Effects of malnutrition and diabetes on treatment outcome and total patient costs in Filipino drug resistant and drug sensitive patients starting anti-TB treatment: A cohort study.

(short study name: **St-ATT**[1])

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[1] **St**arting **A**nti-**T**uberculosis **T**reatment

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1. Abstract

1.1. Background

Undernutrition (malnutrition) is both a risk factor for and consequence of active TB disease. Wasting and malnutrition are common clinical findings in patients with active TB disease and are associated with mortality, but the mechanism/s of effect are not well understood and there is a lack of high quality evidence to determine the efficacy of interventions to prevent or treat malnutrition in TB patients, in the Philippines or globally.

Diabetes mellitus is another known risk factor for active TB disease and has been associated with risk of death and poor treatment outcomes whilst TB may also negatively affect glycaemic control. Under-diagnosis or poor management of diabetes may increase of poor TB treatment outcomes. Co-morbid diabetes may also contribute to an increased financial burden and potentially catastrophic levels of costs.

The aim of this study is to quantify the effects of malnutrition and diabetes in both drug-resistant TB (DR-TB) and drug sensitive[2] (DS-TB) patients attending public facility TB DOTS programmes in the Philippines on TB treatment outcomes. The overall goal is to inform future operational research on optimal screening and management of diabetes in TB DOTS clinics in the context of TB populations who may be experiencing both under and over-nutrition; and, to assess the need for and potential trial design of nutrition support interventions to improve TB treatment outcomes.

1.2. Objectives

The primary objective is to estimate the effect of malnutrition and diabetes on risk of adverse treatment outcome (death, loss to follow-up, default or treatment failure) in DR-TB patients enrolled on the WHO shorter (Bangladesh) regimen and DS TB patients attending TB-DOTs outpatient facilities. A secondary outcome definition will include relapse/recurrent active TB disease within 2 years of completing treatment in the definition of "adverse treatment outcome"

1.3. Methods

Study Design: Prospective cohort study

Population and sample size: 800 TB outpatients attending public facility TB-DOTS clinics in Metro Manila, Negros Occidental and Cebu, including a target of 300 DR-TB patients.

Eligibility: All consenting pulmonary TB patients ≥18 years newly initiating TB treatment from selected TB DOTS clinics including DR-TB, if enrolled on the WHO shorter treatment regimen but excluding pregnant women.

Duration: Recruitment is expected to take 12 months, from April 2018 to March 2019. Follow-up will be until 24 months post-treatment completion.

Primary outcome measures: Adverse TB treatment outcome defined as death, loss to follow-up, default or treatment failure at the end of treatment completion..

Primary exposures: Malnutrition (BMI <17.0 kg/m2) and diabetes (random plasma glucose (RPG)≥11.1mmol/L (200mg/dL) confirmed by HbA1c≥6.5%, or previous diagnosis and on treatment).

[2] DS-TB defined as TB patients enrolled on category I or II ATT regimens who may or may not have had GeneXpert testing to determine rifampicin resistance

2. Background and justification

2.1. Malnutrition and Tuberculosis.

Tuberculosis and malnutrition are known to be closely associated with each other with even mild malnutrition increasing the risk of developing active TB disease [1]; TB can directly contribute to the development of malnutrition by increasing metabolic demands and inducing a catabolic state and decreased appetite and potentially through indirect effects on access to nutritious food through effects on poverty and isolation. Malnutrition in TB has been associated with risk of death in TB patients. Kwon *et al* reported an odds ratio (OR) of 2.8 (95%CI 1.59 – 4.93) for mortality in a Korean cohort of TB patients with a BMI <18.5 kg/m^2 [2]. Whilst in an Indian cohort of 1,523 newly diagnosed TB out-patients, Bhargava et al reported a 22% decreased odds of mortality risk per unit increase in BMI at time of diagnosis (adjusted OR 0.78; 95%CI 0.68-0.90) [3]. Although the evidence for the association between malnutrition and risk of death in active TB is reproducible, there is insufficient information to try to determine causality. In a study of 1181 TB patients in Malawi, despite an odds ratio of 1.8 (95%CI 1.1 – 2.7) for death within the first 4 weeks of treatment in those with moderate/severe malnutrition, the authors concluded that severity of disease or comorbidities such as HIV may confound this finding [4]. Whether interventions to treat protein-energy malnutrition in TB can improve TB-related outcomes is not known. Only 7 trials of macro-nutrient interventions in patients with active TB disease were included in a recent 2016 Cochrane review [5] and WHO policy document [6] and none were adequately powered to assess TB treatment outcomes. Both reports concluded that there is an urgent need for high-quality trial evidence to inform guidance. Furthermore, population specific evidence is required and within the context of recent improvements in diagnosis and treatment of TB.

2.2. Tuberculosis and Malnutrition in the Philippines.

As of the Global Tuberculosis Report 2017, the Philippines is ranked 4th in the world for total TB burden with an estimated incidence of 554 per 100,000 population [7] including the estimated incidence of HIV-TB co-infections of 5.9/100,000 population. The estimated DR incidence rate is 30 per 100,000 population. Estimated mortality rates in HIV-negative TB cases is 21 per 100,000 [7]. There is little published data on nutritional status of TB patients in the Philippines. However, to our knowledge, the best and most recent available data on malnutrition and diabetes in Filipino TB patients is from our recently completed cross-sectional study of patients registered at 5 outpatient TB-DOTS clinics (ISRCTN12506117) in Metro Manila and Negros Occidental in which 90% of patients were on category 1 or 2 treatment regimens. The overall prevalence of moderate and severe malnutrition (BMI<17) was 20.5% (**Table 1**). and when including mild malnutrition (BMI<18.5) 50%. In contrast, around 10% of the general adult population have a BMI<18.5 [8]. Moderate and severe malnutrition rates are higher within 1 month of treatment than at 5 months or more of treatment (26% vs 17%) (**Table 2**). This shows that malnutrition persists above the expected adult malnutrition rates (10%) even after TB treatment, suggesting that treatment of TB alone may not be enough to resolve malnutrition. What is not known is if apparently increased rate of malnutrition at the

end of treatment is due to to the socio-economic effects of TB, likely to affect all household members or due to inherent effect of TB disease. The proportion of TB-DOTS patients determined to be food insecure using the Adapted U.S. Household Food Security Survey Module was 62% in the more rural clinics in Negros Occidental compared to 36% in Metro Manila. In a prospective cohort of Filipino patients with MDR-TB, weight gain in patients who were underweight before treatment was significantly associated with decreased risk of adverse treatment outcome including death, default or treatment failure [9]. Factors identified with a reduced risk of default from treatment in Filipino MDR-TB patients included food provision, travel reimbursement and free provision of drugs for managing nausea/vomiting side effects of the drugs through TB programmes [10] supported by analysis of patient views of barriers to treatment adherence in which 60% of patients included the importance of food provision [11].

Table 1. Prevalence of moderate and severe malnutrition and diabetes in TB-DOTs outpatients

	Moderate & severe malnutrition [BMI<17.0kg/m²]	Diabetes*
Manila (total)	16.7% (56/336)	8.6% (28/324)
Negros Occ. (total)	24.8% (74/298)	11.7% (31/264)
Total of all sites	**20.5% (130/634)**	**10.0% (59/588)**

**previously diagnosed or HbA1c > 6.5%*

Table 2. Prevalence of moderate and severe malnutrition and anaemia by duration of treatment in TB-DOTS outpatients

	Months of treatment				Total
	<1month	**1-2months**	**3-4 months**	**5+ months**	
BMI<17.0kg/m²	25.8% (51/198)	20.8% (33/159)	16.5% (22/133)	16.7% (24/144)	20.5% (130/634)
Mod or Severe anaemia*	20.2% (40/198)	15.1% (24/159)	9.1% (12/132)	7.0% (10/143)	13.6% (86/632)

**Moderate/severe anaemia = Hb< 11.0g/dl for both sexes.*

2.3. Tuberculosis and Diabetes Mellitus.

The burden of diabetes mellitus (DM) has been increasing worldwide. The link between diabetes and TB has long been known since Richard Morton's treatise of Consumptions in 1694. However, the effect of diabetes on immune function dysregulation and its role in increased risk of TB is still not well characterized [12, 13]. A meta-analysis of cohort studies, with most data coming from a single study in South Korea, suggests an age-adjusted RR for risk of active TB of 3.11 [95% CI 2.27-4.26] [14], which is likely to be higher in high transmission settings. It has been estimated that 15% of 10.4 million newly diagnosed adult TB cases may be attributable to diabetes [15]. The risk of MDR-TB also appears to be increased by diabetes, as reported in a recent meta-analysis (OR=1.71 [95% CI 1.32 -2.22]) [16]. Diabetes, has also been associated with an in increased risk of poor treatment outcomes in a meta-analysis of mostly retrospective studies [17] and poor glycaemic control in a relatively large prospective study in South Korea [18], including significant effects for risk culture

positivity at 2 months, treatment failure and death, even after adjustment for important confounders. However, many studies so far are from high-income settings, are retrospective, or rely on clinical records or sub-optimal diabetes testing or have not adequately addressed potential sources of bias and confounding and thus various methodological issues remain, thus leading to uncertainty over these estimates of effect [19]. The effects of diabetes are also likely to be heavily context dependent and thus further epidemiological research of the effect of diabetes on TB treatment outcomes is urgently called for [20].

