A Randomized Trial of Efficacy and Safety of Adjunctive Vitamin D in the Treatment of Active Tuberculosis in India

by
© Peter Daley MD FRCPC DTM+H

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ABSTRACT

Background: Vitamin D supplementation may benefit patients with active tuberculosis (TB)

Design: A randomized, double-blinded, placebo-controlled clinical trial comparing standard active TB treatment to active TB treatment plus supplemental high dose oral vitamin D_3 was performed in India.

Methods: Treatment naïve, smear positive, HIV negative, pulmonary TB patients were randomized into two equal groups.

Results: 247 patients were randomized, 121 to vitamin D and 126 to placebo. Baseline characteristics in both groups were similar. 101 patients in the vitamin D arm and 110 patients in the placebo arm were analyzed. Median time to culture conversion in the vitamin D group was 43.0 days (95% C.I. = 33.3 to 52.8), as compared to was 42.0 days (33.9 to 50.1) in the placebo group (p=0.95 by log rank test). Hypercalcemia was not observed.

Conclusions: Vitamin D supplementation was safe but did not influence time to culture conversion.

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List of Symbols, Nomenclature or Abbreviations

In Order of Appearance

TB	Tuberculosis
HIV	Human Immunodeficiency Virus
RNTCP	Revised National TB Control Program
DOTS	Directly Observed Therapy, Short course
25(OH)D	25-hydroxyvitamin D
$1,25(OH)_2D$	1,25-dihydroxyvitamin D
PTH	Parathyroid hormone
VDR	Vitamin D receptor
ATT	Anti-TB treatment
SAE	Serious adverse events
AE	Adverse events
BMI	Body Mass Index

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Introduction

Tuberculosis (TB) is a disease recognized from antiquity, which continues to remain one of the most important infectious diseases in the world. The World Health Organization annual TB report for 2012, containing data from 204 countries, summarized progress towards TB elimination.(1) The global TB mortality rate has decreased 41% since 1990, and is on target to achieve the Millennium Development Goal of 50% reduction by 2015. Access to TB care has increased significantly, collaborative approaches to TB and Human Immunodeficiency Virus (HIV) coinfection have been initiated, and new diagnostics have been developed. Despite this evidence of progress, there were 8.7 million new cases of TB in 2011, with 1.4 million deaths.(1)

India continues to be the highest TB burden country in the world, with over 2 million cases of active TB every year.(2) TB kills nearly 280,000 men, women and children annually and is one of the leading causes of death in India. While the Revised National TB Control Program (RNTCP) has made progress, TB incidence continues to be high, and serious forms of drug-resistance have emerged, especially in urban hot spots.

TB is caused by *Mycobacterium tuberculosis* complex, a group of bacterial pathogens with a cell wall containing large amounts of mycolic acid, inhaled into the lung, which disseminate throughout the body. It is estimated that one third of humans are infected with TB, however, this infection will remain latent (asymptomatic) for life in most people. The risk of disease activation from latent to active form is considerably increased in the presence of immunosuppression such as that caused by HIV infection.(3) Once activated, the infection damages tissue, and the body creates granulomatous

inflammation in an attempt to contain the spread of the organism. Without treatment among sputum smear positive pulmonary TB cases without HIV, 10 year mortality is 70%.(4)

Diagnostic tools for TB are not ideal.(5) Culture of sputum in solid or liquid medium is the reference standard, but may take as long as six weeks for results. Sputum smear visualizes mycobacteria using acid fast staining, is rapid and cheap and correlates with burden of pulmonary disease, but lacks sensitivity. Chest x-ray is not specific, and lacks inter-rater reliability. However, newer molecular tests such as Xpert MTB/Rif show high accuracy and are being rolled out in many high burden countries.(6)

The treatment of TB prior to the introduction of streptomycin consisted of sanatorium admission for rest, with collapse of affected portions of lung using surgery or injection of air into the pleural space.(7) Early chemotherapies included gold salts, sulphones, nicotinamide and vitamin D.(8) The discovery of streptomycin(9) and description of its activity in guinea pigs prompted the first clinical trial using randomization in the history of medicine, in 1946.(10) Fifty four patients were randomized to bedrest and streptomycin and fifty to bedrest alone. The streptomycin arm had fewer deaths and greater percentage culture negativity, but at five years follow-up, the survival benefit was lost due to the emergence of drug resistance. Modern chemotherapy contains multiple drugs at once in order to prevent drug resistance from creating recurrence of disease after treatment.

It was later discovered that there was no benefit associated with admission to a sanatorium through a randomized trial in India which compared one year of two drug treatment delivered in the sanatorium versus in the home.(11) Treatment outcomes were

similar and family members living with the patient were not more likely to develop TB.(12) Home treatment uncovered the main treatment challenge in the modern era, which is adherence with the entire course of therapy. After patients feel well, they no longer feel motivated to complete additional treatment. Approaches to manage this include directly observed therapy and shortened length of treatment course ("DOTS"), currently limited to a minimum of six months.

Modern chemotherapy of drug susceptible TB includes four drugs (isoniazid, rifampin, pyrazinamide and ethambutol) given for two months followed by two drugs (isoniazid and rifampin) given for four months, each dose under direct supervision, with reporting of treatment outcomes to international surveillance.(13) With appropriate adherence, cure rate without relapse is greater than 96%.(12) TB determined to be resistant to standard treatments requires considerably longer treatment, up to 24 months with more expensive and toxic second line drugs, and carries a poorer prognosis.(14)

The use of vitamin D for TB treatment began in 1849 with the observation that oil from fish liver improved appetite and strength among TB patients.(15) Vitamin D_3 was isolated from fish oil and the physiology of vitamin D was elucidated. Vitamin D_3 is obtained in the diet or synthesized in the skin by ultraviolet light's influence on 7-dehydrocholesterol. In the liver it is hydroxylated into 25-hydroxyvitamin D [25(OH)D] and then in the kidney into 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the active form which binds to the vitamin D receptor on many different tissues. Binding results in transcription of a calcium binding protein which mediates calcium absorption from the gut. The production of $1,25(OH)_2D$ is stimulated by parathyroid hormone (PTH) and decreased by calcium. Adequate $1,25(OH)_2D$ levels will suppress PTH. Deficiency of

vitamin D leads to bone resorption, osteoporosis and fractures, and a disease known as rickets (or osteomalacia) in which new bone is not mineralized appropriately. Deficiency may be defined as the level of 25(OH)D at which serum PTH rises, which is about 75nmol/l, according to most surveys.(16)

Despite adequate sun exposure, rickets and osteomalacia are prevalent in South Asia. Groups of Indians including physicians, soldiers, pregnant women and newborns were assessed in winter and summer, and all groups were found to have deficiency of 25(OH)D, with consequent low calcium and high PTH levels.(17) Populations in other sunny climates such as Hawaii have also been observed to be D deficient.(18) Persons with TB in London, mostly born in India and East Africa, demonstrated low D levels, and a vegetarian diet was considered contributory.(19)

Besides its' role in calcium regulation, $1,25(OH)_2D$ has an antiproliferative effect and downregulates inflammatory markers. It may be synthesized outside the kidney under the influence of cytokines and it is important for the paracrine regulation of cell differentiation and function. It is this immunoregulatory function which may explain the potential role of vitamin D in many diseases.(20-22)

The mechanism of action of vitamin D in TB has been explored *in vitro*.(23) Vitamin D does not have direct anti-mycobacterial effects in the absence of inflammatory cells, unlike vitamin C which has a direct killing effect(24). Macrophages infected with TB within granulomas express 25-hydroxy-vitamin D 1α-hydroxylase, an enzyme which converts 25(OH)D into $1,25(OH)_2D$, and vitamin D receptors.(25, 26) The rate at which this enzyme converts vitamin D is dependent on availability of substrate.(27) The local influence of $1,25(OH)_2D$ is to enhance mycobacterial killing by monocytes and

macrophages, leading to a more successful interaction with the pathogen, and a more accelerated resolution of inflammatory responses during treatment.(28)

Indirect clinical association between vitamin D and TB began with the observation of hypercalcemia among TB patients at diagnosis, or during early treatment.(29) Vitamin D deficiency has been associated with an increased risk of reactivation of latent TB observed among immigrants to the United Kingdom.(30, 31) Several case-control studies confirmed this association.(32, 33) Subsequently, genotypes of the vitamin D receptor (VDR) were associated with increased susceptibility to TB in certain ethnic groups,(34)and polymorphisms in the vitamin D binding protein were similarly associated.(35) It is not clear how these polymorphisms influence interaction with vitamin D. VDR polymorphisms represented in South India are varied, including *Bsm*I, *Apa*I, *Taq*I and *Fok*I.(36)

The most appropriate effectiveness outcome in a clinical trial of novel TB therapy is rate of relapse after treatment, however this design is cumbersome as it requires lengthy follow-up after treatment and large patient numbers, since relapse is rare. Surrogate clinical markers of this reference outcome have been described including proportion of patients with negative sputum culture at two months,(37) time to sputum culture conversion from positive to negative using survival analysis, the rate of reduction in bacterial counts in sputum during the early phase of treatment,(38) or time to detection of growth in serial cultures, representing numbers of bacteria present at the time of collection.(39) Time to culture conversion provides a greater number of data points and is less susceptible to sputum collection variation as compared to a single culture at two months. Challenges with the use of time to culture conversion as an outcome include

variation in laboratory diagnostic techniques, variation in timing and method of collection of specimens, inter-patient differences in response to therapy. The need for novel biomarkers of treatment response in order to detect the efficacy of new TB treatments has been well outlined.(40) Due to the use of multiple drugs at the same time for TB treatment, measuring the benefit of a change in a single drug is expensive and complex.

Seven randomized clinical trials reporting on the effectiveness or safety of the addition of vitamin D supplementation to standard TB treatment have been published, however methods, dosage and outcomes have varied considerably, as summarized in Table 1. Only one of the available randomized trials of vitamin D supplementation in TB treatment reported using a recognized surrogate marker of outcome, time to culture conversion.(41) Others reported change in serum calcium or vitamin D levels,(42, 43) change in weight or symptoms,(44) anti-TB immunity, (45) or clinical scoring systems.(46) A trial by Martineau and colleagues recruited 146 smear positive pulmonary TB patients in the UK, and provided a placebo-matched 2 weekly dose of 2.5 mg of vitamin D, given four times during the first eight week of therapy. 62 patients assigned to vitamin D and 64 assigned to placebo were analyzed, with a median time to culture conversion of 36.0 days in the vitamin D arm and 43.5 days in the placebo arm (adjusted hazard ratio 1.39, 95% C.I = 0.90-2.16, p=0.14 by log rank test). A significant difference was observed among a subgroup with the tt genotype of the Taq1 VDR polymorphism.(41)

Table 1 : Previous Randomized Trials of Vitamin D Supplementation in Tuberculosis

Study	Country	Patients Analyzed	Intervention	Outcome
Gwinup(42)	USA	23 adults	125 µg D_2 daily	No change in serum calcium
Narang(43)	India	30 adults	10-95 µg D* daily	Serum calcium increased in 63%
Morcos(44)	Egypt	24 children	25 µg D* daily	No change in weight or symptoms
Nursyam(47)	Indonesia	67 adults	250 µg D* daily	Smear conversion increased at 6 weeks
Martineau(48)	UK	25 adults	2.5 mg D_2 once	109 nmol/l increase in 25(OH)D at 8 weeks
Wejse(46)	Guinea-Bissau	365 adults	3 doses of 2.5 mg D_3	No effect on TB score
Martineau(41)	UK	146 adults	4 doses of 2.5 mg of D_3	No effect on time to culture conversion
Salahuddin(45)	Pakistan	259 adults	2 doses of 15 mg of D_3	Greater weight gain, improved chest x-ray
Ralph(49)	Indonesia	155 adults	2 doses of 1.25 mg of D_3	No effect on percent culture conversion at 4 weeks. No effect on clinical outcome score

*Form of D used not reported

A high dose of supplemental vitamin D could be associated with risk of hypercalcemia, possibly causing harm to TB patients. Three randomized trials considered change in calcium levels during vitamin D therapy, and only one reported a significant increase.(42, 43, 48) This observation has been controversial, since the dose of vitamin D used was considerably lower than trials in healthy volunteers in which hypercalcemia was not detected.(23) In the Martineau trial, an increase in urinary calcium to creatinine ratio was observed after day 28, but serum calcium was not influenced by allocation to the

vitamin D arm.(41) A recent case of severe hypercalcemia has been described after one 11.5 mg oral dose of vitamin D, a dose four times higher than used in any trial.(50)

The most appropriate dose for vitamin D supplementation is unknown. A single 2.5 mg dose of D_3 (100,000 iu) induced an mean increase of 109.5 nmol/l in 25OH D levels in D deficient TB patients at one week, without hypercalcemia.(48)

Considering the evidence that vitamin D has an immunomodulatory effect among patients with TB and is expensive and easily available, with little evidence of toxicity when used at an appropriate dose, further clinical trials of vitamin D therapy seemed justified. With evidence that vitamin D receptor genotypes are ethnically divergent, vitamin D supplementation could have different effects in different geographic locations. India is a country with a high TB incidence and a well-functioning TB control program. Given the established effectiveness of standard TB treatment, vitamin D would be added to standard treatment. If proven to accelerate culture conversion, supplemental vitamin D might be able to reduce length of treatment.

It is unclear if TB patients would benefit most from a D supplement to restore normal D levels among those with D deficiency, or if supraphysiologic D levels would be more beneficial. In the previous randomized clinical trial in the UK, 146 patients with pulmonary TB in the D arm had a mean D level of 21.1 nmol/l before supplementation, which increased to 101.4 nmol/l, which would be above the standard definition of sufficiency.(41) This was not associated with a significant reduction in time to culture conversion.

The research question proposed was as follows: Among treatment naïve, HIV negative, smear positive pulmonary TB patients in India, does the addition of four oral

doses of 2.5 mg of vitamin D_3 during the first eight weeks of TB treatment, as compared to matching placebo, reduce the time to conversion of sputum culture? The role of Peter Daley in the trial was writing the protocol, acquiring the funding, acquiring ethics permissions, supervising data collection, performing analysis and writing the manuscript.

Methods

Trial Design

The study was a randomized, parallel, double-blinded, placebo-controlled comparison of adjunctive high dose vitamin D supplementation with standard anti-TB treatment (ATT) among new smear positive pulmonary TB patients. Patients were allocated equally into two arms. The protocol was designed and followed in keeping with Good Clinical Practice standards and national ethical guidelines, with expansion from four sites into thirteen sites during the trial, due to initially slow recruitment. This was the only change in protocol after the trial began. Expanded sites were local RNTCP clinics, and were visited by study personnel. Permission was granted by the Drugs Controller General of India, the Health Ministry Screening Committee of the government of India, and the ethics committees of Christian Medical College Vellore, India and Dalhousie University, Canada.

Trial Registration (see Appendices)

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Participants

Previously treatment naïve, HIV negative, pulmonary TB cases (aged 18-75) with at least one recorded sputum smear positive, were eligible for participation if they had taken one dose of TB treatment or fewer. Those with pre-existing liver or kidney disease, concurrent steroid or cytotoxic drug treatment, metastatic malignancy, pregnancy or lactation, active diarrhea, hypercalcemia (corrected serum calcium >2.62 mmol/l) or not expected to survive the duration of the study were excluded. Patients determined to have multi-drug resistant TB on initial culture were removed from the trial and provided second line treatment. Patients were recruited from nine national TB treatment units in Vellore (136/100,000/year TB case notification) and Krishnagiri (79/100,000/year TB case notification) Districts of Tamil Nadu.(2) Patients recruited from the Christian Medical College hospital were followed up in the DOTS clinic, and patients recruited from peripheral clinics were visited in their homes for study visits after recruitment from the DOTS clinic.

Data was collected by two trained study personnel (Jaganathan Vijayakumar at all peripheral sites, and Asha Latha at the Christian Medical College site), who were trained in study protocol and Good Clinical Practice standards. Study personnel worked directly with RNTCP treatment officers, who were responsible for providing ATT. RNTCP officers did not participate in study data collection or intervention.

Intervention

Both arms received standard category 1 ATT according to national guidelines(2), by direct observation through the RNTCP. This treatment category includes new sputum smear positive pulmonary TB diagnoses. Category 1 ATT includes:

- 2 months of Isoniazid 600 mg, Rifampin 450 mg, Pyrazinamide 1500 mg, Ethambutol 1200 mg, each given three times per week, followed by 4 months of Isoniazid 600 mg, Rifampin 450 mg, each given three times per week

Patients randomized to vitamin D received four doses of tasteless, odourless 2.5 mg cholecalciferol (vitamin D_3) oil (100,000 iu/dose) (D Drops™, provided by Reinhold Veith, Toronto) orally, once every two weeks for eight weeks, given by direct observation by study personnel. Patients randomized to placebo received identical carrier oil (Migliol, provided by Reinhold Veith, Toronto). The first dose of vitamin D was provided with the first dose of ATT, and subsequent doses were given 14, 28 and 42 days. Both interventions were stored in identical dark glass dropper bottles at room temperature and protected from light. The vitamin D was stored by the study personnel between doses. One vial was tested for vitamin D content at the end of the trial and was found to contain more than 95% of the original concentration of active ingredient (Elaine Veith, personal communication).

