month	Nutritional counselling 5 kg rice 1.5kg pulses (split pigeon peas) One RDA of micronutrient per adult/adolescent HHC Half of this amount for children less than 10 years.	Nutritional counselling Usual food assistance available to eligible households through public distribution system

RDA = Recommended Dietary Allowance; * approximately 1200 kcal of energy and 52 gm proteins per day. § approximately 750 kcal of energy and 23 gm of proteins per day.

Table 4: Schedule of enrolment, assessments at baseline and follow-up in the RATIONS trial

	Investigations	Base-line	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15	M18	M21	M24
	In index cases																	
1	Informed consent	X																
2	Demography, socio-economic status, co-morbidities, household characteristics, access to PDS	X																
3	Clinical Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	Anthropometry (Height, Weight, MUAC), SpO_2 pedal edema	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	*Laboratory evaluation RBS, HIV, Hb	X																
6	Compliance to Nutritional supplement in new cases, (12 mo. in MDR-TB)	X	X	X	X	X	X	X	X	X	X	X	X	X				
7	Performance status (modified ECOG Scale)	X	X	X				X	X	X	X	X	X	X				
8	*CB NAAT	X							(in case of symptoms of recurrent disease)									
9	*CXR	X						X										
	In subsample of index cases																	
1	Dietary recall of calories, protein intake	X						X										
2	Body composition (By BIA)	X						X										
3	Micronutrient estimation (Vit. A, D)	X																
4	Hand grip strength	X						X										
5	Immunological tests (4^{th} generation IGRA, lymphocyte subsets)	X						X										
	In household contacts																	
1	Informed consent	X																
2	Baseline demography, socio-economic status, co-morbid conditions, household characteristics, Access to PDS	X																

3.	Symptom screen	X	X	X	X	X	X	X			X			X	X	X	X	X
4.	Clinical Evaluation if symptomatic	X	In case of symptoms of active TB															
5	Anthropometry (Height, Weight, Upper mid arm circumference)	X	X	X	X	X	X	X			X			X	X	X	X	X
6	Compliance to Nutritional supplement (Intervention arm); (12 mo. in MDR-TB)	X	X	X	X	X	X	X										
7.	#Review of non-TB infectious illnesses	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	Sputum smear, CBNAAT	In case of symptoms of active TB																
9	@CXR	X	In case of symptoms of active TB															
	In subsample of household contacts																	
1.	Dietary recall of calories, protein intake	X						X										
2	Body composition (By BIA)	X						X										
3	Micronutrient estimation (Vit. A, D)	X																
4	Immunological tests (4th generation IGRA, lymphocyte subsets)	X						X										

* Through public health system; #respiratory infections, diarrhea, hospitalization with fever of any cause, death due to fever < 15 days duration; @ for under-five children, symptomatic contacts.

MUAC=Mid upper arm circumference; SpO2=Oxygen saturation; RBS=Random Blood Sugar; HIV=Human immunodeficiency virus; Hb=Hemoglobin; MDR-TB=Multidrug resistant tuberculosis; ECOG=Eastern Co-operative Oncology Group; CXR=Chest X-ray; CB NAAT=Cartridge based nucleic acid amplification test; BIA=Bio Impedance Analysis; PDS=public distribution system

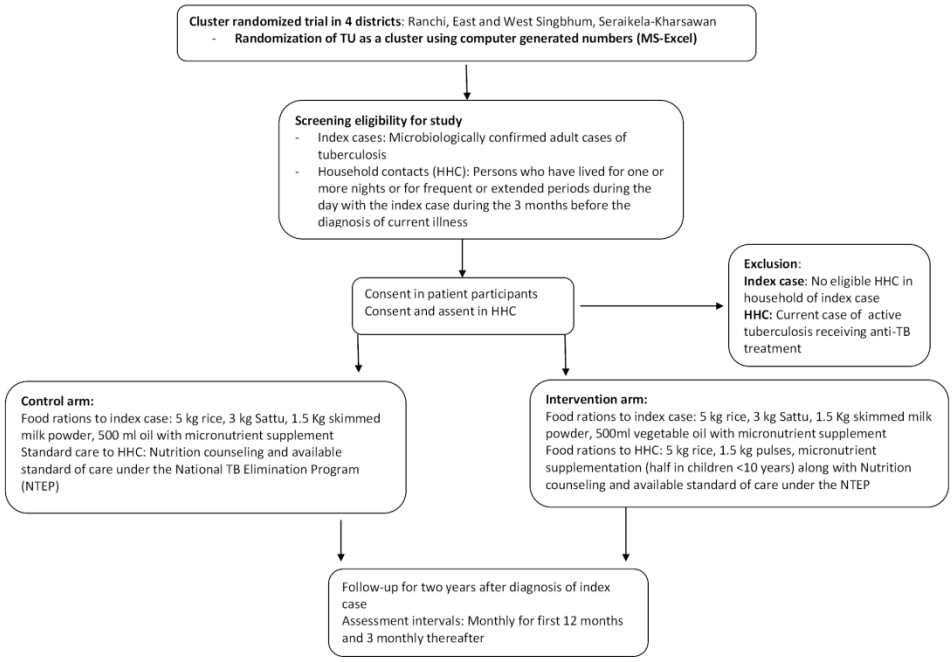
Table 5: Eastern Co-operative Oncology Group (ECOG) scale for functional assessment[24]