2.3.1. Tuberculosis and Diabetes Mellitus in the Philippines.

Type 2 DM is increasing in prevalence in the Philippines. The prevalence of elevated fasting blood sugar (FBS) among Filipino adults based on the National Nutrition and Health Survey (NNHeS) was 5.6% in 2013 [8]. However, a more accurate prevalence of diabetes in a national survey in 2008 which included previous diagnosis by a health practitioner and FBS plus the oral glucose tolerance test (OGTT) reported a prevalence of 7.2% [21]. Thus, at the present time the prevalence of diabetes is probably closer to 8% and it is expected that DM-associated TB cases will also increase [22]. In a recent rapid situational analysis in the Philippines the limited data of DM in TB was highlighted as a barrier to planning a coordinated response [22]. In our recently completed cross-sectional study in TB-DOTs outpatients, the overall prevalence of diabetes was 10%, with 12.5% in the more rural clinics and 8.6% in Manila (**Table 1**), of whom 65% and 52% were previously undiagnosed. Around half of those who with a previous diabetes diagnosis had poor glycemic control.

2.4. Malnutrition, diabetes and immune responses to TB

The observed association between malnutrition and risk of active TB disease is probably due to malnutrition associated depression of cell-mediated immunity leading to increased risk of infection and/or progression to active disease, although a lot of the available evidence is from animal models with very little data on immune functions linked to good nutritional, clinical and epidemiological data [23]. Additionally, despite recent progress, the immune response to TB remains relatively poorly understood [24] and we do not understand the role of the immune response in determining response to treatment. Diabetes may increase the risk of TB infection, active TB disease and adverse treatment outcomes through altered glucose metabolism, and increased inflammation and oxidative stress antigen presenting cells and the balance Treg, Th1-, Th2- mediated responses and neutrophil and phagocyte capacity to kill infected cells [12].
Interferon-gamma release assays measure IFN-γ produced by T-cells in response to TB specific antigens either by counting cells producing IFN-γ (T-SPOT) or the amount of IFN-γ in the supernatant after whole blood stimulation with *M.tb* antigens distinct from those used in BCG vaccination (e.g. QuantiFERON-Gold). In addition, the new version, QuantiFERON-Gold-Plus, uses separate antigens that stimulate $CD4^+$ and $CD8^+$ cell dominated responses. These standardised kits are designed to test for the presence of TB infection as determined by a IFN-γ response over s standardised cut-off, which in the absence of clinical disease is interpreted as indicating latent TB-infection. However, ex-vivo stimulation of blood using these standardised kits also provides the opportunity to interrogate immune responses in more detail including assessment of patterns of multiple cytokine responses, which are being investigated as potential

biomarkers of response to treatment [25] and of development of active TB disease [26]. However, currently most of this work is being developed using populations from either high-income countries or not accounting for potential variation that is likely to be occurring from co-morbid malnutrition and diabetes in the kinds of patients in which such tests are intended for eventual use.

2.5. Tuberculosis Patient costs.

TB is a cause and consequence of poverty [27] potentially trapping patients and their households in a cycle of poverty. Healthcare financing in low-income countries is characterized by out-of-pocket expenditures and a lack of financing mechanisms and weak health insurance structures. If total costs due to TB are greater than 20% of household annual income, the situation may be considered catastrophic as the threshold was most strongly associated with adverse TB outcome [28, 29]

One of the pillars of the WHO End TB strategy is "to ensure that no family is burdened with catastrophic expenses due to TB" [30]. To capture the current situation of TB associated household costs and monitor the progress to achieve this goal, WHO promotes countries with a high a TB burden to conduct baseline and periodic TB patient cost surveys [29]. The current guideline is to conduct TB patient cost study using a cross-sectional design for simplicity and practicality. In the Philippines, the Filipino NTP conducted a nationwide TB patient cost study collaborating with WHO in 2015–2016 and the study assessed direct costs (e.g. costs for TB drugs, consultations, hospitalization, or transportation, or special foods) and indirect costs (e.g. opportunity costs due to time loss to visit and in health facilities, loss of job or unwell to work). The results of the study found a large contribution of "nutritional supplements" and "opportunity costs" to patient catastrophic costs (20% total cost, oral presentation at PhilCAT 2017). However, this study, and all others completed so far [29] have been cross-sectional and have not assessed costs of diabetes diagnosis and treatment in TB patients.

We have already piloted a version of the WHO TB patient cost tool, which we adapted to include additional specific questions on direct and indirect costs of diabetes diagnosis and treatment using the same format as used for TB and which we deployed electronically using Open Data Kit (ODK). Our preliminary results from this pilot in 47 DS patients, 21 in intensive & 26 in the continuation phase of treatment and 4 with co-morbid diabetes found that expenditure on nutritional supplements was twice that of drugs and diagnostic tests and that income losses accounted for >70% of total patient incurred costs.

The Filipino Department of Health introduced a policy for bi-directional screening of TB and DM in 2017, as proposed by the current End TB strategy. However, this policy has not been fully implemented in TB programmes and there is little data or research on which to assess operational feasibility and likely benefits of doing so, including in the potential for reducing patient costs by integration of diabetes services within TB programmes. No data are yet available from other countries on implementation of or cost effectiveness of integration of services or bi-directional screening. As costs for diabetes diagnosis & management are not always fully covered by national insurance or Philippines government [31, 32], though direct costs for TB treatment and diagnosis are covered, this may result in increased and potentially catastrophic costs in patients with TB and co-morbid diabetes and increased needs for social

protection mechanisms. Similarly, if co-morbid malnutrition is not being diagnosed and managed by health facility staff, patients may be spending money on potentially inappropriate supplements in an effort to self-manage.

2.6. Adherence

Risk factors which may affect TB treatment adherence include duration of treatment, combination of several therapies, unpleasant side effects, high patient costs and burden, stigma, depression, lack of social and family support, traditional health beliefs, poor communication between health care providers and patients, and lack of disclosure of diseases status [33]. DM may also affect TB adherence due to increased burden of multiple therapies (costs and time), drug-drug interactions and effects of DM on lifestyle disruption and quality of life and metabolic effects [33, 34]. Malnutrition can increase non-adherence due to poor appetite, metabolic changes and associations with quality of life [35]. MDR-TB is associated with lower health-related quality of life (HRQOL) than DS-TB [37]. However, the association between adherence to treatment and HRQOL has rarely been studied in TB [38], and pathways leading to be non-adherent are not well described.

The main reasons for non-adherence in MDR-TB are usually stated to be the increased number of medications and long duration of TB treatment [40]. The normal MDR treatment duration is 18 months while NTP has introduced the WHO shorter regimen with a duration from 9 to 12 months [41]. This shorter regimen is expected to improve adherence level due to reduced patient burden from duration of treatment and reduced time burden for receiving treatment by change the treatment place from PMDT facilities (which usually have a far distance to be reached) to DOTS [41]. There are no available data or publication assessing the effect of diabetes and malnutrition on TB treatment adherence in the Philippines. Also, information on risk factors associated with non-adherence and of the pathways to be non-adherent are not well known in the Philippines, or elsewhere.

2.7. Long-term Health outcomes and social effects of TB treatment

Although TB is recognized as a globally important cause of mortality, TB associated morbidity after treatment and long-term health effects are not well documented. Limited recent data from diverse populations suggest that TB patients, including those who are who are microbiologically cured, may suffer from significant long-term lung damage as defined by imaging [33] or pulmonary function impairment assessed using spirometry; [34-38] whilst few studies have attempted to relate physiological impairment with quality of life and other important health related outcomes. Recurrent TB, older age and HIV are documented risk factors for post-treatment decreased lung function, but the effects of malnutrition and diabetes are not known, although some studies have reported increased radiological severity in TB-DM patients, particularly those with poor glycaemic control [39], and in those with more severe malnutrition [40]. Patients with long-term lung damage/decreased function are also likely to experience increased risk of developing further lung diseases such as severe pneumonia and obstructive lung diseases such as COPD and bronchiectasis, conditions which already pose a major burden on health expenditure and morbidity in the Philippines.

Previous data from our cross-sectional study in Filipino TB patients indicated 16.5% of patients in the final months of treatment to still have moderate or acute malnutrition and 7% moderate or severe anaemia (Table 2). It is not known how these conditions may evolve post-treatment

or of their effects on productivity (e.g. ability to work) and quality of life. Furthermore, the effects of TB at the level of the household are not well documented or of the long-term effects of TB-associated costs.

Although treatable, TB patients face discrimination from the community as well as self-discrimination post-treatment which may continue to affect individuals psychosocial/mental health even after successful treatment.

There is one currently ongoing multicountry study in 4 African countries that is seeking to systematically assess the long term medical and social sequale of TB; the TB Sequel study [41]. We propose to maximise the use of our large treatment cohort to address these questions in an Asian population using similar methodologies.

3. Study aims and objectives

3.1. Aim

The aim of this study is to measure the effects of malnutrition and diabetes in patients with tuberculosis and investigate associations with treatment outcome through potential effects on treatment compliance, drug side effects, glycemic control, weight gain and nutrition during treatment and cell-mediated immune responses.