There was no advice provided to patients to change their usual diet or sun exposure during the trial.

Randomization

200 bottles containing vitamin D and 200 containing placebo were randomized by computer (Random Allocation Software by M. Saghaei) in Canada into permuted blocks

of four without stratification, then labelled with serial study numbers in their randomized order, before being shipped to India. As each patient was recruited to the trial, the next serially numbered bottle in sequence was assigned by the study personnel.

Blinding

Neither the patient nor the study personnel including all investigators in India, were aware of treatment assignment. The randomization code was maintained in Canada by one investigator (RV). Patients, clinical and laboratory study personnel in India were not aware of assignment. After the study was completed and database locked for analysis, the code was broken and analysis was performed with knowledge of assignment.

Outcome

The primary efficacy outcome was time to liquid culture conversion, measured from the first dose of ATT to the collection of the first negative culture. Sputa were collected by spontaneous expectoration following instructions from study personnel, at treatment days 0, 14, 28, 42, 56 and 180, with an additional sputum collected at day 90 if the day 56 sputum was culture positive. Secondary outcomes included time to culture conversion measured from the first dose of ATT to the collection of the first of two consecutive negative cultures, time to smear conversion, proportion of patients culture positive at 56 days, Karnofsky performance status and body mass index (BMI) at 56 days, rate of rise in time to detection in culture(39), and 25(OH)D concentration at day 180.

The primary safety outcome was incidence of hypercalcemia (corrected serum calcium > 2.62 mmol/l). Secondary safety outcomes included rates of serious adverse events (SAE), defined as death, admission to hospital, life-threatening illness, persistent disability, congenital anomaly, with predefined disease related complications of TB

infection, and adverse events (AE), defined as any untoward medical occurrence after study medication. SAE were reported within 24 hours to the ethics committees of the Christian Medical College and Dalhousie University.

Procedure

At the screening visit, after obtaining informed written consent in a language the patient understood, demographic data, Karnofsky performance index(51), medical history, concurrent medications and height and weight were recorded. One sputum sample for acid fast smear and liquid mycobacterial culture and susceptibility to isoniazid and rifampin, HIV serology, 25 OH-D, calcium, albumin, creatinine, ALT, and for all women of reproductive age, a urine pregnancy test were performed. HIV pre and post-test counselling was provided to all patients. Sputum was tested for acid fast smear (visible organisms) and liquid culture (incubated for growth of organisms). Calcium was repeated at day 4 and 28, and 25 OH-D at day 180.

Laboratory Methods

Sputum smears were performed using auramine phenol stain and fluorescent microscopy and interpreted according to WHO guidelines. Sputum was pretreated with 4% NaOH/N-acetyl-L-cysteine for 15 minutes. Sputum culture was performed using MB BACTEC 9000 automated system (Becton-Dickenson) according to local laboratory procedure, with incubation for 42 days. Contaminated cultures were re-treated and reinoculated into liquid culture. Drug susceptibility testing for rifampin and isoniazid followed the 1% proportion method. Resistant isolates were confirmed using Gene Xpert™ (Cepheid, USA). All testing was performed at a single laboratory by a single technologist, trained in mycobacteriology. The mycobacteriology laboratory at the

Christian Medical College Vellore is certified by the Stop TB Partnership Global Laboratory Initiative.

Sample Size

The effect size estimate was a reduction in median time to culture conversion from 42 days to 28 days due to the effect of adjunctive vitamin D. This estimate was based on collection of sputum at days 42 and 28, and was identical to the estimate of effect in another trial.(41) With a power of 0.80, a two sided analysis and a significance value of 0.05, 96 patients in each arm were required. Loss to follow-up and contaminated cultures were estimated to cause a loss of thirty percent of results, therefore 250 patients were recruited in total (96+96+30%). This calculation was based on a log-rank analysis, assumed an accrual time of 365 days, a follow up time of 180 days, and an equal assignment of patients to two groups. PS software was used (Vanderbilt University). The planned interim analysis at 50% recruitment was not performed because recruitment was completed before culture data from the first half of recruitment was available.

Statistical Methods

A log-rank test was used (SPSS 19.0.0, IBM) to compare time to culture conversion in the vitamin D and placebo arms. Efficacy was analysed as modified intention to treat (all patients who received one dose of intervention and had at least two sputum culture results available). Safety was analysed for all patients who received one dose of intervention.

Role of the Funding Source

Dalhousie University had no influence in the design, conduct or interpretation of the study. The corresponding author had full access to all the data.

Funding and Conflict of Interest

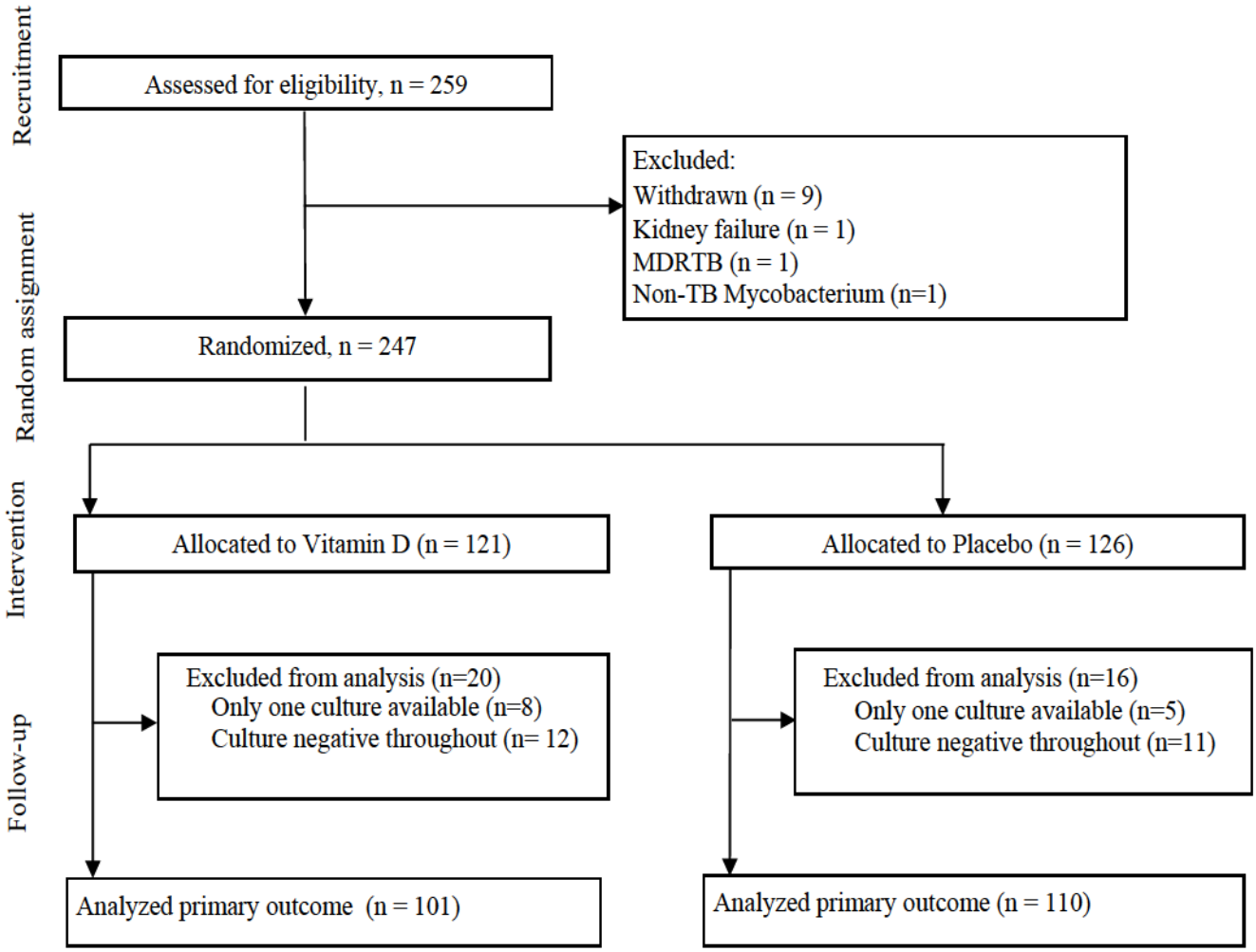
The study was funded by Dalhousie University, Canada, as a University Internal Medicine Foundation Junior Member Grant. The intervention was donated by Reinhold Veith. The funding agencies had no role in the design, interpretation or reporting of the study.

Results

Participant Flow

Patients were recruited as outlined in Figure 1. 259 patients were assessed for eligibility, and 249 patients randomized, 121 to vitamin D and 126 to placebo. One grew a nontuberculous mycobacterium (*M. fortuitum*), and one grew confirmed multidrug resistant TB. Recruitment occurred between 20 January 2010 and 23 August 2011. The last patient follow-up visit was completed on 20 February 2012. The recruitment was stopped when the sample size was reached.

Figure 1: Participant Flow



Baseline Data

The study population is described in Table 2. All patients were ethnically Tamil or Telugu. There were slightly more males in the placebo group (80.2% vs. 72.7% in the

D group). Mean age was similar (43.7 years in placebo, 41.6 years in D) and baseline body mass index was similar and low (17.8 in placebo, 18.0 in D). The vast majority of patients earned less than $95 US per month (94.4% in placebo and 90.9% in D). There were slightly more smokers in the placebo group (31.0% vs. 22.3% in the D group). There was slightly more isoniazid monoresistance among the D group (6.3% in placebo, 11.6% in D). Baseline albumin corrected calcium and vitamin D levels were similar. Mean vitamin D in all patients was well below the threshold of sufficiency. Differences between groups were considered clinically insignificant.

Table 2: Socio demographic characteristics

Variable Name	Vitamin D (N=121) n (%)	Placebo (N=126) n (%)
Male	88 (72.7)	101 (80.2)
Mean Age in Years (SD)	41.6 (15.1)	43.7 (14.3)
Mean Baseline Body Mass Index (SD)	18.0 (2.9)	17.8 (3.0)
Occupation		
Professional	5 (4.1)	3 (2.4)
Skilled worker	23 (19.0)	30 (23.8)
Clerical / Shop Owner / Farm Owner	6 (5.0)	6 (4.8)
Unskilled worker / Manual labor	41 (33.9)	43 (34.1)
Retired / Pensioner	2 (1.7)	2 (1.6)
Unemployed	42 (34.7)	39 (31.0)
Others	2 (1.7)	3 (2.4)
Monthly Income		
< Rs. 5000 (<$95 US)	110 (90.9)	119 (94.4)
Rs. 5000 – 10000 ($95 - $185 US)	7 (5.8)	5 (4.0)
Rs. 10001 – 20000 ($185 - $370 US)	4 (3.3)	2 (1.6)
Education Completed		
Illiterate	24 (19.8)	32 (25.4)
Primary school	39 (32.2)	37 (29.4)
Class VI-IX	25 (20.7)	25 (19.8)
Class X	20 (16.5)	19 (15.1)
Diploma / Bachelor's degree	12 (9.9)	8 (6.3)
Master's degree	1 (0.8)	3 (2.4)

Professional or Doctoral degree	-	2 (1.6)
Baseline Karnofsky Score		
50	4(3.3)	1(0.8)
60	20(16.5)	16(12.7)
70	61(50.4)	65(51.6)
80	33(27.3)	40(31.7)
90	3(2.5)	4(3.2)
Smoking Cigarettes (Presently)		
Yes	27(22.3)	39(31.0)
Chewing Betel Nuts (Presently)		
Yes	2(1.7)	4(3.2)
Consuming Alcohol (Presently)		
Yes	25(20.7)	30(23.8)

Variable Name	Vitamin D (N=121) n (%)	Placebo (N=126) n (%)
Resistant to Isoniazid	14 (11.6)	8 (6.3)
Isoniazid Susceptibility Not Available	20 (16.5)	20 (15.9)
Resistant to Rifampin	1 (0.8)	1 (0.8)
Rifampin Susceptibility Not Available	5 (41.7)	20 (15.9)
Corrected Calcium Baseline (mmol/l) Mean (SD)	2.27 (0.15)	2.28 (0.17)
25 OH D Level Baseline (nmol/l) Mean (SD)	25.3 (18.7)	24.9 (20.5)
Visit 1 Final Culture Results		
Positive	101 (83.5)	108 (85.7)
Negative	19 (15.7)	18 (14.3)
Missing	1 (0.8)	-
Visit 6 Final Culture Result		
Positive	63 (52.1)	76 (60.3)
Negative	42 (34.7)	37 (29.4)
Missing	16 (13.2)	13 (10.3)
Visit 7 Final Culture Result		
Positive	41 (33.9)	46 (36.5)
Negative	61 (50.4)	59 (46.8)
Missing	19 (15.7)	21 (16.7)
Visit 8 Final Culture Result		
Positive	24 (19.8)	26 (20.6)
Negative	73 (60.3)	68 (54.0)
Missing	24 (19.8)	32 (25.4)
Visit 9 Final Culture Result		

Positive	15 (12.4)	16 (12.7)
Negative	76 (62.8)	80 (63.5)
Missing	30 (24.8)	30 (23.8)
Visit 10 Final Culture Results		
Positive	12 (9.9)	17 (13.5)
Negative	87 (71.9)	82 (65.1)
Missing	22 (18.2)	27 (21.4)
Visit 1 Smear		
Positive	101 (83.5)	108 (85.7)
Negative	19 (15.7)	18 (14.3)
Missing	1 (0.8)	-
Visit 6 Smear		
Positive	63 (52.1)	77 (61.1)
Negative	42 (34.7)	36 (28.6)
Missing	16 (13.2)	13 (10.3)
Visit 7 Smear		
Positive	41 (33.9)	48 (38.1)
Negative	61 (50.4)	58 (46.0)
Missing	19 (15.7)	20 (15.9)
Visit 8 Smear		
Positive	24 (19.8)	27 (21.4)
Negative	73 (60.3)	67 (53.2)
Missing	24 (19.8)	32 (25.4)
Visit 9 Smear		
Positive	14 (11.6)	17 (13.5)
Negative	78 (64.5)	81 (64.3)
Missing	29 (24.0)	28 (22.2)
Visit 10 Smear		
Positive	12 (9.9)	16 (12.7)
Negative	88 (72.7)	83 (65.9)
Missing	21 (17.4)	27 (21.4)

Numbers Analysed

All patients with two culture results available were analyzed for the primary outcome, time to culture conversion (time to first negative culture), including those who were culture negative on the first visit but culture positive on the second visit. Eight patients in the D group and 5 in the placebo group did not have culture results available

following the initial visit and were excluded. Twelve patients in the D group and 11 in the placebo group were never culture positive and were excluded. The primary outcome analysis was performed on 101 patients in the D group and 110 patients in the placebo group.

Because there were positive cultures which occurred following negative cultures, an alternative survival analysis was also considered as a secondary outcome (time to culture conversion (time to first of two consecutive negative cultures)). The secondary outcome analysis of time to culture conversion (time to first of two negative cultures) was performed on 81 patients in the D group and 82 patients in the placebo group.

All patients with two smear results available, at least one of which was positive, were analyzed for time to smear conversion (time to first negative smear). Eight patients in the D group and 5 in the placebo group did not have smear results available following the initial visit, and were excluded. Twelve patients in the D group and 11 in the placebo group did not have a positive smear at any point during the trial (except the smear to assess inclusion into the trial), and were excluded. The secondary outcome analysis of time to smear conversion (time to first negative smear) was performed on 101 patients in the D group and 110 patients in the placebo group.

Because there were positive smears which occurred following negative smears, an alternative survival analysis was also considered (time to smear conversion (time to first of two consecutive negative smears)). The secondary outcome analysis of time to smear conversion (time to first of two consecutive negative smears) was performed on 85 patients in the D group and 87 patients in the placebo group.

