आई सी एम आर – राष्ट्रीय यक्ष्मा अनुसंधान संस्थान
स्वास्थ्य अनुसंधान विभाग, स्वास्थ्य और परिवार कल्याण मंत्रालय, भारत सरकार

ICMR - National Institute for Research in Tuberculosis
Department of Health Research, Ministry of Health and Family Welfare, Government of India

Ref No: NIRT/Admin-Stores/Clin.Insurance./Inshort/2023-24

Date: 15.02.2024

QUOTATION ENQUIRY

Sealed Quotations are invited on behalf of the Director, ICMR – National Institute for research in Tuberculosis, Chetpet, Chennai-31, from the recognised firms for clinical trial insurance for the study titled **"Comparative evaluation of intensified short course regimen and standard regimen for adults TB meningitis: an open label randomized controlled trial (INSHORT trial)"** for the period of 3 years and 6 months at ICMR-NIRT. The interested firms may submit their lowest price for the below mentioned specification either by sending through post/courier addressed to **The Director, ICMR - National Institute for Research in Tuberculosis, No.1, Sathyamoorthy Road, Chetpet, Chennai-31** or drop in the quotation box kept at the ground floor (stores & purchase section) or by E-mail (with signature & seal in company letterhead to nirtdirector.ps@icmr.gov.in.). Sealed offers superscribed as Quotation for **"Clinical Trial Insurance- TBM Inshort Trial"** should reach us on or before **06.03.2024 at 3.00 P.M.**

SPECIFICATION

Clinical Trial Insurance – **TBM INSHORT trial**

The details of the study is given below for which Clinical Trial Insurance is required.

Title of the study : Comparative evaluation of intensified short course regimen and standard regimen for adults TB meningitis : an open label randomized controlled trial (INSHORT trial)

We are planning to recruit 372 adults (>18 yrs) with TB meningitis from six sites across India. After the initial pre-screening and screening 372 consenting participants will be recruited. The study has three arms. Participants in the first arm will be given high doses of rifampicin (25mg/kg), moxifloxacin (400mg), aspirin (150mg), and steroids along with isoniazid and pyrazinamide for 2 months followed by rifampicin, isoniazid and pyrazinamide for the next 4 months. In the second arm, the patients will receive all the drugs except aspirin. Participants in the control arm will receive standard therapy (2 HRZE/HRE) as per the National Tuberculosis Elimination program for 12 months. The study will be conducted over 3 years and 6 months. The primary outcome will be to compare the proportion of mortality and disability across three arms.

We wish to obtain clinical trial insurance for the following:

a. Professional Indemnification for 130 investigators physicians, nurses and Field staff and IEC members of the trial sites

b. Compensation for 'Trial related injuries' for study participants as per 'New Drugs and Clinical Trials Rules, 2019, [G.S.R. 227(E)] dated 19 March 2019' and medical management for adverse events related to study drugs and not natural disease progression.

The trial plans to recruit 372 participants meeting the inclusion and exclusion criteria set for the study.

Request for proposals are invited from eligible parties who are interested in providing clinical trials liability policy or liability insurance, indicating the conditions and extent of coverage, date of commencement and expiry of coverage, and conditions thereof, including the premium and other costs, as per rules, for the aforementioned study.

The terms for the policy are –

1. Deductible: Rs. 50,000 in each and every claim
2. Limit of indemnity: Rs. 50,00,000 per claim
   Rs. 15,00,00,000 in aggregate
3. Medical expense: Rs. 1,00,00,000 in aggregate

The PDF of synopsis of the project is enclosed herewith. The rules of compensation can be downloaded from the following link: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

For any further queries/ clarifications, you may call upon the following:
Dr Leeberk Raja. I
Scientist E (Medical)
ICMR- NIRT
Phone : 9611770181
E- mail : leeberk.raja@icmr.gov.in

Study Protocol is attached

TERMS & CONDITIONS

1. This is an enquiry and must not be treated as an order.
2. Late/delayed quotations and unsigned quotations will be summarily rejected and will not be considered under any circumstances.
3. ICMR-NIRT, Chennai will not be responsible for any delay for late receipt of quotations.
4. The interested firm/bidder should mention GST % / amount while submitting the quotation.
5. Any decision taken by the Director, ICMR-NIRT at any point of time in connection related to this process shall be final and conclusive and no claim or dispute from any quarter in this regard shall be entertained.
6. ICMR-NIRT, Chennai does not bind to accept quotation with lowest price only, other criteria like quality etc., will also be considered.
7. ICMR-NIRT, Chennai reserves the right to accept or reject any or all quotations without assigning any reason.