3.2. Primary Objective

The primary objective is to estimate the effect of malnutrition (BMI<17.0 kg/m^2) and diabetes on risk of adverse treatment outcome (death, loss to follow-up, incomplete treatment or treatment failure) in in DS-TB patients[3] and DR-TB patients enrolled on the WHO shorter (Bangladesh) regimen. A secondary outcome definition will also be analysed including relapse/recurrent active TB disease within 2 years of completing treatment in the definition of "adverse treatment outcome"

3.3. Secondary Objectives

1. To investigate the effect of malnutrition, diabetes and pre-diabetes at enrolment on time taken for patients to be negative for *M.tb* bacteria by standard programmatic tests (direct sputum slide microscopy, (sputum culture for DR-TB) as available.
2. To describe management of diabetes in TB patients and glucose control as assessed by 3-monthly HbA1c.
3. To investigate the stability and basis of glucose dysregulation and diabetes during and after TB patient treatment.
4. To determine if malnutrition (BMI <17.0 kg/m^2) and HbA1c, diabetes and pre-diabetes affect cell mediated (CD4 and CD8) immune responses to TB-specific antigens in whole blood samples stimulated with Quantiferon TB Gold-Plus.
5. To estimate total patient costs in patients with DS-TB and DR-TB receiving the shorter regimen and investigate the effect of costs associated with co-morbid malnutrition and diabetes on the percentage of patients with catastrophic costs over the duration of treatment (using adapted WHO costing tool).

[3] DS-TB defined as TB patients enrolled on category I or II ATT regimens who may or may not have had GeneXpert testing to determine rifampicin resistance

6. To determine if malnutrition and anaemia are more common in TB patients compared to household contacts without TB, who share socio-economic and other factors that may affect nutritional status.
7. To assess the effect of malnutrition and DM on TB treatment adherence and investigate potential pathways of effect including depression, stigma, social & family support (SFS), medication side effects and self-esteem.
8. To document the long-term health and psychosocial sequalae in TB patients post-treatment including lung function, diabetes, malnutrition, quality of life, depression and anxiety, and risk of recurrent TB up to 2 years post-treatment and investigate their associated risk factors.

3.4. Significance of the Study

This study will estimate the effect of malnutrition and diabetes among TB patients on their treatment outcomes in a predominantly HIV-negative population. This sets the stage to determine the potential impact of targeted co-interventions to improve nutritional status or improve glycemic control. Furthermore, the amended version to include post-treatment follow-up will determine the previously undocumented long-term health sequalae of TB and their risk factors, adding further evidence of the need/type of interventions to improve TB-associated outcomes. Together with the clinical, immunologic and costing data, the study is well-positioned to provide information that would directly contribute to future research and program direction.

3.5. Research design

This is a facility-based prospective cohort study in TB DOTs facilities in the Philippines.

3.6. Study Population and Locale

Study participants aged 18 or more (adults) who are initiating a new TB treatment regimen to be recruited from participating NTP DOTs and iDOTS centres (i.e. those implementing the WHO shorter regimen to eligible DR-TB patients) within the National Capital Region, Negros Occidental and Cebu. One adult household contact of enrolled TB-index cases will also be enrolled as a comparison group for malnutrition and anaemia.
Current selected sites include:

Manila, NCR
- San Lazaro Hospital
- San Nicholas H/C MHO

Negros Occidental, Western Visayas
- Valladolid H/C
- Bago City H/C

>>Updated [April 2019] active site list since study start as of April 2019.

Negros Occidental, Western Visayas
- Bacolod H/C
- La Carlota H/C
- Pablo O. Torres Memorial Hospital

Cebu, Central Visayas

- Compostela H/C
- Carmen H/C
- Consolacion H/C
- Eversley Childs Sanitarium and General Hospital
- Lapu Lapu City Health Office

None of these sites are currently engaged in other TB or health related research projects, except for SLH, which has multiple research projects for inpatients, including a phase 2 of a TB inpatient study (PI Prof Cox) planned to start in the 2nd half of 2018. Other sites to be selected will include those who are not currently undertaking any research in the TB outpatients – to ensure that patient burden is minimised.

3.7. Eligibility Criteria

Subject Inclusion Criteria: Active TB cases

- Patients initiating a new TB DOTS treatment regimen with bacteriologically confirmed or clinically diagnosed pulmonary TB , including:
    a. new diagnoses,
    b. relapse,
    c. treatment after failure,
    d. treatment after loss to follow-up (TALF),
    e. previous treatment unknown outcome (PTUO)
- DR-TB cases (if initiating the 9-12 month WHO shorter DR-TB regime and registered to be managed at participating iDOTS clinic)
- intending to reside within the study area for the duration of their treatment
- Age ≥18 years old

Subject Inclusion Criteria: Household contacts

- Adult (Age ≥18 years old) household contact (defined as living in the same household for a minimum of 2 months before diagnosis of the index case) of active TB patients enrolled in the St-ATT cohort.
- Screened and diagnosed as not having active TB (as available through programmatic screening).

Subject Exclusion Criteria

- Pregnant woman
- Age <18 years old
- Plan to move away from the study site or do not give consent to participate
- Started the current ATT regimen more than 5 days before enrolment.
- Currently imprisoned*[4]
- Severe medical or psychiatric disorder which in the opinion of the local investigators might interfere with the ability to give true informed consent or to adhere to the study requirements*

[4] * Further exclusion criteria added since starting enrolment.

- Taking part in any investigational product trials related to TB and/or lung disease or diabetes.*

3.8. Definitions of Outcomes and key exposures

- The primary outcome of adverse treatment outcome will be defined as: death, loss to follow-up (default defined as 2 or more consecutive months of interrupted treatment), or treatment failure). A secondary outcome definition of adverse treatment outcomes will include recurrent TB diagnosed clinically or microbiologically as per the local procedures up to years after completing treatment.
- Diabetes will be defined (random plasma glucose (RPG)≥11.1mmol/L (200mg/dL) confirmed by HbA1c≥6.5%, or previous diagnosis and on treatment)
- Malnutrition will be defined using BMI with moderate or severe malnutrition defined as BMI<17 kg/m2 used in the primary analysis.

3.9. Recruitment

Newly registered eligible patients at TB DOTs clinics will be recruited by research staff. The study will be explained to them, and if they agree, a written informed consent will be obtained (see 8.1 below). Once a registered patient is recruited, a separate consent to participate in the study will be obtained from eligible household contacts using the same consent process. A TB patient remains a participant even if the household contact refuses.

3.10. Data Collection

3.10.1. Sample collection and study assessments:

All study participants will be seen by a study research nurse at enrolment and thereafter all participants will be seen at monthly follow-up at the registered TB-DOTS clinic or Barangay health station where receiving/collecting treatment until treatment completion depending on TB treatment regimen. Study assessments samples and data collected during treatment are summarized below (**Table 3A**) and post-treatment in **Table 3B**

Table 3A: Summary of data & sample collection in participants during treatment

Assessment Time points	0M	Monthly	3M	6M	9M[1]	12M[1]
Demographics, clinical history, household information	✓					
TB & Diabetes Medication History, adherence; adverse effects		✓				
TB Classification, diagnosis, regimen	✓					
Sputum Sample [sputum archived]	✓					
Chest x-ray (if required[2])	✓					
Anthropometry [BMI, MUAC, waist:hip ratio]; grip strength, blood pressure, reported appetite	✓	✓				
Bioimpedance Analysis (San Lazaro site)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
Blood (5 ml) for Quantiferon-Gold Plus supernatant aliquot archived for Luminex Cytokine Assay (N=250 subset)	(✓)					
Random Plasma Glucose	✓		✓	✓	✓	✓
HbA1c (for all patients)	✓		✓	✓	✓	✓
Cross-sectional assessment of Fasting blood glucose and insulin [3]	(✓)		(✓)	(✓)	(✓)	(✓)
Oral Glucose Tolerance Test (if Hba1C ≥5.7% to < 6.5%)	✓					
TX history, diabetes co-morbidities in DM & pre-DM cases	✓		(✓)	(✓)	(✓)	(✓)
Household contacts Anthropometry, blood pressure and haemoglobin	✓		✓	✓	✓	✓
Assessment Time points		**End-IP**	**Mid-CP**		**End-CP**	
Total patient costs – WHO patient costing tool	✓	✓	✓		✓	
Hemoglobin (finger prick)	✓	✓	✓		✓	
Household food security	✓	✓	✓		✓	
WHO Quality of Life questionnaire	✓	✓	✓		✓	
Depression, stigma, SFS, Self-esteem, reported side effect of medication	✓	✓	✓		✓	

[1] Included time points for DR-TB patients; [2] please see text below regarding potential chest X ray collection; 3 Cross-sectional study, with 1 measurement per patient with equal numbers at the different time points.
IP = intensive phase of treatment; CP=continuation phase of treatment **(✓) indicates conducted in subset of participants**

Table 3B Summary of data and sample collection in patients post-treatment

Assessment Time points	End of Treatment	6M after Treatment Completion	12 M after Treatment Completion	18M after Treatment Completion	24M after Treatment Completion
Chest x-ray	✓				✓
Anthropometry [BMI, MUAC, waist:hip ratio]; grip strength, blood pressure, reported appetite clinical history	✓	✓	✓		✓
Bioimpedance Analysis (San Lazaro site)	(✓)	(✓)	(✓)		(✓)
HbA1c (for all patients)	✓	✓	✓		✓
Fasting blood glucose and insulin (subset tbd)	✓		✓		✓
TX history, diabetes co-morbidities in DM & pre-DM cases	(✓)				
Lung spirometry and 6 minute walk test	✓		✓		✓
St Georges respiratory Questionnaire	✓		✓		✓
Active TB screening at clinic visit or by telephone		✓	✓	✓	✓
Sheehan Disability scale	✓	✓	✓		✓
Health related behaviors	✓	✓	✓		✓
Symptom history and health seeking behavior	✓	✓	✓	✓	✓
Hemoglobin (finger prick)	✓	✓	✓		✓
Household food security	✓	✓	✓		✓
WHO Quality of Life questionnaire	✓	✓	✓		✓
Depression, stigma, SFS,	✓	✓	✓		✓