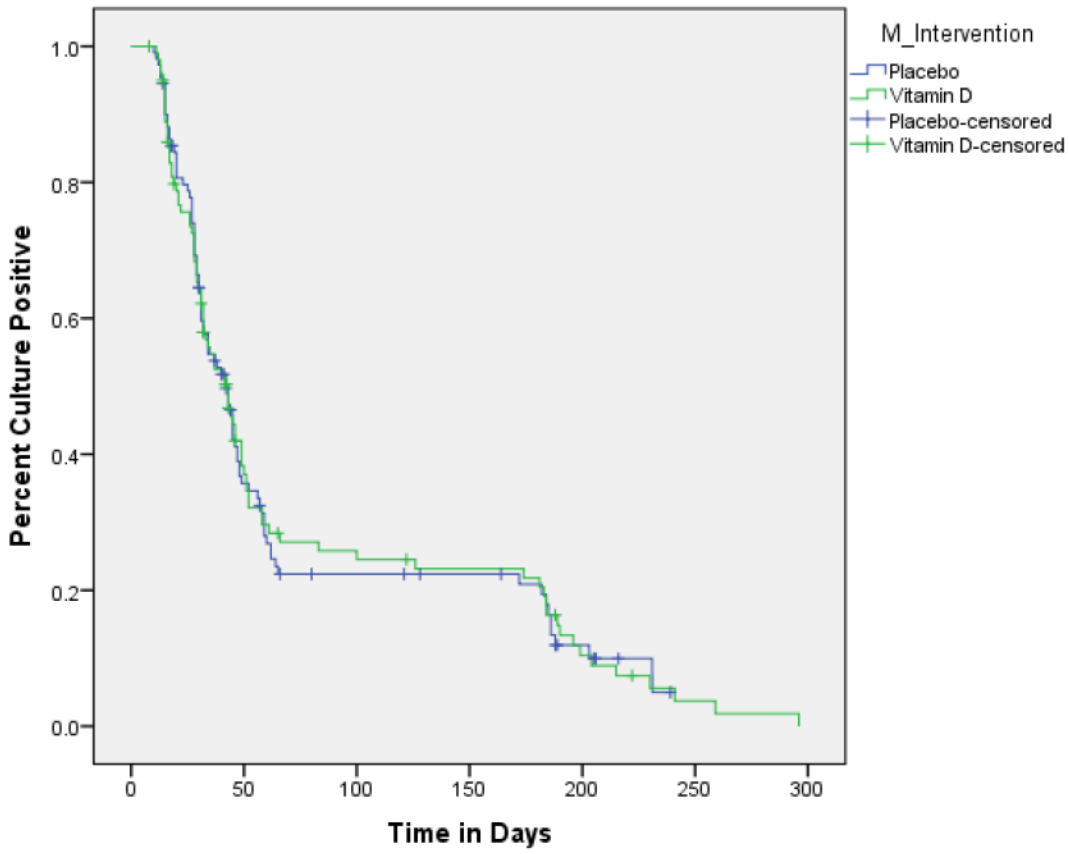
Primary Outcome

The primary outcome was time to culture conversion (first negative culture), and is presented in Table 3 and Figure 2. The median time to culture conversion in the vitamin D group was 43.0 days (95% C.I. = 33.2 to 52.8). The median time to culture conversion in the placebo group was 42.0 days (95% C.I. = 33.9 to 50.1) (p=0.95 by log rank test). This demonstrated no statistically significant difference between the time to culture conversion between the D group and the placebo group.

Table 3: Primary Outcome – Time to Culture Conversion (First Negative Culture)

Group	Number of subjects	Events (%)	Censored (%)	Median Time to Culture Conversion in days (95% CI)	Log Rank Test
Vitamin D	101	85 (84.2)	16 (15.8)	43.0 (33.3 to 52.8)	p = 0.952
Placebo	110	87 (79.1)	23 (20.9)	42.0 (33.9 to 50.1)	

Figure 2 : Primary Outcome – Time to Culture Conversion (First Negative Culture)



Secondary Outcomes

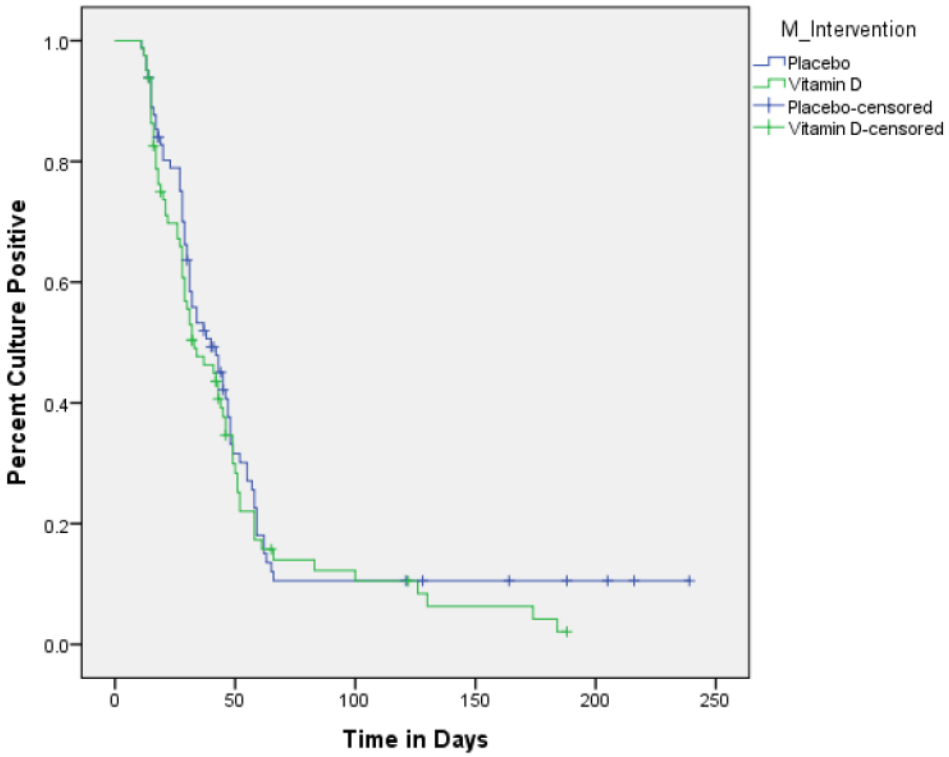
The secondary outcome of time to culture conversion (first of two negative cultures) is presented in Table 4 and Figure 3. The median time to culture conversion (first of two negative cultures) in the vitamin D group was 33.0 days (95% C.I. = 21.5 to 44.5). The median time to culture conversion in the placebo group was 40.0 days (95% C.I. = 29.5 to 50.5) (p=0.33 by log rank test).

Table 4: Secondary Outcome – Time to Culture Conversion (First of Two Consecutive Negative Cultures)

Group	Number	Events (%)	Censored	Median Time to	Log Rank

	of subjects		(%)	Culture Conversion in days (95% CI)	Test
Vitamin D	81	69 (85.2)	12 (14.8)	33.0 (21.5 to 44.5)	p = 0.331
Placebo	82	66 (80.5)	16 (19.5)	40.0 (29.5 to 50.5)	

Figure 3: Primary Outcome – Time to Culture Conversion (First of Two Consecutive Negative Cultures)

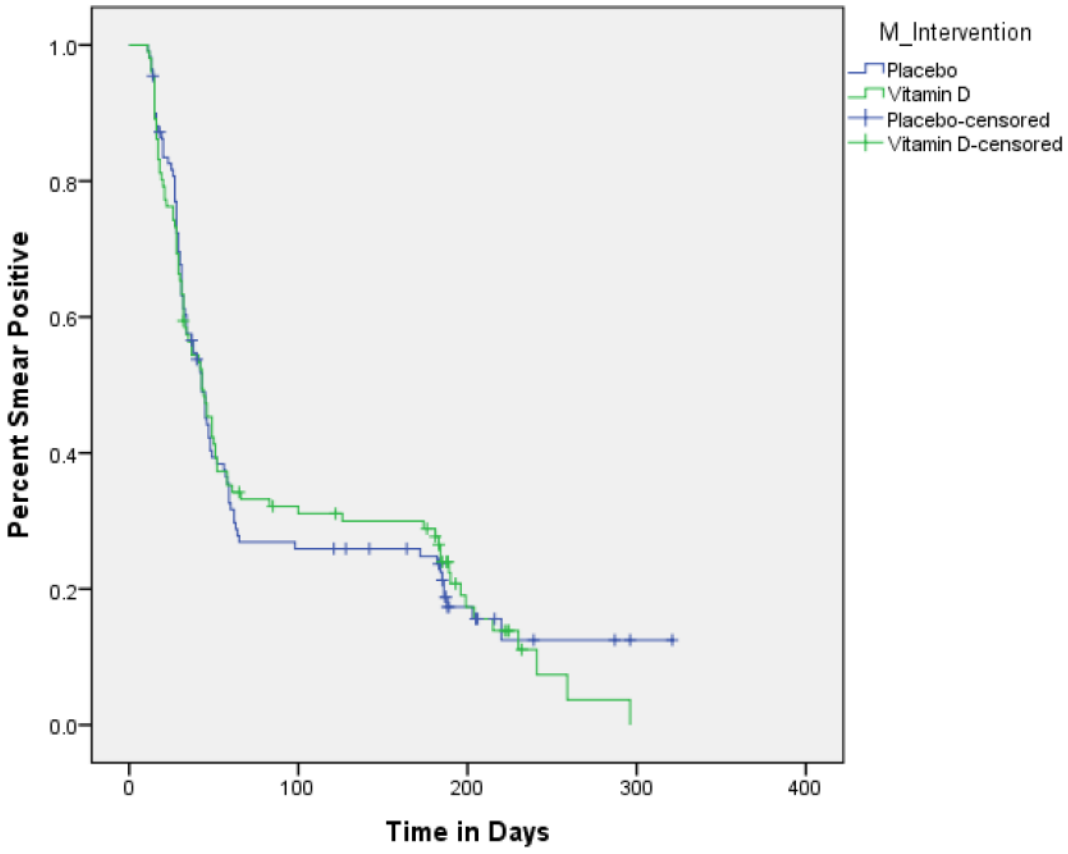


The secondary outcome of time to smear conversion (first negative smear) is presented in Table 5 and Figure 4. The median time to smear conversion in the vitamin D group was 43.0 days (95% C.I. = 33.3 to 52.7). The median time to smear conversion in the placebo group was 43.0 days (95% C.I. = 36.1 to 49.9) (p=0.95 by log rank test).

Table 5: Secondary Outcome – Time to Smear Conversion (First Negative Smear)

Group	Number of subjects	Events (%)	Censored (%)	Median Time to Smear Conversion in days (95% CI)	Log Rank Test
Vitamin D	101	85 (84.2)	16 (15.8)	43.0 (33.3 to 52.7)	p = 0.949
Placebo	110	88 (80.0)	22 (20.0)	43.0 (36.1 to 49.9)	

Figure 4: Secondary Outcome – Time to Smear Conversion (First Negative Smear)



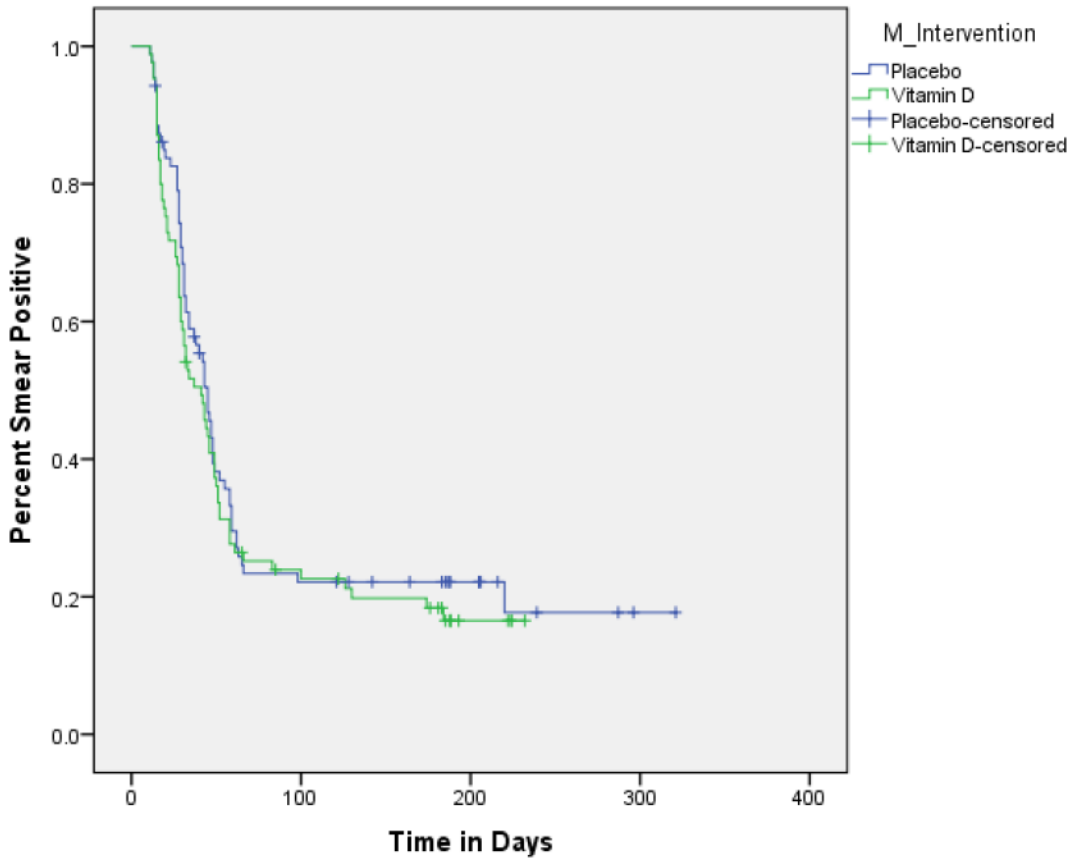
The secondary outcome of time to smear conversion (first of two consecutive negative smears) is presented in Table 6 and Figure 5. The median time to smear

conversion in the vitamin D group was 41.0 days (95% C.I. = 21.5 to 44.5). The median time to smear conversion in the placebo group was 45.0 days (95% C.I. = 29.4 to 52.6) (p=0.45 by log rank test).

Table 6: Secondary Outcome – Time to Smear Conversion (First of Two Consecutive Negative Smears)

Group	Number of subjects	Events (%)	Censored (%)	Median Time to Culture Conversion in days (95% CI)	Log Rank Test
Vitamin D	85	69 (81.2)	16 (18.8)	41.0 (21.5 to 44.5)	p = 0.445
Placebo	87	66 (75.9)	21 (24.1)	45.0 (29.4 to 52.6)	

Figure 5: Secondary Outcome – Time to Smear Conversion (First of Two Consecutive Negative Smears)



Because there were no clinically significant differences between groups at baseline, adjustment for baseline differences was not performed. Survival curves crossed each other in all four analyses, violating the assumptions of the Cox regression model.

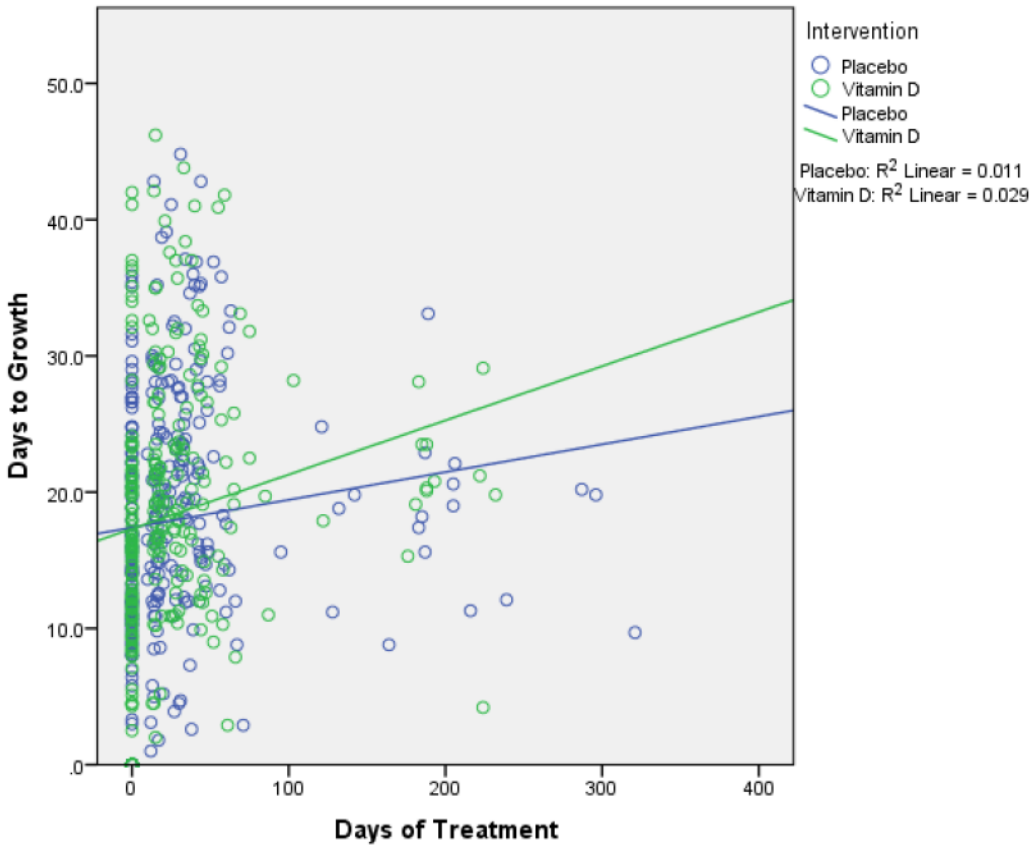
The percent sputum culture negativity at Day 56 in Vitamin D group was 80.8% and in the placebo group it was 82.9% [difference -2.1 (95% C. I = -14.2 to 10.0)]. See Table 7. There is no statistically or clinically significant difference between percent culture negativity at day 56.