ECOG categories	Additional description	Score
Able to carry out normal activity without restriction	No physical restriction	0
Unable to do physically strenuous activity, but ambulatory and able to carry out light work	Able to walk around the neighbourhood, but unable to do any income-generating work	1
Ambulatory and capable of all self-care, but unable to carry out any work; up and about <50% of waking hours	Able to walk around the house and backyard	2
Capable of only limited self-care; confined to bed or chair >50% of waking hours	Able to go to the bathroom,	3
Completely disabled; cannot carry out any self-care; totally confined to bed or chair	Unable to go to the bathroom	4

Table 6: Case definitions for outcomes used in RATIONS trial [6]

Outcome	Case definition
Active tuberculosis	Any patient with microbiologically confirmed tuberculosis or clinically diagnosed TB
Microbiologically confirmed tuberculosis in adults or children	A patient who has a positive sputum smear for mycobacterium tuberculosis and/or - Sputum/gastric aspirate is positive on CB-NAAT - And/or positive on culture
Clinically diagnosed pulmonary TB	A patient who has symptoms suggestive of TB, is smear negative and/or negative on CB-NAAT, and/or who has chest X-ray is suggestive of TB, and where there is no alternative clinical diagnosis
Clinically diagnosed extrapulmonary TB	A patient who is either negative on microbiological testing and/or CB-NAAT, or where an appropriate specimen is not available, and the findings (clinical/ biochemical/ cytological/ histopathological/radiological or direct visualization procedures) are suggestive of tuberculosis, and where alternative diagnosis have been ruled out.
Clinically diagnosed pulmonary TB in children	A patient who has symptoms suggestive of active pulmonary TB (Fever, cough, weight loss or absence of weight gain), and/or a chest X-ray is suggestive of TB, and there is absence of alternative diagnosis, who is negative on CB-NAAT on gastric aspirate or induced sputum, or when bacteriological confirmation has not been possible.

CB-NAAT=Cartridge based nucleic acid amplification test



Study flow for the RATIONS Trial

279x215mm (200 x 200 DPI)

List of Tuberculosis treatment Units (TUs):

1. DTC Seraikela
2. Rajnagar
3. Chandil
4. Adityapur
5. Gamharia
6. Kharsawan
7. Icchagarh
8. Angara-Ratu
9. Bundu
10. Doranda
11. Itki
12. Mandar-Burmu
13. Ormanjhi
14. Sadar (Ranchi)
15. Jagannathpur
16. Chaibasa (Urban)
17. Chakradharpur
18. Jhinkpani
19. Chaibasa (Rural)
20. Manjhari
21. Tantnagar
22. Dalbhumgarh
23. Sadar (Jamshedpur)
24. Mushabani
25. Mango
26. Baharaghoda
27. Jugsalai
28. Potka

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 and 16 CTRI/2019/08/020490), Clinical Trials Registry of India.
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page no.6, 7
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Affiliation in submission website placeholders and protocol contribution: Pg 16
	5b	Name and contact information for the trial sponsor	Page 2, 16

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Appendix- 1
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
	6b	Explanation for choice of comparators	Page 4-6
Objectives	7	Specific objectives or hypotheses	Pages 5-6, Table 1
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pages 6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7, supplementary file
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 11

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pages 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 5-6, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pages 7-10,12, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	We are enrolling consenting patients who have been diagnosed in the National TB program
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pages 8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable as this is an open label cluster randomised trial

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pages8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 8-9, trial participants
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 7-9, Page 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 13

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 13 mentions reporting and oversight in the trial. Decision for audit lies with the trial sponsor. This is not a drug trial so audit by regulatory agency is not involved.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	We shall follow ICMJE guidelines
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix-2 (for editor only)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 15

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.