3.10.2. TB diagnostics:

- TB classification, TB diagnosis (clinical, bacteriological, direct sputum smear microscopy (DSSM) including grade, drug resistance (GeneXpert/line probe assays (Hain test), DSSM, sputum culture – as available), drug regimen and any changes to drug regimen will be obtained from clinical records and patient questionnaires.
- A study sputum sample will be collected for all patients at enrolment to be archived for potential future culture and preservation of isolates for molecular typing and further drug sensitivity testing. Samples will be archived at -80 degrees C for up to 10 years after the end of the study and linked to the anonymised dataset. The study informed consent includes consent for archiving and further testing of these samples for the purpose of TB-related diagnostics for ethically approved research, but no further informed consent from the study participants will be sought. *A funding decision is pending for a research proposal to support the continuation and expansion of this cohort to include follow-up for risk of recurrent TB – and to investigate the role of re-infection compared to treatment failure in recurrent cases. Therefore, this archive will maximise the number of potential isolates for comparison between recurrent and previous infection.
- Study specific chest x-ray at baseline may be collected depending on availability and quality of programmatic films. Degree of cavitation will be assessed as a potential predictor of disease severity and poor outcome. Additional CXRs will be obtained at end of treatment and 24 months post-treatment for those agreeing to participate in the post-treatment follow-up.
- WHO symptom screening will be conducted 6 monthly during the post-treatment follow-up and any found to be positive will be referred for further screening through the usual processes (expected to be GeneXpert MTM/Rif testing). In addition Study specific CXRs will be conducted at 24 months and will be assessed for findings suggestive of new TB disease, and any such cases referred for further testing as above.

3.10.3. Nutritional status and food security:

- Weight, blood pressure, MUAC and grip strength (Jamar Dynamometer, grip strength in kg) and reported appetite in all patients all visits, height (baseline only) and at 6, 12 and 24 months post-treatment. Reported previous weight loss at baseline.
- Hemoglobin (Hemocue 301) point of care test, all patients at baseline, end of intensive treatment phase, end of treatment at month 6/9-12 and 6, 12 and 24 months post-treatment.
- Bioimpedance analysis (BIA) measurement, all patients in San Lazaro Hospital at baseline, monthly follow-up, and end of treatment at month 6/9-12 and 6, 12 and 24 months post-treatment.
- Household food security (using Adapted U.S. Household Food Security Survey Module (US HFSSM)), all TB patients at baseline, end of treatment at month 6/9-12 and 6, 12 & 24 months post-treatment.
- Nutritional status for household contact of enrolled index case, approximately 50% of all enrolled patients at enrolment.

3.10.4. Immune functions:

- 250 TB patients with microbiologically confirmed TB (DR or DS) will be selected to have a 5ml venous blood collection for whole blood stimulation using QuantiFERON-TB Gold Plus (QFT). Plasma from 1ml of blood (if available after aliquoting 4 mls of whole blood for the QFT) will be frozen and archived for future possible TB-related research. QFT supernatants will be frozen and stored for later analysis for multiple cytokines using Luminex. Based on previous data we expect that at least 35% of patients with DS TB will be bacteriologically confirmed. Thus, enrolling a total of 800 patients and 500-600 with DS TB should yield at least 175 DS TB patients eligible for the immune responses assessment, whilst all of the DR-TB patients would be eligible. We will aim for 125 of each.

3.10.5. Diabetes and glycaemic control:

- Random plasma glucose, POC and HbA1C (Unilab, Trinity POC), on finger prick samples, all patients at baseline and 3 monthly until end of treatment followed by 6 months and 12/24 months post treatment.
- Oral glucose tolerance test (OGTT) requiring a venous blood sample, patients whose HbA1c is ≥5.7% to < 6.5% at baseline or in those with severe anemia (<8g/dL) in whom HbA1c measurements may be affected and at very low levels of haemoglobin (approx.<6/7g/dL) will not result in an HbA1c reading . Venous fasting blood sugar before the glucose load and blood sugar 2 hr after the glucose load (mg/dL) will be used to define diabetes (>=126 / >200), pre-diabetes (100-125 / 140- 199) and normal (<100 / <140).
  - Information on therapy/management and glycaemic control for diabetic patients will be obtained from clinical records, patient interviews and 3-monthly HbA1C (months 3, 6 and 9 and 12).
  - Fasting blood glucose and insulin measured in all patients at one time point in a cross-sectional designed to achieve approximately equal numbers of assessments at baseline, end of IP, mid CP and end of CP[5]. Further sub-set sampling during post-treatment will be determined based on the previous results. Approximately 1 ml of fasting blood will be archived for future possible metabolomics/TB research

3.10.6. Patient Cost:

- By interview to patients using adapted electronic version of the WHO catastrophic cost tool deployed on ODK platform.
- Patient costs consist of direct medical cost (e.g. consultation cost, drug cost, diagnostic cost before starting treatment, hospitalization and follow-up costs, direct non-medical cost (e.g. travel cost, food cost, accommodation cost, opportunity costs of visits associated with picking up drugs/consultations) and indirect non-medical cost (e.g. opportunity cost by income and asset loss).
- Information on coping strategies will be obtained from questionnaire about how to finance patient costs (e.g. regular income, selling asset, or borrowing money).

[5] The selected time point for each patients FBS/Insulin will replace the nearest 3 month HbA1c assessment, so that RPG/HbA1c, FBS and insulin are all measured at the same single time point for each patient.

3.10.7. Co-factors

- HIV testing at enrolment will be conducted as per guidelines and will require additional consent.

3.10.8. Adherence and its risk factors

- Adherence to ATT will be assessed by self-report at monthly follow-up visits. In addition, electronic pill boxes (Wisepill evriMED500, as referred to in the WHO Medication adherence handbook (WHO/HTM/TB/2017.30) (https://www.wisepill.com/evrimed) will be used in newly enrolled patients after the protocol amendment is approved. The evriMED500 registers every time the box is opened and the data stored on a disk within. Data is extracted via USB. Battery life is up to 2 years. The reminder alarms and light will not be enabled, so as to have minimal effect on patient drug taking behavior, but simply provide a means of measuring adherence through the proxy of box opening. Local approval from NTP coordinators will be obtained for their use and we will coordinate with participating health centre staff on their use. We will collect the data from the boxes at the study clinic visits (end of IP, mid CP and end of treatment).

- Standardized self-reported questionnaires will used to measure depression by using The Hospital and Anxiety Depression scale (HADS) , social & family support by using Multidimensional scale of perceived social support (MSPSS), stigma using Berger scale of stigma and self-esteem using Rosenberg Self-esteem Scale (RSES). These will be assessed at baseline, end of IP, mid-CP end-CP and at 6, 12 and 24 months post-treatment.

3.10.9. Lung function: spirometry and 6 minute walk test

- St Georges Respiratory Questionnaire (SGRQ) (a validated disease specific tool designed to measure impact on overall health, daily life and perceived well-being in patients with obstructive airway disease, available in Cebuano and Tagalog) (https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php.) will be conducted at end of treatment and at 6, 12 and 24 months post-treatment. This will be supplemented by the Sheehan Disability scale (5 item) http://memorialparkpsychiatry.com/doc/sheehan_disability_scale.pdf) assessed at the same time points.
- Feasibility of the six minute walk test will be investigated at each study site as per the updated guidelines of the American Thoracic and European Respiratory Societies guidelines [42]
- Lung spirometry using NDD EasyOn or EasyOn-PC spirometers and single patient use spirettes (no risk of cross-contamination) to assess obstructive, restrictive or mixed ventilation impairment will be conducted at the end of treatment and 6, 12 and 24 months post-treatment by trained research study nurses. This will be deferred should the subject be found to have TB relapse. Diagnosis of COPD will be based on

GOLD 2019 criteria [43] while diagnosis of asthma will be based on those of GINA 2018 [44].

3.11. Immune function assay methodology

5 ml Lith Hep blood samples will be collected at the health clinics and transported on ice daily to hub sites where blood will be aliquoted into the 4 QFT-Plus tubes and incubated at 37°C as per the manufacturer's instructions and within a maximum of 24 hrs after collection. After incubation, tubes will be centrifuged (15 mins, 2000-3000RCF) and the supernatant aliquoted into cryotubes and stored at -20˚C until monthly transfer to the central laboratory for longer term storage at -80˚C and batch analysis of cytokine responses using a multiplex assay.

4. Sample size

4.1. Primary objective: association between malnutrition and adverse treatment outcome

Assuming 90% power and 5% significance, a sample size of 800 patients will allow a detectable odds ratio of at least 2.1 if 25-30% of patients are malnourished and approximately 10-20% of patients have adverse treatment outcomes.