Table 7: Secondary Outcome - Percent Sputum Culture Negative at day 56

	Vitamin D n/N	Vitamin D %	Placebo n/N	Placebo %	Difference (Vitamin D - Placebo) 95% CI
Sputum culture Negative at 56 days	59 / 73	80.82	68 / 82	82.93	-2.11 (-14.18 to 9.96)

The secondary outcome of time to detection of growth is presented in Figure 6. Time to detection of growth was quite variable, providing a poor fit to a regression line. The rate of rise in time to detection in the vitamin D group was 0.17. The rate of rise in time to detection in the placebo group was 0.11 (difference 0.066, p = 0.59).

Figure 6 – Secondary Outcome - Time to Detection in Liquid Culture by Intervention



Baseline vitamin D level was available for 124 of the patients randomized to placebo (98.4%) and day 180 vitamin D level was also available for 79 (55.5%), providing comparison data for 77 patients. The level increased 2.67 nmol/l (SD 16.09). Baseline vitamin D level was available for 119 of the patients randomized to D (98.3%) and day 180 vitamin D level was also available for 67 (55.3%), providing comparison data for 65 patients. The level increased 5.68 nmol/l (SD 13.63). The difference in increases between the groups was 3.02 nmol/l ($p = 0.235$), see Table 8. There was not a significant difference between the increases in vitamin D in the D group as compared to the placebo group. Because the upper limit of the assay (100 nmol/l) was reached in 8 patients, these results may be a slight underestimate of the true mean. Because measurements were not taken serially throughout the study, the vitamin D level may have increased and then decreased by day 180.

Table 8: Secondary Outcome – Change in Vitamin D Levels

Intervention	n	Mean Difference between Baseline D level and Day 180 D level (nmol/l)	SD	Difference	T test
Placebo	77	2.67	16.09	3.02	$p = 0.235$
Vitamin D	65	5.68	13.63		

Baseline BMI (weight in kg/height in meters^2) was available for all patients, with a mean of 17.9 (SD 2.9). Body mass index was available at day 58 for 213/249 patients (85.5%), with a mean of 18.7 (SD 3.1) ($p < 0.001$ by t test), indicating a significant weight gain over the course of the study. The difference in increases in BMI between the groups was 0.087 more in the placebo group ($p=0.597$).

Baseline Karnofsky performance index (100 point scale of functional capability from perfect health at 100 to death at 0) was available for all patients, with a mean of 71.7 (SD 7.8). Karnofsky performance index was available at day 58 for 212/249 patients (85.1%), with a mean of 83.4 (SD 8.1) ($p < 0.001$ by t test), indicating a significant performance improvement over the course of the study. The difference in increases in Karnofsky performance index was 1.90 more in the vitamin D group ($p=0.115$).

Safety

There were no cases of hypercalcemia detected in either arm through calcium monitoring or symptoms. Figure 7 demonstrates the trend in mean calcium levels through the study. There was no statistically or clinically significant change in calcium levels in either group.

Figure 7: Safety - Calcium levels

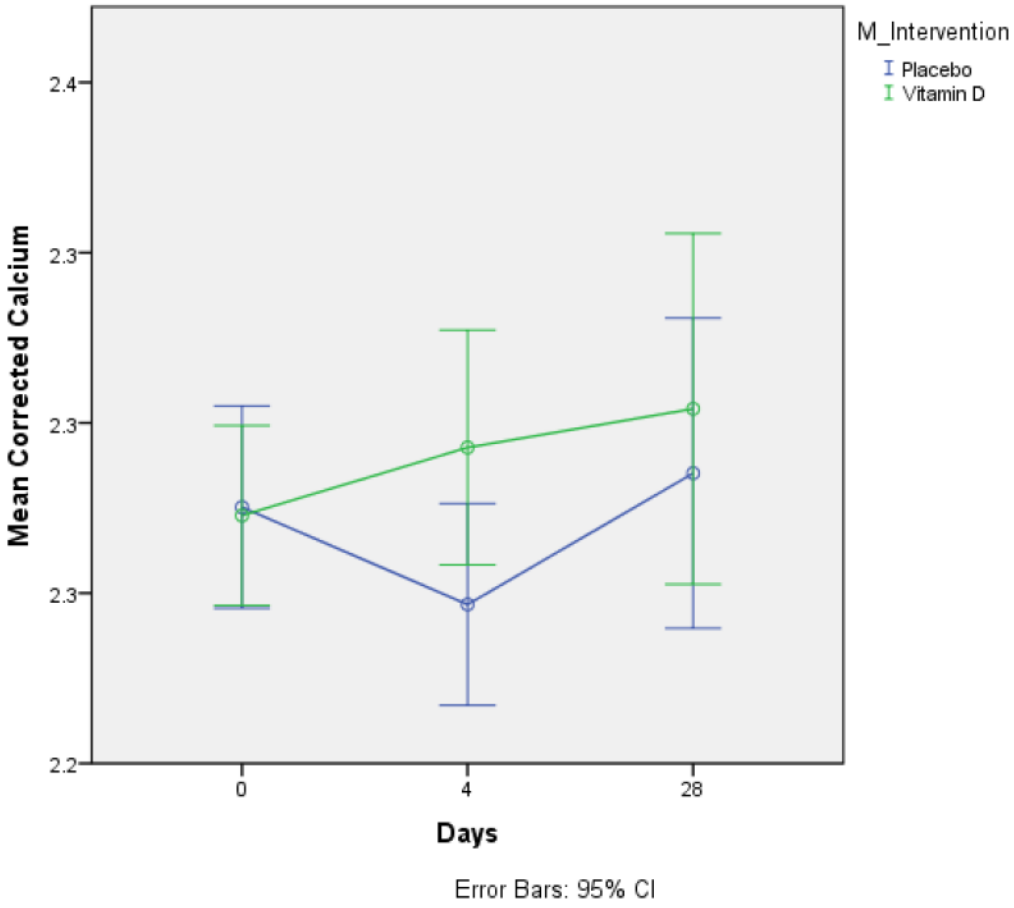


Table 9 summarizes serious adverse events. Four patients died during the study, three on the D arm and one on the placebo arm. No death was considered directly attributable to study intervention. The first death on the D arm was attributed to alcohol ingestion. The second death on the D arm occurred at 3 months and 6 days following the final dose of D, of unknown causes. The third death on the vitamin D arm occurred at 17 days following the final dose of D, of unknown causes. None of the patients who died had hypercalcemia when measured at day 28.

Table 10 summarizes adverse events. There were four adverse events on the D arm and three adverse events on the placebo arm. No adverse event required a change in medical therapy which deviated from the study protocol.

Table 9: Serious Adverse Events (Chronological Order)

Date of Onset	Study Number	Nature of SAE	Date Reported to Ethics Committee of Christian Medical College Vellore	Intervention	Serious Adverse Event Determined Intervention Related?	Description
28-03-2010	5	Hospitalization due to Seizure	03-04-2010	Placebo	No	Enrolled on 24-02-2010, first dose placebo 25-02-2010 and the second on 16-03-2010. Visited at home on 29-03-2010 and found to be drowsy. Admitted 30-03-2010 to 02-04-2010. All metabolic parameters and CT scan of head normal. Corrected serum Ca 2.05 mmol/l.
15-05-2010	5	Death	07-07-2010	Placebo	No	Final study dose given on 08-04-10. Follow-up visit 16-04-10 in good medical condition. Informed he had died during his sleep 19-06-10.
23-09-2010	31	Death	23-12-2010	Vitamin D	No	First dose of study drug on 14-07-10. Withdrew consent and did not receive further study drug.

						Followed as per protocol for two months. Informed on 21-12-10 that he had died on 23-09-10. Massive alcohol consumption just before death.
03-03-2011	142	Death	01-06-2011	Vitamin D	No	Tenth visit on 30-05-11, informed that the patient died on 03-03-2011, 4 months and 18 days after starting ATT.
10-03-2011	171	Hospitalization due to hydro-pneumothorax	14-03-2011	Placebo	No	First dose of study drug administered on 10-03-2011. On the same day he complained of acute breathlessness. Admitted with massive right sided hydropneumothorax, drained with intercostal tube and discharged home 22-03-11.
May 21, 2011	128	Death	May 27, 2011	Vitamin D	No	Ninth follow up visit on 19-05-2011 informed that patient died on 21-05-11.

Table 10: Adverse Events

Study Number	Intervention	Adverse Event 1	Treatment in Addition to Study Protocol	Adverse Event 2	Treatment in Addition to Study Protocol
60	Vitamin D	Giddiness, Vomiting, Chest pain, Tiredness	None	Tooth ache, tired, giddiness	None
74	Vitamin D	Back Pain	None		
80	Vitamin D	Lymph node on neck	None		
79	Placebo	Tiredness	None		
171	Placebo	Acute Breathlessness	Right side intercostal chest drainage		

Discussion

Our results suggest that 2.5 mg of vitamin D_3 given four times during the intensive phase of active TB treatment in a TB endemic country does not reduce the time to culture conversion significantly. One previous randomized trial with similar methods agreed with this conclusion.(41) We did not have the capacity to perform vitamin D receptor polymorphism testing as in that trial, although with the common ethnicity of our patients, we may not have detected much variety.

We were able to demonstrate that patients with active TB in South India have significant D deficiency, with a mean serum level of 25 nmol/l. We were not able to demonstrate a significant increase in serum D levels during the study in either group, possibly due to the timing of sampling at day 0 and day 180 only. Subjects were given vitamin D by direct observation and no doses were missed. The sample size was calculated based on the estimated effect size reported by a previous trial, which was felt

to represent a clinically significant improvement due to the addition of an effective drug to standard TB treatment. The confidence intervals surrounding our estimates of time to culture conversion included 10 days below and above the estimate, which could include a clinically relevant difference. It is possible therefore that the trial was underpowered to detect a clinically relevant difference.

Change in time to culture conversion is an outcome which reflects success of late sterilization, or the elimination of metabolically inactive bacteria to prevent relapse after therapy. The implication of improved late sterilization is reduced total treatment time without loss of 95% treatment efficacy.(52) Reduction in treatment duration could improve treatment compliance. It is not clear what amount of reduction in time to conversion would be considered adequate to propose a reduction in treatment duration.

The primary limitation of our study was missing data. We estimated 30% loss of data due to patient dropout and culture contamination, and we did not exceed this estimate (24%). Patients with active TB are among low socioeconomic strata, and are often migratory or suffering additional social and mental health comorbidity. There was no loss of data due to culture contamination, but an unexpected number of patients were culture negative (smear positive) at baseline. This may have reflected inadequate sputum collection. Sputum transportation was within one day of collection, so loss of viability due to transportation was not likely.

The study performed a single culture at each time point instead of two cultures as in other TB treatment trials, due to financial limitations. This may have contributed to reduced sensitivity, baseline smear positive culture negatives, and the problem we observed of positive cultures occurring following negative cultures during treatment. We

feel the alternative method of survival analysis does compensate somewhat for this problem, and the conclusion of no change in time to culture conversion remained the same under this alternate method. Risk factor (regression) analysis was not performed, as groups were considered comparable at baseline.

The survival analysis technique used can compensate for censored data and variable dates of collection, but the conversion in outcome from culture positive to negative and back to positive, or from negative to positive to negative, is problematic. In order to correct this weakness in the data we performed two survival analyses, based on two interpretations of the endpoint. The first interpretation, time to first negative culture, could reflect the response in the early phase of therapy (rapid killing of metabolically active organisms) but may be susceptible to sampling bias based on a single poor collection. The second interpretation, time to first of two consecutive negative cultures, could reflect the killing of active and some quiescent organisms and may be a more definitive outcome, related to risk of relapse after therapy. In our results, the second interpretation demonstrated a small trend toward more rapid conversion in the vitamin D arm, at 33.0 days (95% C.I. = 21.5 to 44.5) as compared to 40.0 days (29.5 to 50.5).

No previous study has interpreted time to culture conversion using these two definitions. Previous studies have defined the time endpoint as time to all cultures negative,(53) or the *midpoint* between the last positive and the first negative culture.(41) The definition of this endpoint determines the comparability of effect sizes between studies.

Using our definition of the endpoint, the observed time to culture conversion in the placebo group occurred precisely when predicted, at 42 days. We would expect smear

conversion to occur much earlier than culture conversion, since smear detects 10,000 organisms per ml of sputum while culture can detect fewer than 100 organisms per ml of sputum. However, we observed that smear conversion did not occur earlier than culture conversion. This may have been influenced by the timing of sampling of sputum, with no assessment between days 28 and 42.

The addition of high dose vitamin D to standard TB treatment does not appear toxic. No hypercalcemia was observed, and serious adverse events observed were determined unrelated to the intervention. There was significant under-reporting of adverse events as compared to trials in North America, which may reflect cultural differences in reporting, or missing data.

The results of our trial would generalize to ethnically uniform, D deficient patients with active TB and a low HIV coinfection prevalence. Traditional sanitorium treatment of active TB included sunlight exposure and vitamin D supplementation, and in vitro studies have demonstrated benefit, but in two randomized clinical trials using appropriate surrogate outcomes, vitamin D supplementation does not add benefit.

The success of recruitment in our trial was high, with very few patients refusing to be randomized. This reflects a culture in which patients generally accept without question the suggestions of their health care provider. Considerable effort was taken to ensure adequate informed consent, although some patients were illiterate. It is challenging to ethically recruit patients in a TB endemic country, where patients may not fully understand the scientific rationale behind the treatment or the research intervention.

Future studies in vitamin D in TB could be performed, and could be designed to avoid weaknesses in design and interpretation by collecting multiple cultures at each time

point, and following D levels serially. Future studies should explore higher vitamin D dosing. Ideal clinical trial outcomes and trial outcome definitions in TB are unclear, and the definition of immunological and genetic biomarkers may provide additional means of comparison of time to clearance of bacteria.

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Capital Health

A Clinical Trial to Measure the Effect of Vitamin D as a Supplemental Therapy to Conventional Tuberculosis Treatment

Mathai D, Daley P, Martineau A, John KR, Veith R, Michael J, Smieja M

Appendix 1
Consent Form

Patient Information Sheet and Consent Form

This document provides information for new tuberculosis patients, to seek their participation in a clinical research trial. If you sign it, you be able to participate in this trial.

1. You are being invited to take part in a research trial

This trial involves research of the drug Vitamin D in TB patients. Before giving consent for participation please read carefully, understand and clarify with us if you have any doubt in this trial research. Take this format home, discuss with your family members, relatives, friends &doctors about the trial.

2. Purpose of this trial?

This study is to determine if vitamin D will help in addition to the normal TB treatment to cure TB faster. Cure is determined by a sputum test.

3. Why have I been chosen?

You are being asked to take part in this study because you have pulmonary tuberculosis.

4. Your Participation:

You can choose to be in this trial or not to be in it. If you do decide to take part, you will be asked to sign a consent form. You are free to stop at any time during the trial. If you stop, you will still get your TB treatment and care.

5. Trial Treatment & Randomization:

Trial treatment involves giving each dose of 3.3 ml Migliol oil orally or with food once every 2 weeks for 2 months (4 doses totally) along with normal TB medicine. This oil may contain the trial drug Vitamin D or plain oil. This is decided by random.

6. Trial Procedure:

The trial procedure involves 9 visits. The study visits are also coming on the same days as your TB clinic visit. At each visit you will be asked to provide sputum samples to observe the TB status and blood samples to check the calcium levels.

7. Your Responsibilities:

a. To return for the scheduled study visits and to follow procedures as instructed.
b. To take the study medication as prescribed.
c. To report all changes in your physical or mental condition, any symptoms, any side effect or injury during the study.
d. To continue your regular medication.
e. To tell the study coordinator all medicines you take.

8 .Your Rights:

a. You have the right to refuse or withdraw in this study at any time
b. You have the right to get regular medical treatment & care.
c. You have the right to understand the way the study works.
d. You have the right to ask questions about the study

9. Who can participate?

New TB patient with positive sputum test within the age of 18 to 75 years
HIV patient with TB can also participate if CD4 count is >50 cells.
We will screen for some other tests in blood and decide whether you are included in the study.

11. Risks:

Vitamin D may cause your calcium level to rise temporarily. If your calcium level rises too high we will stop the vitamin D temporarily. We will provide medical care if you get sick because of high calcium.

12. Expected Benefits:

Vitamin D is expected to reduce the period of TB Treatment. But we don't know fully. We will only know after this trial completes.