Yours faithfully,

15/2/24

ADMINISTRATIVE OFFICER

Protocol Summary

Protocol title	**Comparative evaluation of intensified short course regimen and standard regimen for adults TB meningitis : an open label randomized controlled trial (INSHORT trial)**
Objectives	***Primary objective*** To compare the intensified short course (6 months) ATT regimen containing high dose Rifampicin and Moxifloxacin and standard ATT regimen (12 months) in reducing composite outcome of mortality and disability among adults with TB Meningitis. ***Secondary objective*** 1. To compare the pharmacokinetic parameters of ATT administered in the plasma and CSF between the intervention and control arms. 2. To assess the safety and tolerability of high dose Rifampicin and Moxifloxacin when given daily for 8 weeks and pyrazinamide administration for 6 months. 3. To compare the health related quality of life between the intervention and control arms. ***Explorative objectives*** 1. To evaluate the diagnostic accuracy of Truenat MTB in the CSF for the detection of TBM in adults. 2. To validate the accuracy of recently identified host CSF biomarkers as candidates for diagnosis of tuberculous meningitis. 3. To evaluate the diagnostic value of metagenomic next-generation sequencing (mNGS) on cerebrospinal fluid for rapid detection of tuberculous meningitis
Study design	Open-label randomized controlled trial
Study sites	1. Rajiv Gandhi General Hospital, Chennai 2. Christian Medical College, Vellore 3. All India Institute of Medical Sciences, Jodhpur.

	4. Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 5. Rural Development Trust Hospital, Ananantapur. 6. North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong
Study population	We will include all the patients with definite, probable or possible TBM
Intervention	***Arm 1 (Intensified ATT with Aspirin):*** Participants in this arm will receive a high dose of Rifampicin (Single dose - Once daily 25 mg/kg) and a weight-based dose of Moxifloxacin (400mg once daily) along with Isoniazid and Pyrazinamide. They will also receive dexamethasone or equivalent dose of prednisolone as a tapering dose beginning with parenteral administration and switching over to orally later. Patients with MRC grade-1, grade-2 and 3 will receive steroids for 6 weeks and 8 weeks respectively. This regimen will also be intensified with 150mg of Aspirin once daily. This regimen will be continued for 2 months after which the patients will receive standard doses of Isoniazid, Rifampicin and Pyrazinamide for the next 4 months ***Arm 2 (Intensified ATT without Aspirin):*** Participants in this arm will receive intensified ATT regimen similar to arm 1, but without aspirin. Aspirin (150mg) will be given once daily for 2 months along with intensified ATT. They will also receive dexamethasone or equivalent dose of prednisolone as a tapering dose beginning with parenteral administration and switching over to orally later. Patients with MRC grade-1, grade-2 and 3 will receive steroids for 6 weeks and 8 weeks respectively. This regimen will be continued for 2 months after which the patients will receive standard doses of Isoniazid, Rifampicin and Pyrazinamide for the next 4 months

Control arm	The control arm will receive treatment according to the standard national guidelines for EPTB. They will receive a first-line regimen consisting of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) in fixed-dose combination (FDC) pills followed by 10 months of Rifampicin, isoniazid, and ethambutol (HRE) daily in a fixed-dose combination as per various weight bands in NTEP. They will also receive tapering dose of steroids at the discretion of treating clinician.
Outcomes	**Primary Outcome** Mortality and disability The primary outcome will be mortality and disability as measured by modified Rankin scale at 12 months and 24 months. i.e., time from randomization to death during the follow-up period. Survivors will be censored at the date they were last known to be alive (i.e., date of last follow-up visit, loss to follow-up or withdrawal). ***Secondary outcomes*** 1. Pharmacokinetic parameters Plasma concentrations of HRhZ and Moxifloxacin will be estimated and the effects of baseline patient covariates on trial drug pharmacokinetics and associated clinical endpoints will be evaluated. 2. Grade 3 or 4 adverse events Comparison of the number of participants who develop Grade 3 or Grade 4 adverse events (according to Division of AIDS (DAIDS) criteria) during treatment. 3. Quality of life QoL at baseline and at 6 months, 12 months, and 24 months will be assessed using a WHO Short form -36 (SF-36) questionnaire which covrs physical, mental and social well-being components of the patients.
Sample size	A systematic review and meta-analysis on treatment outcomes in TBM done by Anna M. Stadelman et.al reported the proportion of mortality and disability after treatment is 24% and 32% respectively. [4] The proportion