4.2. Primary objective: Association between diabetes and adverse treatment outcome

Assuming 90% power, and 5% significance a sample size of 800 patients will allow a detectable odds ratio of at least 2.8 if 10-12% of patients have diabetes and approximately 10-20% of patients have adverse treatment outcomes.

4.3. Secondary objective: malnutrition on cell mediated immune responses

Assuming 90% power and 5% significance and 30% malnutrition at enrolment a sample size of 250 (limited to those with bacteriological confirmation) should allow a difference in mean IFN-γ concentrations (in response to TB-specific antigen stimulation) equivalent to half a standard deviation to be detected between BMI groups <17 vs ≥17kg/m^2. This is based on estimates using previous IFN-γ data from 25 TB patients at San Lazaro Hospital who had not yet started ATT with BMI<17 compared to those with BMI >17 tested using with QFTGold (Appendix 1). No suitable data was available for other cytokine responses.

4.4. Secondary objective: prevalence of post-treatment adverse health outcomes

Assuming 600 of the original 800 participants can be traced at 24 months post-treatment, this sample size will provide at least 90% power to estimate the prevalence of adverse outcome, e.g. proportion with a total score >=8 on SGRQ of predicted value within ±4%, if the true prevalence is 20% allowing for a design effect of 1.5 and with increased relative precision at higher prevalence of the selected outcome or with a lower design effect.

4.5. Sampling Strategy

800 study participants >18 years newly starting anti-TB treatment during the study enrolment period at selected TB DOTS clinics from within Metro Manila, Negros Occidental and Cebu

will be approached for enrolment. The final selection of TB-DOTS centres will be based on achieving 200-300 DR-TB patients out of the total 800, and balanced between urban and semi-urban/rural sites. Logistical considerations including the number of Barangays being served by each Health Centre and distances from regional hub sites for the processing of blood samples (patient sub-set for immune responses) will also be taken into account. Currently sites will include those in which we have already worked including San Lazaro Hospital and San Nicolas Health Centre in Manila and Bago City and Valladolid Health Centres in Negros Occidental. >> updated 2nd May 2019 >> *Please see updated list of study sites in section 3.6.*

5. Data collection

Trained research nurses will be based in each study site to recruit newly diagnosed TB patients into the cohort study. For the DS TB patients in the more rural sites in Negros and Cebu, where patients may reside far from the Health Centre TB DOTS clinic, after registration, routine care is transferred from the managing health centre TB DOTs clinic to Barangay health stations and directly observed treatment is done by the Barangay health workers and designated treatment partners. Thus, the monthly follow-up visits will be conducted by our research nurses at either the Barangay health stations or at the managing TB-DOTS health centre as per the patients' routine treatment requirements. For the patient cost assessment, those that agree to participate will have home visits scheduled for the patient cost interview to be conducted by a trained research nurse. Data for the post-treatment follow-up will be collected by the research study nurses at the health centres. WHO symptom screening at 18 months post-treatment will be done by telephone and a clinic visit facilitated if they are screen positive, to receive further testing for active TB disease as per local procedures.

6. Data Management and Security

Research nurses will directly enter data into tablets using the Open Data Kit (ODK) platform (Open source) supported by the London School of Hygiene and Tropical Medicine. Tablets will be password secured and stored in a locked cabinet in a locked room when not in use. No patient data will remain on the tablet hard drive once data entry has been confirmed in real time. Paper-based data collection will be available if significant technical problems occur. Encrypted data from the tablets will be automatically uploaded to a secure and backed up server. Data quality will be continuously monitored by Philippines based co-investigator, and can be reviewed remotely by approved DOTS administrative and ethical board members subject to setting up access account. Data may only be reviewed but not altered.

7. Data Analysis

Data analysis will be conducted in Stata 14.1 (StatCorp LP).

The prevalence of each outcome will be presented as a percentage with corresponding 95% confidence intervals, overall and by region. Descriptive data summaries will correspond to data type; mean (SD) and median (range) for continuous and discrete data, raw numbers and percentages for binary and categorical variables.

The strength of evidence for associations between exposure variables of interest will be investigated using tests appropriate to data type; chi-squared tests (or Fisher's exact test as

appropriate) for association between categorical variables, spearman's correlation test, t-test, ANOVA or non-parametric tests for continuous data and categorical data associations.
Univariable analyses to quantify associations between exposures and the primary outcome of adverse treatment outcome, including death, treatment failure or default will be explored using logistic regression. *A priori* adjustments will be made, in the final model for each exposure (malnutrition and diabetes), for age and sex; These are known to be associated with TB, diabetes and lifestyle risk factors for each outcome. Adjustment will also account for any chance variability in age and sex distribution by study site. Final multivariable models for each exposure will be built using a step-wise strategy with inclusion and exclusion criteria of 0.1 (10% significance).

8. Ethics

8.1. Informed consent

All patients will be consented in the local language (Tagalog, Hilagaynon[6], or Cebuano) prior to inclusion in the study. Study information will be provided in written form and translated from English into Filipino, Hilagaynon and Cebuano. Consent forms will be back-translated to ensure accuracy of content.
Research nurses will complete the informed consent in a quiet and private location to ensure patients have free and voluntary consent uninfluenced by health centre staff. Privacy will be promoted to the highest level possible in the facilities where consent is obtained but at minimum it will be asked that the regular staff of the health centre are not present at time of consent to avoid coercion into the study. It will be stressed throughout the consent process that the research is voluntary and will not impact the care they receive from the clinic.
The patient may choose not to participate in this study and may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which they would otherwise be entitled. They do not have to explain why they do not wish to participate or why they want to withdraw. Refusing to take part in this study will not alter the treatment they are receiving in any way.

Optional HIV screening will be consented through a separate informed consent process, following the DOH protocols for HIV Counselling and Testing (HCT) – with consent being obtained by an individual who has received the appropriate DOH training.

For participants who are already enrolled in St-ATT, additional consent will be sought to participate in the post-treatment follow-up at the end of continuation phase clinic visit. For patients newly enrolling after the post-treatment follow-up has started, informed consent for both follow-up periods will be sought. For patients who have already completed ATT before post-treatment-follow up has started, they will be contacted by phone and invited to participate, starting with the first 6 month follow-up visit, unless the 6 month post-treatment follow-up period has already passed.

[6] Hilagaynon – is the correct term, corrected from Illongo before V2.0.

8.2. Patient confidentiality

All patient data will be anonymized using unique patient identifier numbers. The database will be stored as an encrypted file, with end-to-end encryption transfer of data. Only approved primary and co-investigators will have full access to modify dataset, all other team members may have access to view but not modify data. Only anonymized data will be used in the final analysis dataset and be made available after completion of the study and analysis of the main objectives on request by other researchers.

8.3. Referrals

Patients who screen positive for possible diabetes (HbA1C >=6.5%) will be referred to the doctor at the local health centre for further diagnostic tests and follow-up care, and therefore the MDs in the LHCs will be involved and government resources maximized (ie, medications, counselling). This will be implemented through letters from the study investigators to the LHC MDs listing participant lab results and indicating those that require further management. This study also has physicians as study co-investigators/team members (Dr Juan Solon, Dr Mary Christine Castro), and therefore the LHC MDs also can involve them to decide further managements for patients. Study participants who agree to HIV screening and are found to be reactive will need to have a serum sample submitted to an approved lab for confirmatory testing. Individuals will have been pre-informed during their HCT counselling about the steps that will occur if their result on the rapid screening test is reactive. Normal DOH referral procedures will be followed and the appropriate individuals notified. Patients are moderately or severely anemic (hemoglobin <11.0 g/dL) are referred back to their respective health facilities. Patients who are found during the post-treatment follow-up to meet the diagnostic criteria (or other criteria as advised by local specialists) for chronic obstructive pulmonary disease (COPD) or asthma will be reviewed by the study specialist collaborators who will refer to local facilities as appropriate with copies of the spirometry test and any other relevant data.

8.4. Subject remuneration

Based on local advice and procedures and our previous experience we are proposing to provide small remunerations at each study visit in the form of phone credit (from any of the main networks). In rare circumstances in which the participant does not have access to a mobile phone, a cash equivalent will be provided.

For TB patients: At the baseline visit they will receive the equivalent of PHP 150 and then PHP 50 at each monthly follow-up visit completed. If they agree to participate in the TB patient cost study they will receive an additional PHP 250 for each home visit (4 times in total). TB patients who agree to provide a fasting blood sample at a selected clinic visit during treatment or after TB treatment will be provided with breakfast at the clinic and an additional PHP 50. Participation in clinic visits at 6, 12 and 24 months post-treatment will be compensated the equivalent of PHP 250 at each visit.

For HHCs: At the baseline visit they will receive the equivalent of PHP 250 and then PHP 150 at each 3-monthly follow-up visit completed

9. Proposed Budget and Funds

The total budget for this project is 30,000,000 JPY (approx. PHP 14.05 million) supported by research funding from Grants-in-aid for Scientific Research (Kakenhi) awarded to Professor Sharon Cox at Nagasaki University and Nagasaki University research funding.