13. Information on Substudy for participation (optional):

The optional part of the trial (substudy) is the Vitamin D Receptor Polymorphism Substudy. You can choose to participate in the main part of the trial without participating in the substudy. In this substudy we will take an additional of 30 ml of blood sample during the first visit. All blood samples will then be sent to a lab, with a study code without identifying your name.

In this study we analyze the blood of people with tuberculosis to see whether there are certain markers in part of their blood (called DNA), that can predict whether people will develop tuberculosis or not. These are sometimes called "genetic markers" or Bio markers.

14. Will the study pay me?

The study will provide the necessary transportation costs for every visit (Rs 50).

15. Confidentiality:

We will not share your medical information with anyone else.

16. What will happen to the results of the research trial?

The results of this research may be published at the end of the study. Your name will not be mentioned in any report/publication. Your information belongs to the trial, even if you leave the trial.

17. Who has reviewed the trial?

The Ethics Committee of the CMCH has reviewed this proposal because it is research using human subjects. They have approved the proposal.

18. What use will be made of the data collected from this trial?

The trial may help other TB patients in India.

19. Contact for further information

If you have any questions or concerns now or at any time about the trial, your safety or your rights, please ask your study coordinator or the contact person(s) indicated below.

Principal Investigator:
DR. DILIP MATHAI
Infectious Diseases Training and Research Center
5th floor, above State Bank of India
CMCH
Vellore
Phone: 04162282804

Clinical Trial Coordinator,
Mr. VIJAYAKUMAR.
Infectious Disease Training and Research Centre,
CMCH,
Vellore.
Mobile: 09366111098.

A Clinical Trial to Measure the Effect of Vitamin D as a Supplemental Therapy to Conventional Tuberculosis Treatment

Mathai D, Daley P, Martineau A, John KR, Veith R, Michael J, Smieja M

Subject Initials:	Subject Name:	Date of Birth:
Clinical Trial Coordinator:		Trial Number:

Title of Research Project: VITAMIN D TRIAL

CONSENT FORM

AGREEMENT TO PARTICIPATE IN A CLINICAL TRIAL

1. I confirm I have read and understand the information sheet dated 28th August 2007 for the above Trial and have had the chance to ask questions. The study was explained to me in a language I can understand.
2. I understand that I chose to enter the trial and that I am free to leave at any time, without my medical care or legal rights being affected.
3. I agree to allow the study doctors or the CMCH Ethics Committee to look at my health records for the trial or for future studies even if I leave the study
4. I agree to an HIV test.
5. I understand that some participants will get vitamin D and some won't.
6. I will not prevent the use of the information in the trial.
7. I agree to take part in the above trial.

☐8. I agree to take part in the Vitamin D Receptor Polymorphism Substudy (involves a blood draw).

☐ I do not agree to take part in the Vitamin D Receptor Polymorphism Substudy.

☐ Having agreed to take part in the Vitamin D Receptor Polymorphism Substudy, I agree to have my blood sample kept for 10 years for future research as outlined above.

Subject Name	**Signature/thumb print**	
Signed by Subject:		**Date:**
Witness name		
Signed by witness		**Date:**
Investigator Name		
Signed by Investigator		**Date:**

Appendix 2
Tamil Consent Form

Capital Health

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம்

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

மத்தாய் D, டேலி P, மார்டினியு A, ஜான் K.R, வீத் R, மைக்கேல் J, ஸ்மைஜா M

தகவல் படிவம்

இந்த படிவம் புதிதாக கண்டறியப்பட்ட காசநோயாளிகளுக்கு இந்த ஆராய்ச்சி குறித்து முழு விவரங்களை வழங்கி பங்கு கொள்வதற்கான ஒப்பந்தத்தை பெறுதல். கையொப்பமிடுதல் பங்கு கொள்பவரின் ஒப்பந்தத்தை உறுதிபடுத்தும்.

1. **இந்த சோதனை ஆராய்ச்சியில் உங்களை பங்குகொள்ள அழைக்கப்படுகிறீர்கள்:**
இந்த ஆராய்ச்சியானது வைட்டமின் Dயை காசநோயாளிகளுக்கு கொடுத்து சோதிப்பது பற்றியது. தயவுகூர்ந்து அதிக நேரம் எடுத்து கீழ்வரும் தகவல்களை படித்து உங்கள் குடும்ப உறுப்பினர்கள், உறவினர்கள், நண்பர்கள் மற்றும் குடும்ப மருத்துவரிடம் பகிர்ந்து கொள்ளுங்கள். உங்களுக்கு ஏதேனும் சந்தேகம் இருக்குமானால் எங்களிடம் கேட்டு அறிந்து கொள்ளுங்கள்.

2. **இந்த ஆராய்ச்சியின் நோக்கம் என்ன?**
வைட்டமின் D ஆனது TB குணப்படுத்த உட்கொள்கின்ற மருந்துடன் சேர்க்கும் பொழுது விரைவில் TB நோய் குணமடைகின்றதா என்பதனை சோதிப்பதாகும். TB குணமடைந்ததை சளி பரிசோதனையில் அறிதல்.

3. **நான் ஏன் தேர்ந்தெடுக்கப்பட்டேன்?**
உங்களுக்கு காசநோய் இருப்பதால் இந்த சோதனை ஆராய்ச்சிக்கு நீங்கள் தேர்ந்தெடுக்கப்பட்டீர்கள்.

4. **நான் பங்கு கொள்ளவேண்டுமா?**
பங்கு கொள்பதும் பங்கு கொள்ளாததும் உங்கள் விருப்பம். பங்கு கொள்ள முடிவெடுத்தால் இந்த ஒப்புதல் படிவத்தில் கையெழுத்து போடலாம். இந்த ஆராய்ச்சியில் எப்போது வேண்டுமானாலும் நீங்கள் விலகிக்கொள்ளலாம். அதனால் உங்கள் காசநோய் சிகிச்சை எந்த விதத்திலும் பாதிப்பு ஏற்படாது.

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

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5. சோதனை முறை மற்றும் வாய்ப்பு சதவிதம்:

இந்த சோதனையானது 3.3 மி.லி. மிகிலியால் எண்ணையை இரண்டு வாரத்திற்கு ஒரு முறை இரண்டு மாதத்திற்க்கு (மொத்தம் நான்கு டோஸ்) வழக்கமாக அளிக்கப்படும் காசநோய் மருந்துடன் சேர்த்து அளிக்கப்படும். இதனை உணவுடனோ அல்லது வாயின் மூலமோ எடுத்துக் கொள்ளவேண்டும். இந்த எண்ணையில் வைட்டமின் D கலந்திருக்கும் அல்லது வைட்டமின் D இல்லாத வெறும் எண்ணை மட்டும் இருக்கும். அவை உங்கள் வாய்ப்பை பொறுத்தது.

6. சோதனை செயல்முறை:

இந்த சோதனையில் நீங்கள் 9 முறை மருத்துவரை சந்திக்க கூடும். அனைத்து நாள்களும் நீங்கள் காசநோய் சிகிச்சைக்கு வரும்போது பார்க்கப்படும். ஒவ்வொருமுறை வரும்போதும் TB அளவை பரிசோதனையில் அறிந்து கொள்ள சளி மற்றும் இரத்தம் கொடுக்க நேரிடும்.

7. உங்கள் பொறுப்பு:

a. நீங்கள் திட்டமிட்டபடி மருத்துவமனைக்கு வரவும் மற்றும் வழிமுறைகளை கூறியபடி கடைப்பிடிக்கவேண்டும்.
b. சோதனை மருந்துகளை கூறியபடி உட்கொள்ளவேண்டும்.
c. உடலில் - மனதில் நடக்கும் மாற்றங்களை, பக்க விளைவுகளை தெரிவிக்க வேண்டும்.
d. வழக்கமாக அளிக்கப்படும் மருந்துகளை எடுத்துக்கொள்ள வேண்டும்.
f. வேறு எனனென்ன மருந்துகளை எடுத்தக்கொண்டீர்கள் என்பதனை ஆராய்ச்சி மருத்துவரிடம் தெரிவிக்க வேண்டும்.

8. உங்கள் உரிமை:

a. எந்த நேரத்திலும் ஆராய்ச்சியில் இருந்து விலகிக்கொள்ள உங்களுக்கு உரிமையுண்டு.
b. வழக்கமான காசநோய் மருந்துகள் கிடைப்பதற்கு உங்களுக்கு உரிமையுண்டு.
c. இந்த சோதனை ஆராய்ச்சி எப்படி வேலை செய்கிறது என்று அறிந்து கொள்ள உங்களுக்கு உரிமையுண்டு.
e. இந்த சோதனை ஆராய்ச்சியினை பற்றி கேள்வி எழுப்ப உங்களுக்கு உரிமையுண்டு.

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

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9. யார் இந்த ஆராய்ச்சியில் பங்கு கொள்ள முடியும்?

1. புதியதாக சளியில் TB கிருமி கண்டறியப்பட்டு இருக்க வேண்டும்.
2. உங்கள் வயது 18ற்கு மேல் 75க்குள் இருக்க வேண்டும்.
3. காசநோய் தாக்கியுள்ள HIV நோயாளிகள் தங்களின் CD4 எண்ணிக்கை '50'ற்கு மேல் இருக்கவேண்டும்.
4. இரத்தத்தில் இதர சோதனை மூலம் நீங்கள் பங்கு கொள்வதை உறுதிபடுத்துகிறோம்.

10. ஆபத்து?

வைட்டமின் D தற்காலிகமாக கால்சியத்தின் அளவை உயர்த்தும். ஒரு வேளை கால்சியத்தின் அளவு உயர்ந்தால் வைட்டமின் D தற்காலிகமாக நிறுத்தப்படும். அதிக கால்சியத்தினால் சுகவீனம் ஏற்பட்டால் மருத்துவ உதவி அளிக்கப்படும்.

11. எதிர்பார்க்கப்படும் பலன்:

வைட்டமின் D காசநோய் சிகிச்சையின் கால அளவை குறைக்கும் என்று எதிர்பார்க்கப்படுகிறது. ஆனால் எங்களால் ஆராய்ச்சியின் முடிவில் மட்டுமே அதனை அறிந்து கொள்ள முடியும்.

12. கால அளவு மற்றும் மொத்த நோயாளிகள் அளவு:

இந்த சோதனை ஆராய்ச்சி 450 காசநோயாளிகளை 6 மாத கால அளவில் பங்கு கொள்ளச் செய்து சோதனை மேற்கொள்ளப்படும்.

உட்பிரிவு ஆராய்ச்சி பற்றிய தகவல் படிவம் (உங்கள் விருப்பம்)

நீங்கள் விரும்பினால் இந்த உட்பிரிவு ஆராய்ச்சியிலும் பங்கு கொள்ளலாம். அல்லது முக்கிய ஆராய்ச்சியில் மட்டும் பங்கு கொள்ளலாம். இந்த ஆராய்ச்சி வைட்டமின் D மரபியல் பரிசோதனை பற்றியதாகும். இதற்கு நீங்கள் 5 மி.லி. இரத்தம் மட்டுமே கொடுக்க நேரிடும். இந்த இரத்தம் ஆராய்ச்சி கூடத்திற்கு உங்கள் ஆராய்ச்சி எண் மட்டுமே கொடுக்கப்படும். உங்கள் பெயர் தெரிவிக்கமாட்டோம்.

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

மத்தாய் D, டேலி P, மார்டினியு A, ஜான் K.R, வீத் R, மைக்கேல் J, ஸ்மைஜா M

இந்த ஆராய்ச்சியில் அளிக்கப்பட்ட இரத்தத்தை கொண்டு ஒரு நபருக்கு மரபியல்ரீதியாக காசநோய்க்கான காரணிகள் இருக்கின்றதா என்பதனை பரிசோதிப்போம். இதனால் ஒரு நபருக்கு காசநோய் வருமா, வராதா என்பதனையும் அறிந்து கொள்ள உள்ளோம். இதனை சிலசமயம் 'மரபணு காரணிகள்' அல்லது 'உயிர் காரணிகள்' என்று அழைக்கப்படும்.

13. உங்களுக்கு இதில் பங்கு கொள்ள பணம் அளிக்கப்படுமா?

இந்த ஆராய்ச்சியில் வந்து செல்வதற்கான போக்குவரத்து செலவு ஒவ்வொருதடவை வரும்போதும் அளிக்கப்படும் (ரூ.50)

14. ஆய்வு இரகசியம்:

உங்களுடைய மருத்துவ தகவல்கள் இரகசியமாக இருக்கும். யாருடனும் பகிர்ந்து கொள்ள மாட்டோம்.

15. இந்த சோதனை ஆய்வுக்காக சேகரிக்கப்பட்ட தகவல்கள் எவ்வாறு பயன்படுத்தப்படும்?

இந்த ஆராய்ச்சியின் முடிவுகள் மருத்துவ புத்தகங்களில் வெளியிடப்படும். இந்த தகவல்கள் வெளியிடப்பட்டாலும் தன் நபரின் பெயர் இடம்மாறாது. நீங்கள் விலகினாலும் இந்த ஆராய்ச்சியின் தகவல்கள் எங்களுக்கு சேரும்.

16. யார் இந்த ஆராய்ச்சிக்கு அங்கீகாரம் அளித்தது?

இது மனிதர்களிடையே நடைபெறுகின்ற ஆய்வு என்பதால் சி.எம்.சி. நீதிநெறி குழுவின் அங்கிகாரம் பெற்று நடத்தப்படுகின்றது.

17. இந்த ஆராய்ச்சியில் அறிந்து கொள்ளப்பட்ட தகவல்கள் எதற்கு உபயோகப்படும்?

இந்த ஆராய்ச்சியின் முடிவு இந்தியாவில் உள்ள மற்ற காசநோயாளிகளுக்கு உபயோகமாக இருக்கும்.

Capital Health

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம்

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

மத்தாய் D, டேலி P, மார்டினியு A, ஜான் K.R, வீத் R, மைக்கேல் J, ஸ்மைஜா M

18. **தொடர்பு முகவரி:**
பங்கு கொள்கின்ற உங்களுக்கு பாதுகாப்பீலோ, உரிமையிலோ சந்தேகமிருப்பின் தயவுகூர்ந்து, கீழ்காணும் சோதனை ஆராய்ச்சி மருத்துவரை அணுகவும்.

முதன்மை ஆராய்ச்சியாளர்:

Dr. திலீப் மத்தாய்
ஐடிடிஆர்சி,
5வது மேல்மாடி (ஸ்டேட் பாங்க் ஆப் இந்தியா மேல்)
கிருத்துவ மருத்துவ கல்லூரி மருத்துவமனை
வேலூர் - 632 004, இந்தியா
தொலைபேசி எண்: 0416-228 2804.

ஆராய்ச்சி ஒருங்கினைப்பாளர்:

Mr. விஜயகுமார்
ஐடிடிஆர்சி,
கிறிஸ்துவ மருத்துவ கல்லூரி மருத்துவமனை
வேலூர் - 632 004
அலைபேசி எண்: 9366111098

Capital Health

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம்

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

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பங்கு கொள்பவரின் கையொப்பம்	பங்கு கொள்பவரின் பெயர்	பிறந்த தேதி
ஆராய்ச்சி ஒருங்கிணைப்பாளர்		சோதனை எண்

ஆராய்ச்சியின் பெயர் - வைட்டமின் D சோதனை

ஒப்பந்த படிவம்

இந்த மருத்துவ சோதனையில் பங்கு கொள்வதற்கான ஒப்பந்தம்

1. நான் 5 செப்டம்பர் 2009 தேதியிட்ட ஆராய்ச்சியின் தகவல்களை படித்து புரிந்து கொண்டு சந்தேகங்களை தீர்த்து கொள்ள வாய்ப்பு பெற்றேன். இந்த ஆராய்ச்சியை நான் பேசுகின்ற மொழியில் எனக்கு விளக்கினார்கள்.
2. நான் தான் ஆர்வமாக இந்த ஆராய்ச்சியில் பங்கு கொள்கின்றேன். எந்த நேரத்திலும் நான் இதில் இருந்து காரணம் இல்லாமல் என்னுடைய மருத்துவ சிகிச்சை பாதிக்காமலும் மற்றும் என்னுடைய உரிமை பாதிக்காமலம் நான் விலகிக் கொள்ளலாம்.
3. நான் என்னுடைய மருத்துவ குறிப்பேடுகளை சோதனை ஆய்வாளர்களும், சி.எம்.சி. நீதிநெறி குழு ஆகியோர் பார்க்க அனுமதி அளிக்கிறேன். இந்த ஆராய்ச்சியில் இருந்து நான் வெளியேறினாலும் இவை பொருந்தும்.
4. எச்.ஐ.வி. பரிசோதனைக்கு நான் சம்மதிக்கிறேன்.
5. சிலருக்கு மட்டும் வைட்டமின் D வழங்கப்படும். எனினும் சிலருக்கு வழங்கப்படாது என்றும் அறிந்திருக்கிறேன்.
6. இந்த ஆராய்ச்சியில் இருந்து வெளிவரும் தகவல்களை பயன்படுத்து கொள்ள சம்மதம் தெரிவிக்கிறேன்.
7. நான் மேற்கூறிய சோதனை ஆராய்ச்சியில் பங்கு கொள்ள சம்மதம் தெரிவிக்கிறேன்.