	of composite outcome (death and disability) is 56%. We assume a 20% reduction of composite outcome in the intervention arm (i.e., from 56% to 36%). Hence, to study the impact of "Intervention" compared to "Standard care" in reducing the composite outcome death and disability, expecting a minimum difference of 20% between intervention arm without aspirin (arm 2) and control arm (arm 3), assuming 85% power of the study, 5% level of significance, 2-sided significance test; the required sample size was 112 patients in each arm. Considering 10% lost to follow up, the total sample size was calculated as 372 with 124 in each arm.
Study Procedure	All newly diagnosed patients diagnosed with TB Meningitis based on the Lancet consensus scoring system will be screened for the trial. Those who fulfil the inclusion criteria will be enrolled for the study. The Ethics Committee approved Participant Information sheet in the local language will be used to inform about the study. Written informed consent will be obtained prior to study related procedures. Enrolled study participants will be followed up till treatment completion, and for a period of 12 months after treatment completion.
Eligibility criteria	*Inclusion Criteria* A patient will be eligible for entry to the trial if ALL of the following conditions are satisfied 1. Adults (> 18 years) with or without HIV infection 2. Possible, probable or definite TBM according to Lancet consensus diagnostic criteria 3. Willing to give written informed consent 4. Is willing to have an HIV test. 5. Residing within 100 km of the study sites 6. Express willingness to attend the treatment centre for supervised treatment 7. Express willingness to adhere to the trial procedures and follow-up schedule.

8. Agrees to use effective barrier contraception during the period of the treatment in case of female participants

Exclusion Criteria

Patients will not be eligible for the trial if they meet ANY of the following criteria

1. Known current/previous drug resistance to ATT (Rifampicin, INH, FQ)**
2. Concurrent or known diagnosis any other meningitis such as bacterial, viral, and fungal.
3. Currently having an uncontrolled cardiac arrhythmia or ECG abnormalities which are contradiction for the administration of moxifloxacin including prolonged QTc. QTc value define as >450 ms in males and >460 ms in females measured in lead II or V5 on a standard 12-lead ECG.
4. Has clinical icterus or hepatic impairment characterized by serum bilirubin level above the normal laboratory reference range with abnormal liver enzymes, or isolated alanine aminotransferase (ALT) and/ or aspartate aminotransferase (AST) levels above 5 times the upper limit of the normal laboratory reference range
5. Previous history of anti-TB treatment, If any, should not exceed one month in the past and not more than 7 days in the preceding one month.
6. pregnant or lactating women
7. rapid clinical deterioration or very sick and moribund during the screening process, renal failure, liver disease or any condition (social or medical) that in the opinion of the investigator would make trial participation unreliable or unsafe.
8. Has a known allergy to any of the drugs proposed to be used in the trial regimen

** All participants with Rifampicin resistance will be excluded at baseline from the study. Participants with H, FQ and Z resistance identified from

	MGIT results done at baseline will be referred back to NTEP for appropriate management and their numbers will be compensated.
Screening assessments	***Pre-screening visit:*** Any patient with symptoms and signs suggestive of TBM and undergoing lumbar puncture will be pre-screened for the trial after obtaining written informed consent. During pre-screening, CSF collected will be sent for gram staining, bacterial culture and sensitivity, AFB smear, MGIT, Gene Xpert/Xpert Ultra, Truenat and any other laboratory studies as per the treating clinician's advice. Excess CSF samples available after testing will be stored for future studies. If the lumbar puncture is traumatic or blood-stained CSF, we will repeat the lumbar puncture after a clinically accepted interval. ***Screening assessment:*** The following will be done after explaining about the study with PIS and obtaining informed consent, • Interview to obtain demographic details, socio-economic status and medical history (prior diagnoses and treatment, concomitant disease and medication and current symptoms). • Sociological assessment of the suitability of the patient in terms of likely compliance with treatment and other study procedures, and to permit home visits. • Record contact information: all patients must have an identifiable address as part of the inclusion criteria. • Clinical examination includes height, weight, vital signs (temperature, pulse rate, spO_2, systolic and diastolic blood pressure and respiratory rate) and system examination. • Detailed neurological examination including Glasgow Coma Scale (GCS) and Modified Rankin Score (MRS) • Urine for sugar and pregnancy test in case of females. • Complete blood count (haemoglobin, red blood cell (RBC) count, white blood cell count (WBC), WBC differential count