10. Investigators

Primary Investigator

- Professor Sharon Cox (Nagasaki University School of Tropical Medicine & Global Heath, Japan & The London School of Hygiene & Tropical Medicine, UK)

Co-investigators

- Dr Juan Solon (Nutrition Centre Philippines)
- Dr Celine Garfin (National TB Programme, Philippines)
- Professor Koya Ariyoshi (Nagasaki University School of Tropical Medicine & Global Heath, Japan)
- Mary Christine R. Castro (Nutrition Center of the Philippines)

Study statistician & Co-investigator

- Dr Tansy Edwards (The London School of Hygiene & Tropical Medicine, UK)

Collaborators

- Dr. Naomi R. Saludar (SLH) – DOTS program
- Dr. Nelson Dela Fuente (Valladolid MHO)
- Dr. Georgina Hufanda (Bago City MHO)
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- Dr Elizabeth Hollero (Dept of Radiology, Pablo O. Torres Memorial Hospital, Bacolod, Negros Occidental.
- De Pen Pablo-Villamor (Consultant Pulmonologist, Vicente Sotto Hospital, Cebu City, Cebu)

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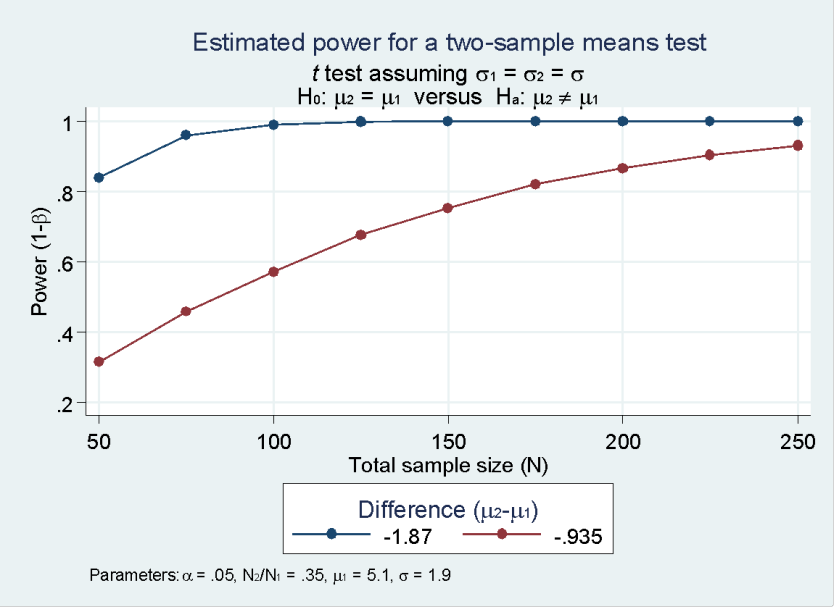
Appendix 1. Sample size calculation for immune function analysis using QuantiFERON-TB Gold Plus

Sample sizes were based on calculations using data as shown in the table below:

Table A1: Geometric mean and geometric standard deviation calculated using previous IFN-γ data from TB inpatients and outpatients in SLH (Unpublished data, Ariyoshi et al, Nagasaki University)

	Geometric mean	Geometric standard deviation
Not on ATT (N=25)	4.81	1.87
BMI<17.0 kg/m^2 (N=14)	4.24	1.72
BMI≥17.0 kg/m^2 (N=10)	5.06	1.82

Figure 1: Power provided by different sample sizes to detect a difference of 1 or 0.5 of a SD for IFN-γ responses in response to QFTGold antigen stimulation.



A sample size of 250 with a ratio of BMI<17.0 kg/m^2 vs BMI≥17.0 kg/m^2 (1:3) is estimated to provide 90% power to detect a difference in the geometric mean IFN-γ equivalent to half a geometric standard deviation.

Appendix 2. Document submission and modification history

Version	Date of change or submission or approval	Submission/reason for change	Changes (in status or in material content)
D6.0_180131	31st Jan 18	Submitted TMGH	Approved March 1st 2018.
D6.1_180206	6th Feb 18		Minor Updates, clarifications and corrections based on feedback from WPRO reviewer and in preparation for LSHTM submission. Limited to pulmonary TB cases. Added cut-offs for OGTT to confirm pre-diabetes/diabetes/normal in those with intermediate HbA1C. Changed terminology
D6.2_180207	7th Feb 2018		Changed terminology to DS instead of non-DR TB Changed Ref 28.
D6.2_180207	12th Feb 2018	Submitted LSHTM LEO	
D6.3_180312	12th Mar 2018	Submitted AEI	Added GANTT chart and dummy tables.
D6.4_180418	20th April 2018	Resubmitted AEI	Minor additions from AEI comments [minor changes to IC sheets from AEI & LSHTM]
D6.4_180418	23rd April 2018	Resubmitted LSHTM	Minor additions from AEI comments [minor changes to IC sheets from AEI & LSHTM]
V1.0_180615	15th June	Approved version	Edited to include details of all obtained approvals and change to a version. This may be further edited for additions in details and clarity. Before data collection starts the final version "in use" should have APPROVED watermark added and that version included to the study document control log. All minor amendments to be added as V1.X and recorded here.
D2.2_20180626	28th June	Submitted San Lazaro Hospital site specific protocol	Version based on V1.0_180615 but with additional SLH specific requirements /budget section, required appendices and description of linked activities for separate but related immuno sub-study with its own submitted protocol.
V1.1_180801	1st August		Correction to an error in units in random plasma glucose and clarification of inconsistency in text about criteria for HbA1C testing – text in red.
V1.2_180920 (equivalent to AEI D6.5_180920)	20th Sep	Amendment submitted to AEI	Addition of assessments of Depression, using the Hospital Anxiety Depression Scale (HADS) tool, Social & family support using Multidimensional scale of perceived social support (MSPSS), Stigma using Berger scale of stigma & self-esteem using Rosenberg Self-esteem Scale (RSES) at baseline, end of intensive phase, mid continuation and end of continuation phase. Additional text for background and justification section 2.6 added. Additional secondary objective,

			section 3.3. More references added. Table 3 modified to show extra assessments and time points, plus in the Data collection appendices. Additional Co-investigator added. Dr Elizabeth Hollero, Riverside Hospital, Philippines.
D2.2_0180626	2nd October	Approval from SLH	NB. SLH specific informed consent documents approved [SLH_V5.4 SLH_HHC V3.2, SLH_HIV_1.1] All dated Sep 27 2018. Added site specific CBC to those participating in immune-sub study.
SLH_V1.0_20181129	29th November	SLH Approved Version	SLH specific Approved version in use [Added specific CBC instead of Hemocue to those participating in immune-sub study].
V1.2_180920	5th October	Submitted to Pablo O. Torres Memorial Hospital as a new site for site-specific ethical approval	
V1.2.1_181018	18th Oct	Amendment submitted to LSHTM	Minor formatting changes, typos. Correction, removing "self administered" from the questionnaires for depression … [HADS, MPSS & RSES]". These will be administered by the research nurse as for the other questionnaires.
V1.2.2_181207	7th December	RE-Submitted to Pablo O Torres Memorial Hospital [Riverside]	Edits to the list of co-investigators and collaborators – Dr Elizabeth Hollero (Dr. Pablo O. Torre Memorial Hospital [Riverside]) changed from Co-investigator to collaborator. Dr Mary Castro, Nutrition Center Philippines added as a Co-investigator
V2.0_190503			

Appendix 3. Questionnaires

For our data collection we will be using the ODK tablet based data collection platform. All questions will be built into an ODK readable form and uploaded to the server for download onto individual tablets. Data to be collected is summarised below

a. Questionnaire: Baseline at start of treatment

- Demographic Factors
    - Date of Questionnaire Completion (dd/mm/yyyy)
    - DOTS Center participant recruited from (where registered)
    - Location of interview (Barangay Health Station name/ home/local health centre)
    - Study ID
    - DOB (dd/mm/yyyy)
    - Sex (M/F)
    - Phone number
    - Area of residence: Barangay level
    - Educational Level (none, primary, secondary, tertiary, vocational)
    - SLH social service categorization (A, B, C1, C2, C3, D)
    - Occupation
    - Cigarette smoker (Y/N/Ex-smoker) and burden (# of pack-years)
- Clinical Management
    - Basis of current TB diagnosis and diagnostic results (smear+/- & grade), (culture+/-;), Gene Xpert, Clinical diagnosis - and dates of tests/diagnosis
    - Symptom history (cough, fever, night sweats, unintentional weight loss, haemoptysis, other) including date of start of symptoms and date of diagnosis.
    - DR-TB or DS-TB
    - Previous TB treatment history – relapse; treatment after loss to follow up [TALF]; treatment after failure or previous treatment outcome unknown [PTOU].
    - Anti-TB medication regime and indication including date of initiation (dd/mm/yyyy) and doses taken since initiation
        - Which anti-MTB medications (Checklist)
            - First line; Isoniazid, Rifampin, Rifapentine, Rifabutin, Ethambutol, Pyrazinamide
            - Second line; Cycloserine, Ethionamide, Levofloxacin, Moxifloxacin/gatifloxacin, p-Amino-salicylic acid, Amikacin/kanamycin, capreomycin
    - Known diabetes (date of diagnosis–year) and its management (Metformin/Gliclazide/other medication use and dietary modifications)
    - Co-morbidities (HIV, chronic kidney disease, chronic obstructive pulmonary disease, hypertension, other)
    - Chest x-ray results
- Nutritional Status
        - Height (metres)
        - Weight (kg)
        - BMI (kg/m^2)
        - Grip strength (kg; Jamar Hydraulic Hand Dynamometer Lafayette Instruments, USA)
        - Mid-upper arm circumference (MUAC) in cm