Capital Health

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம்

காசநோய் சிகிச்சையில் வைட்டமின் D ஒரு கூடுதல் மருந்தாக பயன்படுத்தி மருத்துவ சோதனை மூலம் அதனுடைய விளைவுகளை ஆராய்தல்.

மத்தாய் D, டேலி P, மார்டினியு A, ஜான் K.R, வீத் R, மைக்கேல் J, ஸ்மைஜா M

உட்பிரிவு ஆராய்ச்சி - வைட்டமின் D மரபணு பரிசோதனை		
8. ❑ நான் இந்த உட்பிரிவு ஆராய்ச்சியான வைட்டமின் D மரபணு பரிசோதனையில் பங்கு கொள்ள சம்மதிக்கிறேன் (இரத்தம் கொடுத்தல்). ❑ நான் இந்த வைட்டமின் D மரபணு பரிசோதனையில் (இரத்தம் கொடுத்தல்) பங்கு கொள்ளமாட்டேன். ❑ வைட்டமின் D மரபனு பரிசோதனையில் பங்கு கொண்டு என்னுடைய இரத்தம் 10 ஆண்டுகள் வரை பதப்படுத்தப்பட்டு எதிர்கால ஆராய்ச்சிக்கு உபயோகப்படுத்திக்கொள்ள சம்மதிக்கிறேன்.		
பங்கு கொள்பவரின் பெயர்	கையொப்பம் / கை முத்திரை	
பங்கு கொள்பவரின் கையொப்பம்		தேதி:
சாட்சியின் பெயர்		
சாட்சியின் கையொப்பம்		தேதி
ஆராய்ச்சியாளர் பெயர்		
ஆராய்ச்சியாளர் கையொப்பம்		தேதி

Appendix 3
Christian Medical College Ethics Approval

CHRISTIAN MEDICAL COLLEGE
VELLORE - 632 002, INDIA.
INSTITUTIONAL REVIEW BOARD (IRB)

Dr. George Thomas, D.Orth
Editor Indian Journal of Medical Ethics
Chairman, Ethics Committee

Dr. Shuba Kumar, PhD
Deputy Chairman, Ethics Committee

Dr. L. Jeyaseelan, MSc,PhD
Secretary, IRB

Dr. George Mathew, MS,MD,FCAMS
Chairman, Research Committee &
Principal

Dr. Gagandeep Kang, MD,PhD,FRCPath
Deputy Chairman, IRB &
Additional Vice Principal (Research)

November 20, 2009

Dr. Dilip Mathai
Professor
Department of IDTRC
Christian Medical College
Vellore 632 004

Sub: EXTERNAL Research grant project NEW PROPOSAL (Dalhousie University)
A double blind, randomized, parallel, placebo control design study to determine the effect of addition of vitamin D to conventional anti TB therapy.
Dr. Dilip Mathai, Professor & Head, IDTRC, Dr. Peter Daley, Lecturer, IDTRC, Dr. K.R. John, Community Health , Dr. D.J. Christopher, Pulmonary Medicine, Dr. L. Jeyaseelan, Biostatistics, Dr. Joy Sarojini Michael, Clinical Microbiology.

Ref: IRB Min. No. 6832 dt. 10.06.2009

Dear Dr. Mathai,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A double blind, randomized, parallel, placebo control design study to determine the effect of addition of vitamin D to conventional anti TB therapy" on June 10, 2009.

The Committees reviewed the following documents:

1. Format for application to IRB submission.
2. Study Protocol version 3 dated 30 July 2008
3. Memorandum of Agreement between Christian Medical College and Dalhousie University, Halifax Canada.
4. Patient Information Sheet and Consent Form (English & Tamil)
5. Investigator Brochure
6. Advertisement for Patient recruitment
7. Cvs of investigator Drs. Dilip Mathai, Joy Sarojini Michael and K.R. John.
8. A CD containing documents 1-7.

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788
e-mail : research@cmcvellore.ac.in

CHRISTIAN MEDICAL COLLEGE
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Chairman, Research Committee &
Principal

Dr. Gagandeep Kang, MD,PhD,FRCPath
Deputy Chairman, IRB &
Additional Vice Principal (Research)

The following Ethics Committee members were present at the meeting held on June 10, 2009 at 10:00 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. George Thomas	MBBS, D.Ortho	Chairperson (IRB) & Orthopaedic Surgeon, St. Isabel Hospital, Chennai & Editor, Indian Journal of Medical Ethics	Non-CMC Staff.
Dr. Shuba Kumar	MA, MSc, Ph.D.	Dy. Chairperson (IRB) & Social Scientist, SAMRATH, Chennai.	Non-CMC Staff.
Dr. Thambu David (on behalf of Dr. Lionel Gnanaraj)	MBBS, MS, M.Ch. (Urol)	Medical Superintendent, CMC.	
Mrs. Shirley David (on behalf of Mrs. Bharathy Jacob)	M.Sc. (Nursing), RN, RM	Dean, College of Nursing, CMC.	
Rev. Dr. T. Arul Dhas	M.Sc., BD, Ph.D.	Chaplain, CMC	
Mr. Harikrishnan	BL.	Lawyer	Non-CMC staff.
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Dr. Binu Susan Mathew(On behalf of Dr. Denny Fleming)	MBBS, MD	Professor, Pharmacology Dept. CMC.	
Mrs. Radha Anil	M.Sc.	Correspondent, Apple Kids, Sathuvachari, Vellore.	Non-CMC staff.
Rev. Dr.S.G.Immanuel	PhD, MDIV	Pastor, Vellore	Non-CMC-Staff
Mrs. S. Pattabhiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC-Staff
Dr. Srinivas Babu	MSc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC	
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

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e-mail : research@cmcvellore.ac.in

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Dr. George Mathew, MS,MD,FCAMS
Chairman, Research Committee &
Principal

Dr. Gagandeep Kang, MD,PhD,FRCPath
Deputy Chairman, IRB &
Additional Vice Principal (Research)

Administrative committee's approval is to be obtained for opening the account-head, employing any personnel or purchasing any equipment. The investigator also needs to present to Administrative Committee, the terms and condition of the Funding agency for approval.

Yours sincerely,

L. Jeyaseelan

Dr. L. Jeyaseelan Ph.D.
Secretary, Institutional Review Board

Secretary
Institutional Review Board
(Ethics Committee)
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788
e-mail : research@cmcvellore.ac.in

Appendix 4
Dalhousie Ethics Approval

Capital Health

Research Ethics Board
5790 University Avenue
Room 118, Centre for Clinical Research
Halifax, NS B3H 1V7
Phone: 473-5726
Fax: 473-5620

May 16, 2007

Dr. Peter Daley
Dalhousie University
Department of Medicine
Division of Infectious Diseases
Room 5014, Dickson Building

ATTENTION: ***Ms. Heather Haldane***

Dear Dr. Daley: ***Final Approval Letter***
(April 16, 2007 - April 16, 2008)

RE: ***A Double Blind randiomized parallel, placebo control design study to determine the effect of the addition of Vitamin D to conventional anti TB therapy on time to smear conversion.*** ***REB FILE #: CDHA-RS/2007-109***

Thank you for responding to the concerns of the Research Ethics Board and for forwarding a copy of the clarifications requested regarding this protocol. Documents available at the time of review included:

Documents resubmitted for review included:

- Email – From: Peter Daley – Subject: response to Dal ethics review (dated 2007-05-15 9:48 am)
- Cover Letter (dated May 15, 2007)
- Christian Medical College (CMC) – Institutional Review Board (Ethics Committee) – Approval Letter (dated 21st December 2005)
- Revised Ethics Approval Submission Form (not signed or dated)
- Copy of Consent To Take Part In A Clinical Trial – Includes the following: Supplemental Brochure for Research Involving Genetics: "Informed Consent: Taking Part in Genetic Research" (no version number or date)

I have reviewed your amended protocol on behalf of the Board and note that all requested changes have been incorporated. I am now pleased to confirm the Board's full approval for this research submission at the Capital District Health Authority. This includes approval for:

- Cover Letter (dated April 05, 2007)
- Researcher's Checklist For Submissions (signed and dated by Dr. Peter Daley on 2007/04/05)
- Letter of Support (signed and dated by Dr. B. Lynn Johnston on 2007/03/01)
- Dalhousie University - Department of Medicine Research Committee – Funding Approval letter (dated March 30, 2007)

- Protocol – ID TB-Vitamin D – Includes the following: Appendix 1. Visit Schedule (Version date 10th August, 2006)
- Vitamin D – General Monograph – Pharmacists Association – Copyright © 2002 Canadian Pharmacists Association.
- Email – From: Peter Daley – Subject: response to Dal ethics review (dated 2007-05-15 9:48 am)
- Cover Letter (dated May 15, 2007)
- Christian Medical College (CMC) – Institutional Review Board (Ethics Committee) – Approval Letter (dated 21st December 2005)
- Revised Ethics Approval Submission Form (not signed or dated)

The Research Ethics Board for the Capital District Health Authority complies with the Tri-Council Policy Statement, the ICH Harmonized Tripartite Guidelines: Good Clinical Practice, and Division 5 of the Food and Drug Regulations, Title 21 and 45 of the Code of Federal Regulations of the United States.

The Board would remind you that, in accordance with ethical guidelines, once a study has been approved, the investigator assumes responsibility to submit an annual progress report 30 days prior to the anniversary date *(April 16, 2007 - April 16, 2008)*.

If you do not have your Annual Approval approved prior to the Anniversary date you are working outside the approval of the Capital Health Research Ethics Board and the study is subject to suspension.

The Board should also be made aware of any:

- ❖ Serious adverse events.
- ❖ Changes to the initial submission or closure of the study within 90 days of the event.
- ❖ Should any material be designed for advertisement or publication with a view to attracting patients, the Research Ethics Board should review it first.
- ❖ Approval studies may be audited, should your research be selected for audit, the Board will advise you and indicate any other requests at that time.

This letter is in lieu of the Health Canada Research Ethics Board Attestation Form.

For future correspondence concerning this project, you must refer to the Research Ethics Board assigned file number (CDHA-RS/2007-109).

Yours very truly,
Research Ethics Board

Chris MacKnight, MD, FRCPC
Co-Chair

/ac

Capital Health

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Visit 1 Day 0

Appendix 5
Case Report Form Clinical

PART I: **IDENTIFICATION FORM**

Name

Hospital No:

Contact Information:

Father's name:

Temporary address:

Pin Code:

Permanent address:

Pin Code:

Telephone Number

Mobile Number

Signature of clinical research officer ----------

Capital Health

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐☐☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date Month year

Email ID

Mobile No of Family Member: ☐☐☐☐☐☐☐☐☐☐ Relationship: _____

PART 2:SOCIO-DEMOGRAPHIC DATA

Date of Birth: ☐☐ ☐☐ ☐☐☐☐
Date Month Year

Age: ☐☐ years

Sex: Male ☐ Female ☐

Height: ☐☐☐ cms

Weight: ☐☐☐ Kg

Educational status: What is the highest level of education you have **completed**?

1☐ Illiterate
2☐ Primary school (class I-V)
3☐ High school (class VI-IX)
4☐ Class X completed
5☐ Class X
6☐ Diploma/Bachelor's degree
7☐ Master's degree
8☐ Professional or doctoral degree
9☐ Other: _____

Occupation:

1☐ Professional (eg. Lawyer, accountant, nurse)
2☐ Skilled worker (eg. Carpenter, computer operator)
3☐ Clerical/Shop Owner/ Farm Owner
4☐ Unskilled worker/manual labor (eg. Driver, sweeper)
5☐ Retired/pensioner
6☐ Unemployed
7☐ Other: _____
9☐ do not want to respond

Work Address:

Capital Health

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Average monthly income of entire family

1☐ < Rs.5000
2☐ Rs 5000 – 10,000
3☐ Rs 10,001 – 20, 000
4☐ Rs 20, 001 – 30,000
5☐ > Rs 30,000
9☐ do not want to respond

Visit 1 Day 0

INCLUSION CRITERIA

S.No	Criteria	Yes	N0
1	The subject or parent/legal guardian if applicable has given written informed, dated consent		
2.	Are 1 or more current sputum smears Positive? (1+ or greater)		
3.	No Previous antituberculosis therapy		
4	Is the patient between 18 and 75 years of age?		
5	Patient with firm home address and are willing and able to comply with the study protocol		

N.B: A 'no' response for questions 1 to 3 will result in exclusion from the study.

EXCLUSION CRITERIA

S.No	Criteria	Yes	No
1.	*Does the patient have a positive pregnancy test or is she currently lactating?		
2.	Is the patient HIV positive?		
3.	Does the patient have only extra pulmonary Tuberculosis?		
4.	Is the Patient receiving steroids or cytotoxic drugs?		
5.	Is the patient is in post transplant condition or having metastatic malignancy?		

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

6.	Is there any clinical or laboratory [i.e. INR or serum creatinine two times the upper limit of normal range] evidence of hepatic or renal disease?		
7.	Does the patient have active diarrhea with steatorrhea for more than 15 days in the last 30 days?		
8.	Is the patient expected to die within the period of ATT?		

*Women of Child Bearing Potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization or is not post-menopausal. Even women who are using oral, implanted or inject able Contraceptive hormones or mechanical products (intrauterine devices, barrier methods) to Prevent pregnancy, who are practicing abstinence, or who have a partner that is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

N.B. A 'yes' response for questions 1 to 8 will result in exclusion of the study.

VISIT 1 DAY 0

Copy of the consent form given to the subject: YES ☐ NO ☐

If no, specify why ----------

Child bearing potential

a. If the subject is female, is she of child bearing potential?

Yes ☐

No ☐

b. If yes, pregnancy test outcome

Positive ☐

Negative ☐

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STUDY NUMBER ☐☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

CONTACT DETAILS OF DOTS PROVIDER CLOSE TO PATIENT ACCESS

NAME OF THE DOTS PROVIDER:

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

ADDRESS:

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

MOBILE NO:

☐☐☐☐☐☐☐☐☐☐

LANDLINE NO:

☐☐☐☐☐☐☐☐☐☐☐

Study Specimen Collection ON SCREENING VISIT 1

1. Two Spot sputum specimen collected visit day 1 (minimum 4 ml, saliva to be rejected) in sterile labeled screw top container for Smear, Culture & Drug sensitivity Test: delivery date:

dd☐☐/mm☐☐/yy☐☐ Check if induced ☐

2. Urine sample from women collected and sent to Clinical Pathology lab delivary date:

dd☐☐/mm☐☐/yy☐☐

3.Whole blood for Serum creatinine, albumin, SGPT,

4. Whole Blood for HIV collected in red capped tube labeled and sent ICTC lab.
Delivery date:

dd☐☐/mm☐☐/yy☐☐

calcium, Vitamin D (25 OH), collected in a labeled plain tube and sent to Clinical Biochemistry Lab).

Delivery date:

dd☐☐/mm☐☐/yy☐☐

Capital Health

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date Month year

VISIT I: ICTC

Have you ever had a HIV test before? 1☐ yes 2☐ no

If tested, date of most recent HIV test: mm☐☐/yy☐☐

Result: 1☐ positive 2☐ negative 3☐ don't want to answer

Where was the previous HIV test performed? 1☐CMC- Virology 2☐CMC - VCTC 3☐CHAD 4☐Other, Specify

_____

If the patient has a written result of HIV testing (negative within the last one month, positive ever), repeat ICTC can be avoided. A photocopy of the HIV result must be attached to the CRF. The study prefers ICTC testing since the cost is lower and counseling is included.

If HIV positive, is patient on ART? 1☐ yes 2☐ no

Most recent CD4 count and date _____ Previous CD4 and date _____

Viral load if available and date _____ Previous viral load and date _____

Current ART treatment (drug, dose, date of initiation)

_____

_____

_____

_____

Previous ART treatment (drug, dose, date of initiation)

_____

_____

_____

_____

2.ICTC result 1☐ positive 2☐ negative

Date of ICTC:
dd☐☐/mm☐☐/yy☐☐

If ICTC result is not available, explain why_____

_____

ICTC counselor initials

_____

If HIV positive, send and record current CD4 Count _____ (study will pay for this)

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

If CD4 available within the last 3 months, it can be used instead of sending a new test.

VISIT 1: Radiology

1. Previous CXR available?
   1☐ yes
   2☐ no
   9☐ unknown

Previous CXR result is acceptable, **only** if it was requested as part of the workup of the current illness. Radiologist's interpretation is required for the study.