	(neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, peripheral smear). • Serum biochemical tests (total, direct and indirect bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), Total protein, albumin, globulin, blood urea, serum creatinine, glucose, glycosylated haemoglobin (Hb1Ac), uric acid) • Serum electrolytes • Blood test for HIV and HbsAg • Contrast CT brain /MRI brain • CSF for AFB smear, bacterial culture and sensitivity, gram staining, Xpert/Xpert Ultra, Truenat, MGIT and DST for first-line and second-line ATT if culture positive • Sputum AFB smear, MGIT and LJ culture at the baseline if a patient has pulmonary symptoms and could produce sputum for testing ***Enrolment:*** The following will done during enrolment, • medical history (prior diagnoses and treatment, concomitant disease and medication and current symptoms) • Clinical examination including height, weight and vital signs (temperature, pulse rate, spO_2, systolic and diastolic blood pressure and respiratory rate) and detailed neurological examination including CGS and MRS • Blood test for immunological biomarkers (CRP, TNF-α, monocyte & dendritic cell functions and other cytokines) & storage of the left-over sample • Chest X-ray postero-anterior (PA) view
Follow-up	During the study period, patients will be followed as per the study schedule attached (Table 1). After admission to the study and treatment allocation,

patients will be followed

- every week for the first 2 months (till completion of IP) and monthly till the completion of the treatment will undergo clinical examination including detailed neurological examination and adverse event monitoring.
- Sputum AFB smear, MGIT and LJ culture if symptomatic during treatment and follow-ups.
- Women in the reproductive age group will undergo a urine pregnancy test monthly till treatment completion
- RFT and LFT once in two weeks during the intensive phase then at month 4,6,9,12.
- CBC, RBS once a month
- CSF PK* (Single time point at 2 hours after ATT at week 1 (maybe planned till week 2 based on the clinical condition of the patient) in a subset of the participants.
- Intensive PK* in blood at week 1 (1, 2, 4, 6, 8 and 12 hours) in a subset of the participants.
- Sparse PK* in blood at weeks 4 and 8 in a subset of the participants.
- CSF sample storage at week 4.
- Contrast CT/MRI will be performed at 6^{th} month for patients in the both arms and the decision to continue ATT based on imaging parameters in the intervention arm will be left to the discretion of the treating clinician.
- Blood and serum storage at weeks 1, 4, 8, and at 6^{th}, 9^{th} and 12^{th} month. Any other investigations as deemed necessary based on the clinical condition of the patient

PK studies to be planned in subset of willing participants in selected sites

Post-treatment follow up

After the end of treatment, patients in both arms will be followed up once in three months for a period of 12 months. Participants in the intervention arm will complete 12 months of post-treatment follow-up at the 18th-month study visit and participants in the control arm will complete their

	post-treatment follow-up at the 24th-month study visit.
Data analysis	Modified Intent to Treat (MITT) and a Per Protocol (PP) analysis will be conducted at 12 months and 24 months after the treatment initiation. All categorical observations will be presented using frequency and percentages, all continuous measurements will be described using mean and standard deviation or Median and inter quartile range based on the distribution. Baseline parameters will be compared between intervention and control group using Independent Sample t-test or Mann Whitney U test for the continuous measurements after checking normality assumption and Chi-square test or Fisher's exact test will be applied for the categorical observations based on the expected frequency. Multivariate logistic regression analysis will be carried out to assess the risk factors for Mortality and Disability. The intent-to-treat analysis will be conducted for comparing the safety and tolerability of High dose Rifampicin and Moxifloxacin given along with other drugs used in the intervention arm. Safety and tolerability analysis will include all patients who have received at least 1 dose of the drug. The survival time and disability free survival time will be estimated using Kaplan-Meir survival estimate and it will be compared between treatment regimens using Log rank test. The factors associated with Time to death or disability will assessed using Cox proportional regression analysis. P-value will be considered significant at 5% level of significance for all comparisons.
Study duration	3.5 years