        - Waist -Hip ratio
        - Unplanned weight loss in the last 3-6 months
        - Current appetite
- Clinical investigations
    - Blood pressure
    - Random plasma glucose (RPG) – finger prick sample.
    - HbA1c - diabetes point of care test using fingerprick blood sample if RPG ≥6.1mmol/L (110 mg/dL)
    - Oral glucose tolerance test if HbA1C>5.7 &<6.5%
    - Haemoglobin – anaemia point of care test using fingerprick blood sample
    - HIV rapid diagnostic test (if consent given) – point of care test using finger prick sample
- Household food security (using Adapted U.S. Household Food Security Survey Module (US HFSSM))[18] :

    In the last 12 months:

    - 1. Were you worried that your food would run out before you had money to buy more?
      A) Yes B) No – Go to question 2
    - 1a. How often did this occur?
      1) Often 2) Sometimes 3) Rarely
    - 2. The food you had didn't last, and you did not have enough money to buy more?
      A) Yes B) No
    - 3. Did you have to eat the same foods daily because you did not have money to buy other foods?
      A) Yes B) No
    - 4. Have you or any other adult in your household cut the size of your meals because you did not have enough money to buy food?
      A) Yes B) No
    - 5. Did you skip some of your daily meals because you did not have enough money for food?
      A) Yes B) No
    - 6. Did you ever eat less than you felt you should because you did not have enough money to buy food?
      A) Yes B) No
    - 7. Were you ever hungry and did not eat because you did not have money to buy enough food?
      A) Yes B) No
    - 8. Did you lose weight because you did not have enough money to buy food?
      A) Yes B) No
    - 9. Did you or another adult in your household ever not eat for a whole day because you did not have enough money to buy food?
      A) Yes B) No
- Quality of life using the WHO-BREF WHOQOL [Questions will be converted into ODK compatible format]
- Total patient costs, adapted WHO costing tool (Tool to estimate Patients' costs, USAID). At baseline questions will concern the costs associated with health seeking behaviour and diagnosis from the onset of symptoms – specific to TB and to DM - If applicable. Repetitions of the questionnaire will be cover the relevant periods, e.g. from start of treatment to completion of the intensive phase and be specific to TB and DM. Questions, developed as a result of our previous pilot will also ask about health seeking behaviour, and costs associated with other co-morbidities

including managing drug side-effects, malnutrition, digestion and general wellbeing – including purchase of special foods, supplements or herbal/other remedies

- Direct Medical Costs
  - Outpatient Service Cost
  - Registration Cost
  - Diagnosis/Laboratory Cost
  - Dispensing Cost
  - Drug Cost
  - Supplements/herbal remedies Cost
  - Hospitalization Cost
  - Other Service Cost
  - Expenditure at other facilities
- Direct Non-Medical Costs
  - Transportation Cost
  - Accommodation Cost
  - Special Meal/Drink Cost
  - Informal/Traditional Care Cost at home & outside of home
  - Cost of Facilities/Equipment at home
  - Number of visits to facilities
  - Time Loss for facility visit for Patient
  - Time Loss for facility visit for Accompanies
  - Payment to paid caregivers
- Indirect Costs
  - Current and previous income to estimate income Loss due to Work Absence of Patient and household member
  - Cost of Permanent Disability
  - Payment of Interest due to Loan
- Coping Strategies
  - Using cash/mobilizing savings
  - Sales of assets
  - Taking loans
  - Support from relatives or community
  - Income Diversification by Using Leisure Time
  - Working as a Wage-Labor
  - Drop out of child's schooling

- Risk factors related to adherence
  - Depression using Hospital Anxiety Depression Scale (HADS)
  - Social & family support by using Multidimensional scale of perceived social support (MSPSS)
  - Stigma using Berger scale of stigma
  - Self-esteem using Rosenberg Self-esteem Scale (RSES).

b. Questionnaire: Monthly (All participants)

- Demographic Factors
  - Date of Questionnaire Completion (dd/mm/yyyy)
  - DOTS Center where registered – check if changed
  - Location of interview (Barangay Health Station name/ home/local health centre)
  - Study ID
  - Phone number – check if changed
  - Area of residence: Barangay level – check if changed
  - Cigarette smoker (Y/N/Ex-smoker) – check if changed
- Nutritional Status & Blood pressure
  - Weight (kg)
  - BMI (kg/m^2)
  - Mid-upper arm circumference (MUAC) in cm
  - Grip strength (sub-set)
  - Body composition by bio-impedance analysis (San Lazaro site only)
  - Blood pressure
  - Unplanned weight loss in the last month
  - Current appetite
- TB Treatment adherence (from patient treatment record and patient interview (last seven days)
  - Check if change in regimen – and reasons why
  - Adherence (last 7 days) – and reasons why if non-adherent
- DM treatment and monitoring (if applicable)
  - Check if any change in treatment – and reasons why
  - Adherence – if applicable (last 7 days) and reasons why if non-adherent
  - Blood glucose monitoring in the last month - Y/N, last result if available.
- Occurrence of TB side-effects (extraction from routine records and by patient interview, last 7 days)

c. Questionnaire: End of intensive treatment phase, mid continuation and end of continuation – to include and replace usual monthly data collection (All participants)

- Clinical investigations
  - Haemoglobin – anaemia point of care test using fingerprick blood sample
- Household food security (using Adapted U.S. Household Food Security Survey Module (US HFSSM))[18] - as described at baseline, but adapted to ask about the relevant period since the last assessment:
- Quality of life using WHO BREF tool (https://www.who.int/substance_abuse/research_tools/en/english_whoqol.pdf) [Questions will be converted into ODK compatible format
- Total patient costs, adapted WHO costing tool – as described at baseline
- Risk factors related to adherence
  - Depression using Hospital Anxiety Depression Scale (HADS)
  - Social & family support by using Multidimensional scale of perceived social support (MSPSS)
  - Stigma using Berger scale of stigma
  - Self-esteem using Rosenberg Self-esteem Scale (RSES).

d. Questionnaire: Household contacts: Baseline

- Demographic Factors
    - Date of Questionnaire Completion (dd/mm/yyyy)
    - Location of interview (Barangay Health Station name/ home/local health centre)
    - Study ID and name/ID of enrolled TB contact and relationship to the TB patient
    - Duration of residence in same household as TB patient
    - DOB (dd/mm/yyyy)
    - Sex (M/F)
    - Phone number
    - Area of residence: Barangay level
    - Educational Level (none, primary, secondary, tertiary, vocational)
    - SLH social service categorization (A, B, C1, C2, C3, D)
    - Occupation
    - Cigarette smoker (Y/N/Ex-smoker)
- TB screening tests done: CXR Y/N, smear Y/N , GeneXpert Y/N and dates/results of tests
- General health status and co-morbidities
    - Any previously diagnosed conditions – including diabetes and hypertension
    - Any medications – prescribed, being taken.
- Clinical investigations
    - Haemoglobin – anaemia point of care test using fingerprick blood sample
- Nutritional Status & Blood pressure
    - Weight (kg)
    - Height
    - BMI (kg/m^2)
    - Mid-upper arm circumference (MUAC) in cm
    - Grip strength
    - Body composition by bio-impedance analysis (San Lazaro site only)
    - Blood pressure
    - Unplanned weight loss in the last month
    - Current appetite

e. Questionnaire: Household contacts: Follow-up at 3, 6, 9* & 12* months (* 9/12 months if HHC of DR-TB patient)