2. Previous CXR Date:
   dd☐☐/mm☐☐/yy☐☐

3. Previous CXR Result:
   1☐ normal
   2☐ cavitary
   3☐ non-cavitary: consistent w/ TB
   4☐ non-cavitary: NOT consistent w/TB
   5☐ needs further review
   9☐ unknown

Record exact radiologist's interpretation (or attach photocopy)

_____
_____
_____
_____

4. Study CXR Date:
   dd☐☐/mm☐☐/yy☐☐

5. Study CXR Result:
   1☐ normal
   2☐ cavitary
   3☐ non-cavitary: consistent w/ TB
   4☐ non-cavitary: NOT consistent w/TB
   5☐ needs further review
   9☐ unknown

Record exact radiologist's interpretation (or attach photocopy)

_____
_____
_____
_____

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Visit 1 Day 0

SCREENING LABORATORY RESULT ELIGIBILITY CHECKLIST

Date form filled out ☐☐ ☐☐ ☐☐☐☐

Date *Month* *Year*

Date Blood Drawn ☐☐ ☐☐ ☐☐☐☐

Date *Month* *Year*

TEST	RESULT	LAB RESULT ELIGIBILITY	MEETS ELIGIBILITY CRITERIA
Serum Creatinine		<1.5 mg/dl	YES ☐ NO ☐
Serum Calcium		mg/dl	
Serum Albumin		g/dl	
Serum SGPT		IU/L	
Corrected Serum Calcium		For every↓ in albumin of	

Signature of clinical research officer ----------↑

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

		1g/dl,calcium by 0.7 mg/dl	
Urine Pregnancy Test		Negative	YES ☐ NO ☐
HIV antibody		Negative	Yes No
Vitamin D – 25 OH Vitamin D3		ng/ml	

VISIT 1 DAY 0

Karnofsky Performance Index Tool

Functional Definition	Rating (%)	Criteria
Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance frequent medical care
Unable to care for self;	40	Disabled; requires special care and

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

requires equivalent of institutional or hospital care; disease may be progressing rapidly		assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Karnofsky Performance Index of the Subject: ☐☐☐

VISIT 1 DAY 0

SIGNIFICANT MEDICAL HISTORY

PRESENT PULMONARY TUBERCULOSIS

Date of Diagnosis	☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*

Sputum Smear done at trial site:

Smear Results	**Date**	**Result**	**Reporting Lab**
Smear 1	☐☐ ☐☐ ☐☐☐☐		

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date Month year

	Date	*Month*	*Year*		

Sputum Culture Results	**Method**	**Date**	**Susceptibility**	**Reporting Lab**
Positive Yes ☐ No ☐	1. --------- 2. ---------	☐☐ ☐☐ ☐☐☐☐ *Date Month Year* ☐☐ ☐☐ ☐☐☐☐ *Date Month Year*	Drug | Sus INH | RIF |	

PRESENT PULMONARY TUBERCULOSIS (*contd*)

VISIT 1 DAY 0

Smear Results	**Date**	**Result**	**Reporting Lab & Location**
Smear 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
	☐☐ ☐☐ ☐☐☐☐		

Signature of clinical research officer ----------

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date Month year

Smear 2	*Date Month Year*		

Sputum smears done outside trial site:

Smear 3	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		

TREATMENT:

CATEGORY	**TREATMENT CHART**
CAT I ☐ CAT II ☐ CAT III ☐	

DRUG	**DOSE**	**INTERVAL**	**DURATION**	**DOSES MISSED**

VISIT 1 DAY 0

Category of Pulmonary Tuberculosis:

SNo	Category
1	New ☐

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

2	Transferred in ☐
3	Relapse ☐
4	Failure ☐
5	Treatment after default ☐
6	Others(Specify) ☐ ----------

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date Month year

VISIT 1 DAY 0

PREVIOUS TUBERCULOSIS:

Status	Pulmonary ☐ Extra pulmonary ☐ No ☐
Date of Diagnosis	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*

How Diagnosed?

Smear Results	**Date**	**Result**	**Reporting Lab**
Smear 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 2	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 3	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		

Sputum Culture Results	**Method**	**Date**	**Susceptibility**	**Reporting Lab**
Positive Yes ☐ No ☐	1. ---------- 2.	☐☐ ☐☐ ☐☐☐☐ *Date Month Year* ☐☐ ☐☐ ☐☐☐☐	Drug | Sus INH | RIF |	

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date Month year

	---	*Date Month Year*		

VISIT 1 DAY 0

PREVIOUS TUBERCULOSIS {*contd*}

CHEST X RAY INTERPRETATION:

TEST	**DATE**	**REPORT**
CXR 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*	
CXR 2	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*	

TREATMENT:

CATEGORY	**TREATMENT CHART**
CAT I ☐ CAT II ☐ CAT III ☐	**Date of Treatment:** ☐☐ ☐☐ ☐☐☐☐ To ☐☐ ☐☐ ☐☐☐☐ *Date Month Year Date Month Year*

DRUG	**DOSE**	**INTERVAL**	**DURATION**	**DOSES MISSED**

STUDY NUMBER ☐☐☐ SITE NUMBER ☐☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date *Month* *year*

RNTCP Outcome?	Cured ☐ Defaulted ☐	Completed Treatment ☐ Transferred out ☐		Failure ☐	

PREVIOUS PULMONARY TUBERCULOSIS (Contd)

Sputum smears done outside trial site:

Smear Results	**Date**	**Result**	**Reporting Lab & Location**
Smear 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 2	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 3	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

VISIT 1 DAY 0

HISTORY OF RESPIRATORY DISEASE:

DISEASE	PAST	PRESENT	PERTINANT DETAILS INCLUDE SURGICAL PROCEDURE AND CURRENT TREATMENT
Disease 1: ----------	☐	☐	
Disease 2: ----------	☐	☐	

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Disease 3: ----------	☐	☐	

VISIT 1 DAY 0

HISTORY OF CARDIOVASCULAR DISEASE

DISEASE	PAST	PRESENT	PERTINANT DETAILS INCLUDE SURGICAL PROCEDURE AND CURRENT TREATMENT
Disease 1: ----------	☐	☐	
	☐	☐	

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Disease 2: ----------			
Disease 3: ----------	☐	☐	

VISIT 1 DAY 0

HISTORY OF GASTROINTESTINAL OR LIVER DISEASE

DISEASE	**PAST**	**PRESENT**	**PERTINANT DETAILS INCLUDE SURGICAL PROCEDURE AND CURRENT TREATMENT**

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Disease 1: ----------	☐	☐	
Disease 2: ----------	☐	☐	
Disease 3: ----------	☐	☐	

VISIT 1 DAY 0

HISTORY OF ENDOCRINE DISORDERS

DISEASE	PAST	PRESENT	PERTINANT DETAILS INCLUDE SURGICAL

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

			PROCEDURE AND CURRENT TREATMENT
Disease 1: ----------	☐	☐	
Disease 2: ----------	☐	☐	
Disease 3: ----------	☐	☐	

VISIT 1 DAY 0

HISTORY OF HAEMATOLOGICAL DISEASE

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

DISEASE	PAST	PRESENT	PERTINANT DETAILS INCLUDE SURGICAL PROCEDURE AND CURRENT TREATMENT
Disease 1: ----------	☐	☐	
Disease 2: ----------	☐	☐	
Disease 3: ----------	☐	☐	

VISIT 1 DAY 0

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date *Month* *year*

HISTORY OF NEUROLOGICAL DISEASE

DISEASE	PAST	PRESENT	PERTINANT DETAILS INCLUDE SURGICAL PROCEDURE AND CURRENT TREATMENT
Disease 1: ----------	☐	☐	
Disease 2: ----------	☐	☐	
Disease 3: ----------	☐	☐	

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

VISIT 1 DAY 0

HISTORY OF ALLERGY

ALLERGY TO	**DATE OF REACTION**	**TYPE OF REACTION**
DRUG 1 _____	☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*	
DRUG 2 _____	☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*	
DRUG 3 _____	☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*	
DRUG 4 _____	☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*	
DRUG 5 _____	☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*	

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Date *Month* *year*

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

VISIT 1 DAY 0

Current Drug Sheet

	Generic Name of the Drug	Dose/Route/ Interval	Start Date *Date* *Month* *Year*
1			☐☐ ☐☐ ☐☐☐☐
2			☐☐ ☐☐ ☐☐☐☐
3			☐☐ ☐☐ ☐☐☐☐
4			☐☐ ☐☐ ☐☐☐☐
5			☐☐ ☐☐ ☐☐☐☐
6			☐☐ ☐☐ ☐☐☐☐
7			☐☐ ☐☐ ☐☐☐☐
8			☐☐ ☐☐ ☐☐☐☐
9			☐☐ ☐☐ ☐☐☐☐
			☐☐ ☐☐ ☐☐☐☐

Signature of clinical research officer ----------

Capital Health

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

10			

Capital Health

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

VISIT 1 DAY 0

HABITS

TYPE OF HABITS	PAST	PRESENT	NO	DETAILS
SMOKING	☐	☐	☐	QUESTION / ANSWER: Cigarettes/day; Year Started; Year Stopped; Years smoking
BETEL NUTS	☐	☐	☐	QUESTION / ANSWER: Quids/day; Year Started; Year Stopped; Years Chewing
ALCOHOL	☐	☐	☐	QUESTION / ANSWER: Ounces/day; Year Started; Year Stopped; Years Drinking

If Included, Patient randomized to receive treatment bottle number: ◯

Signature of Trial Coordinator offer visit 1 Signature of Investigator offer visit 1

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

VISIT 2 Day 2

Informed Consent signed or thumb printed and stored at IDTRC in locked cupboard

[1] Yes ☐

[2] No ☐

ATT:

First dose of ATT provided as required?

[1] Yes ☐

[2] No ☐

If no, reason ----------

Study drug dose 1 given directly observed:

Yes ☐

No ☐

If no, reason ----------

Visit 3 Day 4

ATT:

ATT doses provided as required?

Signature of clinical research officer ----------

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Have there been any adverse events since last visit?

[1] Yes ☐

[2] No ☐

* If yes fill the details in adverse events report form

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Visit 6 Day 16

ATT:

ATT doses provided as required?

[1] Yes ☐

[2] No ☐

If no, how many doses missed? ☐

Reason: ----------

Trial drug:

Second dose of trial drug provided directly observed?

[1] Yes ☐

[2] No ☐

If no,

Reason: ----------

Adverse events:

Have there been any adverse events since last visit?

[1] Yes * ☐

[2] No ☐

*if yes, fill the details in adverse event form

1. Spot sputum specimen 1 collected Visit 6 (minimum 4 ml, saliva to be rejected) if patient can produce, in sterile labeled screw top container for culture delivery date:

dd☐☐/mm☐☐/yy☐☐ Check if induced ☐

☐

Signature of clinical research officer ----------☐

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Signature----------

VISIT 7 Day 30

ATT:

ATT doses provided as required?

[1] Yes ☐

[2] No ☐

If no, how many doses missed? ☐

Reason: ----------

Trial drug:

Third dose of trial drug provided directly observed?

[1] Yes ☐

[2] No ☐

If no,
Reason: ----------

Adverse events:

Have there been any adverse events since last visit?

[1] Yes * ☐

[2] No ☐

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

* If yes fill the details in adverse events report form

2. Spot sputum specimen 1 collected Visit 7 (minimum 4 ml, saliva to be rejected) if patient can produce, in sterile labeled screw top container for Culture & Smear delivery date:

dd☐☐/mm☐☐/yy☐☐ Check if induced ☐

Blood for calcium testing collected:

Yes ☐

No ☐

If no, reason ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Visit 8 Day 44

ATT:

ATT doses provided as required?

[1] Yes ☐

[2] No ☐

If no, how many doses missed? ☐

Reason: ----------

Trial drug:

Fourth dose of trial drug provided directly observed?

[1] Yes ☐

[2] No ☐

If no, how many doses missed? ☐

Reason: ----------

Adverse events:

Have there been any adverse events since last visit?

[1] Yes * ☐ [2] ☐

*if yes, fill the details in adverse event form

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

3. Spot sputum specimen 1 collected study visit 8 (minimum 4 ml, saliva to be rejected) if patient can produce, in sterile labeled screw top container for culture.delivery date:

dd☐☐/mm☐☐/yy☐☐ Check if induced ☐

Signature----------

Visit 9 Day 58 END OF INTENSIVE PHASE

ATT:

ATT doses provided as required?

[1] Yes ☐

[2] No ☐

If no, how many doses missed? ☐

Reason: ----------

ATT Compliance:

How many doses of ATT taken in the intensive phase ☐

How many doses of ATT missed in the intensive phase? ☐

Trial Drug compliance:

4 doses received ☐

If not, how many doses missed? ☐ **Doses Missed** **Reason**

Signature of clinical research officer ----------

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Dose1 [day 2] ---- ☐ ----------

Dose 2 [day16] --- ☐ ----------

Dose 3 [day 30] -- ☐ ----------

Dose 4 [day 44] -- ☐ ----------

Signature of clinical research officer ----------

STUDY NUMBER ☐☐☐ SITE NUMBER ☐☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

VISIT 9 DAY 58

Adverse events:

Have there been any adverse events since last visit?

[1] Yes * ☐

[2] No ☐

*if yes, fill the details in adverse event form

4. Spot sputum specimen 1 collected study visit 9 (minimum 4 ml, saliva to be rejected) if patient can produce, in sterile labeled screw top container for culture (to be repeated only if last culture positive) delivery date:

dd☐☐/mm☐☐/yy☐☐ Check if induced ☐

Karnofsky Performance index of the subject:

☐☐☐ %

Weight of the Subject:

☐☐☐ Kg

Sputum smears done outside trial site(End of Intensive Phase)

Smear Results	**Date**	**Result**	**Reporting Lab & Location**
Smear 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 2	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
	☐☐ ☐☐ ☐☐☐☐		

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date Month year

Smear 3	*Date Month Year*		

Sputum smears done outside trial site (end of two months continuation period)

Smear Results	**Date**	**Result**	**Reporting Lab & Location**
Smear 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 2	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 3	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		

Sputum smears done outside trial site (end treatment period)

Smear Results	**Date**	**Result**	**Reporting Lab & Location**
Smear 1	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 2	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		
Smear 3	☐☐ ☐☐ ☐☐☐☐ *Date Month Year*		

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Concomitant drug sheet [Day 58]

SNo	Generic Name of the Drug	Dose/Route/ Interval	Start Date *Date* *Month* *Year*	On going
1			☐☐ ☐☐ ☐☐☐☐	☐
2			☐☐ ☐☐ ☐☐☐☐	☐
3			☐☐ ☐☐ ☐☐☐☐	☐
4			☐☐ ☐☐ ☐☐☐☐	☐
5			☐☐ ☐☐ ☐☐☐☐	☐
6			☐☐ ☐☐ ☐☐☐☐	☐
7			☐☐ ☐☐ ☐☐☐☐	☐

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

8				
9			☐☐ ☐☐ ☐☐☐☐	☐
10			☐☐ ☐☐ ☐☐☐☐	☐

VISIT 10 Day 182 FINAL VISIT

ATT:

Doses provided as required?

[1] Yes ☐ Weight ☐

[2] No ☐

If no, how many doses missed? ☐

Reason: ----------

Adverse events:

Have there been any adverse events since last visit?

[1] Yes * ☐

[2] No ☐

- If yes fill the details in adverse events report form
-

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

2. Spot or morning sputum specimen 1 collected on study visit 10 (minimum 4 ml, saliva to be rejected) if patient can produce, in nonsterile labeled screw top container for Culture delivery date:

dd☐☐/mm☐☐/yy☐☐ Check if induced ☐

•

VISIT 10 DAY 180

Blood sample collected for Vitamin D testing:

Yes ☐

No ☐

If no, reason----------

Outcome of RNTCP:

☐ Cured

☐ Default

☐ Failure

☐ Treatment completed

☐ Died

☐ Transferred Out

Signature of clinical research officer ----------

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Here are the RNTCP treatment outcome definitions:

Cured : Smear positive that becomes smear negative during last month of treatment and at least once prior.

Complete : Completed treatment but not cured or failed

Died : Any reason during treatment

Failed : Smear positive interrupted for two consecutive months or more

Transferred out: Transferred to a new reporting unit and outcome unknown.

Protocol violations

SNo	Date [dd/mm/yy]	Visit Number	Type of violation	Reason
	__ __/__ __ /__ __			
	__ __/__ __ /__ __			
	__ __/__ __ /__ __			
	__ __/__ __ /__ __			
	__ __/__ __ /__ __			

Vitamin D Randomized Controlled Trial Case Report Form Version 2 1st Nov 2009

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

	__ __/__ __/__ __			
	__ __/__ __/__ __			
	__ __/__ __/__ __			
	__ __/__ __/__ __			
	__ __/__ __/__ __			
	__ __/__ __/__ __			
	__ __/__ __/__ __			

HYPERCALCAEMIA REPORT

ADVERSE EVENT ☐

SERIOUS ADVERSE EVENT ☐
[Complete the SAE form]

Signature of clinical research officer ----------

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date Month year

Hypercalcemia : Symptomatic ☐ Asymptomatic ☐

Serum calcium >13.9mg/dl : Yes ☐ No ☐

Serum calcium 10.4 to 13.9mg/dl : Yes ☐ No ☐

SNo	SYMPTOMS OF HYPERCALCEMIA	DATE OF ONSET *Date Month Year*
1		☐☐ ☐☐ ☐☐☐☐
2		☐☐ ☐☐ ☐☐☐☐
3		☐☐ ☐☐ ☐☐☐☐
4		☐☐ ☐☐ ☐☐☐☐
5		☐☐ ☐☐ ☐☐☐☐

Tested as part of protocol ☐

Tested outside of protocol ☐

Severity Mild ☐ Moderate ☐ Severe ☐

Hypercalcemia report *{Contd}*

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

HYPERCALCEMIA TREATMENT SHEET

Specific treatment given: [1] Yes ☐

[2] No ☐

Hospital admission needed? [1] Yes ☐

[2] No ☐

If Yes, Date Admitted: ☐☐ ☐☐ ☐☐☐☐

Date Discharged : ☐☐ ☐☐ ☐☐☐☐

Out come of treatment [1] improved ☐

[2] Cured ☐

[3] Worsened ☐

Treatment details: ----------

----------,

Signature of the Physician treating.

Hypercalcemia report *{Contd}*

Study treatment consequence:

Signature of clinical research officer ----------

STUDY NUMBER ☐☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date *Month* *year*

Action:

No action ☐

Subject:

Withdrawn from the study ☐

Treatment given
[Specify in concomitant treatment sheet] ☐

Complete the following section at the time the event resolves or at the end of study, In the investigator's judgement, was the study treatment the most likely cause of the hypercalcaemia?

Yes ☐

No ☐

* If no what was the most likely cause of the hypercalcaemia

☐ [1] Disease under study

☐ [2] Other illness [specify]

_____

☐ [3] Concomitant treatment –Drug or Non drug

_____

☐ [4] Others [specify]

_____

Does this AE quantify as an SAE

YES ☐

NO ☐

Signature of clinical research officer ----------

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

Investigator's signature

Adverse events [others]

NO	Adverse event	Severity 1=mild 2=moderate 3=severe	Start date	Stop date	Ongoing	Treatment
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	

STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐
Date *Month* *year*

Signature

Adverse events [others] {*contd.*}

no	Adverse event	Severity 1=mild 2=moderate 3=severe	Start date	Stop date	Ongoing	Treatment
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	
		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	

Capital Health

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

SNo	Date of Missed Visit *Date* *Month* *Year*	Reason for missed visit	Contact method	Changes made to prevent further missed visit	Outcome of retrieval

		☐	__ __/__ __/__ __	__ __/__ __/__ __	☐	

Signature

Record on Retrival Action

Signature of clinical research officer ----------

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date *Month* *year*

1	☐☐-☐☐-☐☐☐☐				
2	☐☐-☐☐-☐☐☐☐				
3	☐☐-☐☐-☐☐☐☐				
4	☐☐-☐☐-☐☐☐☐				
5	☐☐-☐☐-☐☐☐☐				
6	☐☐-☐☐-☐☐☐☐				
7	☐☐-☐☐-☐☐☐☐				
8	☐☐-☐☐-☐☐☐☐				
9	☐☐-☐☐-☐☐☐☐				

Appendix: Visit Schedule

Study periods and extension	Screening	TB Treatment

Capital Health

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STUDY NUMBER ☐ SITE NUMBER ☐ DATE OF VISIT ☐☐ ☐☐ ☐☐☐☐

Date Month year

Clinical visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Participation Day	0	2	4	6	9	16	30	44	58	182
TB Treatment Day	-2	0	2	4	7	14	28	42	56	180
Demographics	*									
Informed consent	*	*								
Inclusion/exclusion criteria	*									
Medical history	*									
Screening Physical Exam	*									
Karnofsky Performance Index	*								*	
HIV	*									
Serum creatinine	*									
Pregnancy testing	Only if child bearing potential									
Serum albumin	*									
Serum SGPT	*									
Serum calcium	*		*				*			
Chest X-ray	*									
Sputum smears(if sputum available, using induction as necessary)	*									
Sputum culture(if sputum available, using induction as necessary)	*					*	*	*	* (to be repeated at day 90 and 150 if positive at day 56)	*
Sputum DST	*									
Vitamin D level		*								*
Anti-TB Therapy		*	*	*	*	*	*	*	*	*
Trial drug administration (Vitamin D or placebo)		*				*	*	*		
Adverse events recording			*	*	*	*	*	*	*	*

Capital Health

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Appendix 6
Case Report Form Lab

BASE LINE LABORATORY SCREENING RESULT

CLINICAL BIOCHEMISTRY REPORT

VISIT 1

Identification Details

1. STUDY NUMBER _____

Date Blood sample received ☐☐ ☐☐ ☐☐☐☐

Research officer entering the report ----------

TEST	RESULT	DATE OF REPORT
Serum Creatinine		☐☐ ☐☐ ☐☐☐☐
Serum Calcium		☐☐ ☐☐ ☐☐☐☐
Serum Albumin		☐☐ ☐☐ ☐☐☐☐
Serum SGPT		☐☐ ☐☐ ☐☐☐☐
Corrected Serum Calcium		☐☐ ☐☐ ☐☐☐☐
Urine Pregnancy		☐☐ ☐☐ ☐☐☐☐
Vitamin D – 25 OH Vitamin D3		☐☐ ☐☐ ☐☐☐☐

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Identification Details

1. STUDY NUMBER*_____

SERUM CALCIUM REPORT ON FOLLOWUPS

TEST	VISIT NUMBER & DATE BLOOD SAMPLE RECEIVED	RESULT	DATE OF REPORT
Sr. Calcium	**VISIT 3:** ☐☐/mm☐☐/yy☐☐		☐☐/mm☐☐/yy☐☐
Sr. Calcium	**VISIT 7:** ☐☐/mm☐☐/yy☐☐		☐☐/mm☐☐/yy☐☐

Vitamin D – 25 OH Vitamin D3	**Visit 10** ☐☐/mm☐☐/yy☐☐		☐☐/mm☐☐/yy☐☐

Capital Health

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CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM
VISIT 1

Identification Details
Study No: _____

Day 0 - Sputum Liquid Culture Results

1. Date specimen received in laboratory:
   dd☐☐/mm☐☐/yy☐☐
2. Date culture inoculated:
   dd☐☐/mm☐☐/yy☐☐
3. Date Culture Inoculated:
   dd ☐☐/mm☐☐/yy☐☐
4. Research officer performing NALC/NaOH _____
5. Research Officer inoculating Culture _____
6. Results of culture (circle one)
   - Positive
   - Negative at 42 days
   - Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd☐☐/mm☐☐/yy☐☐
Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM

Capital Health

Vitamin D Randomized Controlled Trial -Laboratory Case Report Form

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VISIT 1

Identification Details

Study No: _____

Day 0: Sputum Susceptibility Report

Sputum Culture Results	Method	Date	Susceptibility
Positive Yes ☐ No ☐		Date of Inoculation: ☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year* Date of Reading: ☐☐ ☐☐ ☐☐☐☐ *Date* *Month* *Year*	Drug | Susceptibility INH RIF

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM

Capital Health

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VISIT 6

Identification Details

Study No: _____

Day 16 - Sputum Liquid Culture Results

7. Date specimen received in laboratory:
   dd□□/mm□□/yy□□
8. Date culture inoculated:
   dd□□/mm□□/yy□□
9. Date Culture Inoculated:
   dd □□/mm□□/yy□□
10. Research officer performing NALC/NaOH _____
11. Research Officer inoculating Culture _____
12. Results of culture (circle one)
    - Positive
    - Negative at 42 days
    - Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd □□/mm□□/yy□□

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM

Capital Health

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VISIT 7

Identification Details

Study No: _____

Day 30 - Sputum Liquid Culture Results

13. Date specimen received in laboratory:

dd☐☐/mm☐☐/yy☐☐

14. Date culture inoculated:

dd☐☐/mm☐☐/yy☐☐

15. Date Culture Inoculated:

dd ☐☐/mm☐☐/yy☐☐

16. Research officer performing NALC/NaOH _____

17. Research Officer inoculating Culture _____

18. Results of culture (circle one)

- Positive
- Negative at 42 days
- Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd ☐☐/mm☐☐/yy☐☐

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM

VISIT 8

Capital Health

Vitamin D Randomized Controlled Trial -Laboratory Case Report Form
Version 3 30th March 2010
Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

Identification Details
Study No: _____

Day 44 - Sputum Liquid Culture Results

19. Date specimen received in laboratory:
dd□□/mm□□/yy□□

20. Date culture inoculated:
dd□□/mm□□/yy□□

21. Date Culture Inoculated:
dd □□/mm□□/yy□□

22. Research officer performing NALC/NaOH _____

23. Research Officer inoculating Culture _____

24. Results of culture (circle one)

- Positive
- Negative at 42 days
- Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd □□/mm□□/yy□□

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM
VISIT 9

Capital Health

Vitamin D Randomized Controlled Trial -Laboratory Case Report Form
Version 3 30th March 2010
Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

Identification Details
Study No: _____

Day 56 - Sputum Liquid Culture Results

25. Date specimen received in laboratory:

dd☐☐/mm☐☐/yy☐☐

26. Date culture inoculated:

dd☐☐/mm☐☐/yy☐☐

27. Date Culture Inoculated:

dd ☐☐/mm☐☐/yy☐☐

28. Research officer performing NALC/NaOH _____

29. Research Officer inoculating Culture _____

30. Results of culture (circle one)

- Positive
- Negative at 42 days
- Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd☐☐/mm☐☐/yy☐☐

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM
VISIT 10

Identification Details
Study No: _____

Vitamin D Randomized Controlled Trial -Laboratory Case Report Form
Version 3 30th March 2010
Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

Day 182 - Sputum Liquid Culture Results

31. Date specimen received in laboratory:
dd☐☐/mm☐☐/yy☐☐

32. Date culture inoculated:
dd☐☐/mm☐☐/yy☐☐

33. Date Culture Inoculated:
dd ☐☐/mm☐☐/yy☐☐

34. Research officer performing NALC/NaOH _____

35. Research Officer inoculating Culture _____

36. Results of culture (circle one)

- Positive
- Negative at 42 days
- Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd ☐☐/mm☐☐/yy☐☐

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM

Unscheduled Visits (only if day 56 is Positive)

Identification Details

Study No: _____

Capital Health

Vitamin D Randomized Controlled Trial -Laboratory Case Report Form
Version 3 30th March 2010
Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

Day 90 - Sputum Liquid Culture Results

37. Date specimen received in laboratory:

dd☐☐/mm☐☐/yy☐☐

38. Date culture inoculated:

dd☐☐/mm☐☐/yy☐☐

39. Date Culture Inoculated:

dd ☐☐/mm☐☐/yy☐☐

40. Research officer performing NALC/NaOH _____

41. Research Officer inoculating Culture _____

42. Results of culture (circle one)

- Positive
- Negative at 42 days
- Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd☐☐/mm☐☐/yy☐☐

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

CLINICAL MICROBIOLOGY - LABORATORY CASE REPORT FORM

Unscheduled Visit (only if day 56 is positive)

Identification Details

Study No: _____

Capital Health

Vitamin D Randomized Controlled Trial -Laboratory Case Report Form

Version 3 30th March 2010

Mathai D, Daley P, John KR, Jayaseelan L, Christopher DJ, Micheal JS, Joel N, Arun JoseN

Day 150 - Sputum Liquid Culture Results

43. Date specimen received in laboratory:

dd☐☐/mm☐☐/yy☐☐

44. Date culture inoculated:

dd☐☐/mm☐☐/yy☐☐

45. Date Culture Inoculated:

dd ☐☐/mm☐☐/yy☐☐

46. Research officer performing NALC/NaOH _____

47. Research Officer inoculating Culture _____

48. Results of culture (circle one)

- Positive
- Negative at 42 days
- Contaminated

Days from inoculation until positive _____

If contaminated, actions taken _____

Reinoculation date dd☐☐/mm☐☐/yy☐☐

Results of reinoculation culture (circle one)

Positive Negative at 42 days Contaminated

Days from reinoculation until positive _____

Date of reading	Growth Index

Appendix 7
Drugs Controller General of India Permission

F.No 12-01/2006-DC (Pt.51)
Directorate General of Health Services
Office of Drugs Controller General (India)
(New Drug Division)

FDA Bhawan,
Kotla Road, New Delhi
Dated 11 SEP 2009
14/89/09

To,
Dr. Dilip Mathai,
Christian Medical College,
Dept. of Medicine Unit 1 & Infectious Diseases,
Ida Scudder Road, Post Box No.3
Vellore 632 004, Tamilnadu.

Subject: Clinical trial entitled "A double blind, randomized, parallel, placebo control design to determine the effect of addition of Vitamin D to conventional anti TB therapy - regarding.

Reference: Your letter dated 13.07.09.

Sir,

This Directorate has no objection to your conducting clinical trials with the said drug under the supervision of the investigators mentioned in your letter and as per the protocol forwarded to this Directorate. At the time of submitting clinical trials reports to this Directorate for evaluation you are required to comply with the following requirements:-

1. Submit complete report of clinical trials as per the approved protocol from the individual investigator duly signed by him along with his observations / remarks on the drug.

2. Indicating the date of commencement and conclusion of the clinical trial at each center (in case the study is multi-centric).

3. Approval of the Ethical Committee of the concerned center/institution for conducting the clinical trial with the said drug.

You are requested to submit to this Directorate an annual status report on each clinical trial viz. ongoing, completed or terminated. In case the trial is terminated the reasons for the same should be communicated to this Directorate. In case any unexpected serious adverse reaction is observed during trial, the same should be immediately communicated.

It may kindly be noted that merely granting permission to conduct clinical trials with the drug does not convey or imply that based on the clinical trial data generated with the drug, permission to market this drug in the country will automatically be granted to you.

You are also requested to follow Ethical aspects of the clinical trial as described in the booklet "Ethical Guidelines for Biomedical Research on Human Subjects" published by Indian Council of Medical Research (ICMR), New Delhi, and 'GCP' guideline issued by this Department and to obtain Ethical Committee clearance of the Institute before initiation of the study. Ethical Committee clearance should be obtained before initiation of the study.

It is mandatory to register this clinical trial at ICMR clinical trial registry at www.ctri.in before enrolling first patient in the study.

In future correspondence, you may intimate this Directorate that you have registered the study as mentioned above.

Yours faithfully,

(A.K.Pradhan)
Asst. Drugs Controller
For Drugs Controller General (India)

Appendix 8
Health Ministry Screening Committee Permission

13-JUL-2009 12:40 FROM TO 04162211991 P.01

दू.भा.एक्स./PABX : 26588980, 26588707, 26589336, 26589745, 26589873, 26589414
फैक्स/FAX 011-26588662, 011-26589791, 011-26589258

तार/GRAM वैज्ञानी/SCIENTIFIC
Web-site www.icmr.nic.in
E-mail icmrhqdir@vsnl.net.in

भारतीय आयुर्विज्ञान अनुसंधान परिषद
INDIAN COUNCIL OF MEDICAL RESEARCH

स्वास्थ्य अनुसंधान विभाग (स्वास्थ्य एवं परिवार कल्याण मंत्रालय)
वी. रामलिंगस्वामी भवन, अन्सारी नगर, नई दिल्ली - 110 029

DEPARTMENT OF HEALTH RESEARCH (MINISTRY OF HEALTH & FAMILY WELFARE)
V. RAMALINGASWAMI BHAWAN, ANSARI NAGAR, NEW DELHI - 110 029

Dr. Dipali Mukherjee
Scientist 'F'

5/8/9/66/2007-ECD-I
13.7.09

Subject : Project entitled "A double blind, randomized, parallel, placebo control design study to determine the effect of addition of Vitamin D to conventional anti TB therapy"

Dear Dr. Mathai

This has reference to the above mentioned project which was submitted for consideration in Health Ministry Screening Committee (HMSC) meeting for assistance/collaboration from Dalhousie University, Internal Medicine Research Foundation, Canada The meeting was held on 8.6.09. The relevant portion of the minutes is reproduced below

"Approved".

You may take necessary action at your end. Kindly let us know the date of initiation of the project. You are also requested to submit 6 monthly progress report of the project to our office with a copy to International Health Division (IHD) of ICMR for necessary action.

With Regards,

Yours sincerely,

Dipali Mukherji

Dr. Dilip Mathai,
Professor & Head,
Dept. Of Medicine,
Christian Medical College,
Vellore – 632 004

TOTAL P.01