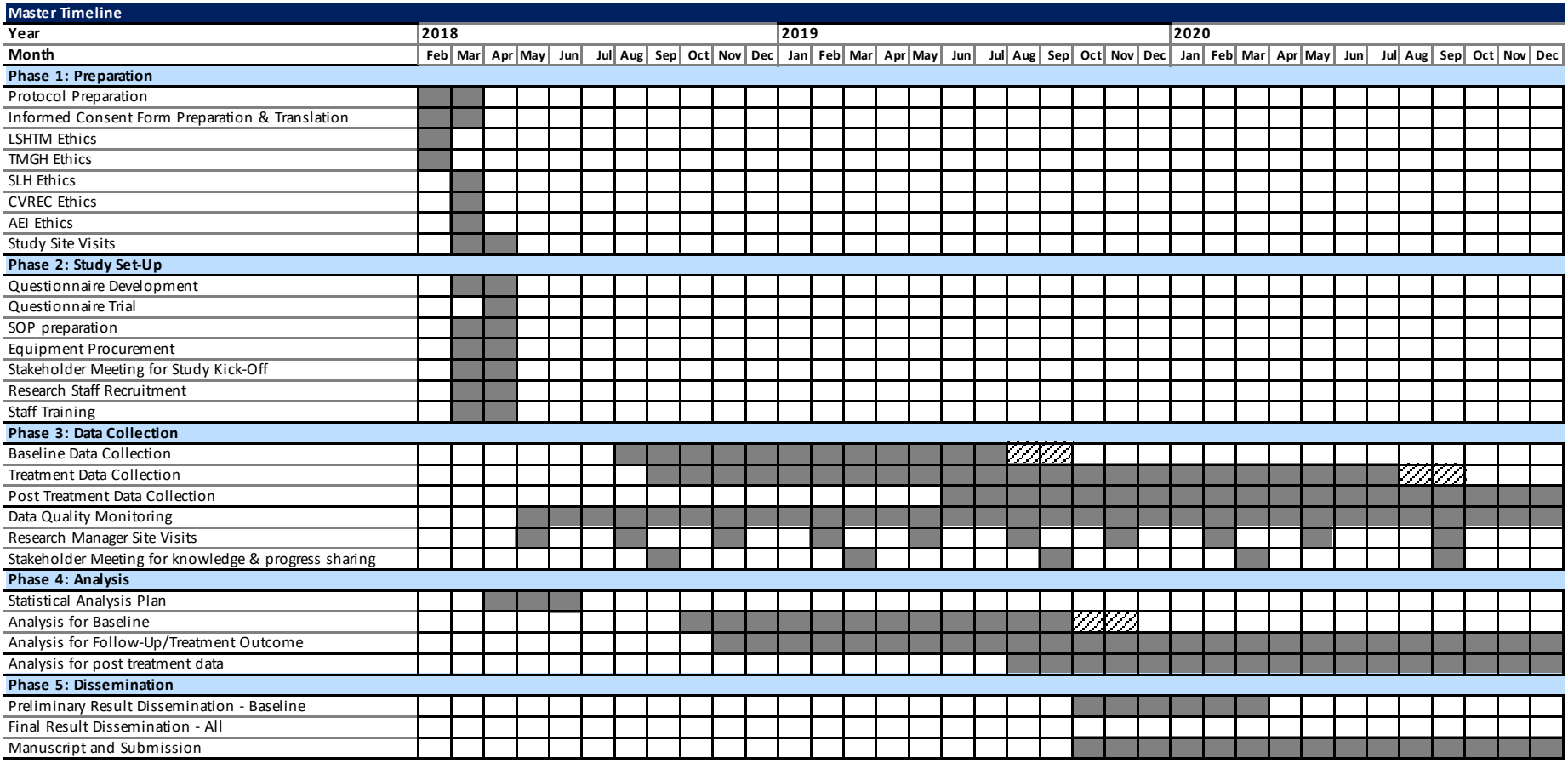
- Demographic Factors
    - Date of Questionnaire Completion (dd/mm/yyyy)
    - Location of interview (Barangay Health Station name/ home/local health centre)
    - Check if still resident in same household as enrolled TB patient
    - Phone number – check if changed
- Clinical investigations
    - Haemoglobin – anaemia point of care test using fingerprick blood sample
- Nutritional Status & Blood pressure
    - Weight (kg)
    - BMI (kg/m^2)
    - Mid-upper arm circumference (MUAC) in cm
    - Grip strength
    - Body composition by bio-impedance analysis (San Lazaro site only)
    - Blood pressure
    - Unplanned weight loss in the last month
    - Current appetite

f. End of Treatment and Post-treatment Data Collection at 6, 12 (18) and 24 months post treatment

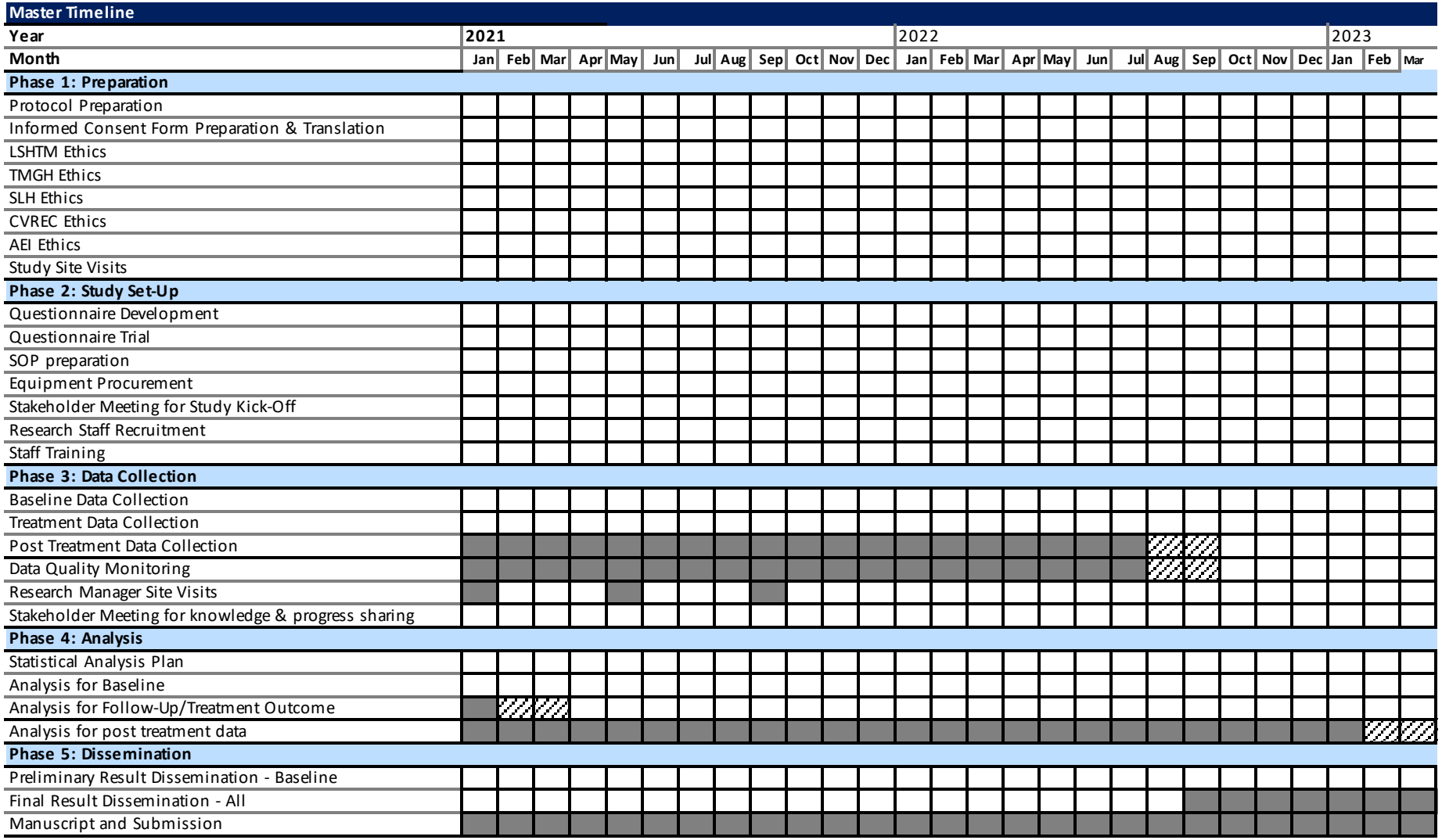
- **Chest X-Ray** (end of Treatment, 24M after treatment completion) -As described at baseline
- Anthropometry (end of treatment, 6M, 12M, and 24M after treatment completion) – As described at baseline
- Haemoglobin (finger prick) (end of treatment, 6M, 12M, and 24M after treatment completion)
- Bioimpedence Analysis (end of treatment, 6M, 12M, and 24M after treatment completion for SLH patients) – As described at baseline
- HbA1c (end of treatment, 6M, 12M, and 24M after treatment completion) – As described at baseline
- Diabetes/other co-morbidities medical treatment. (end of treatment, 6M, 12M, and 24M after treatment completion) – As described at baseline
- **Active TB screening at clinic visit or by telephone** (6M, 12M, 18M and 24M after treatment completion)- WHO symptom screening - Follow local NTP processes (if your symptom screening is positive, we call patients in)
- **Lung spirometry and 6 minute walk test** (end of treatment, 12M and 24M after treatment completion)
    - Forced Vital Capacity (FVC)
    - FEV1
    - FEV1/FVC ratio
    - VC
- **Modified Medical Research Council Dyspnea Score, (MMRC)** (end of treatment, 6M 12M and 24M after treatment completion)
- **St Georges Respiratory Questionnaire** (end of treatment, 6M 12M and 24M after treatment completion)
    - 50-item questionnaire including three domains: symptoms, activity and impact to calculate a total score to measure health status in patients with respiratory disease.
- **Sheehan Disability scale** (End of treatment, 6M, 12M and 24M after treatment completion)
    - 5-item self-report tool to assess functional impairment on three domains: work/school, social life, and family life
- Health related behaviours: smoking, alcohol, drug-use, changes in behaviour post-treatment (End of treatment, 6M, 12M, and 24M after treatment completion)
- Occupation & Income – changes since completing treatment; 6M, 12M, and 24M after treatment completion)
- Symptom history and health seeking behaviour -changes since completing treatment, 6M, 12M, 18M and 24M after treatment completion)
- Household food security (end of treatment, 6M, 12M, and 24M after treatment completion as described at baseline)
- **WHO-BREF Quality of Life Questionnaire** (end of treatment, 6M, 12M, and 24M after treatment completion as described at baseline)

  Depression, stigma, SFS (End of treatment, 6M, 12M, and 24M after treatment completion as described at baseline)

Appendix 4. Gantt chart (updated)



Gantt chart (updated)-continued.



Appendix 5 Dummy tables (needed for AEI? Not needed for LSHTM/TMGH)

Table 1. Demographic information

	Treatment Success n=x (%)	Adverse Treatment Outcome n=y (%)	P-value	All n=x+y (%)
Sex Male Female				
Age Mean±SD				
Education None Primary Secondary Tertiary				
Employment Status Employed Unemployed				
Marital Status Single Married Widow/Divorced				
Family Size ≦5 >5				
Household Income Mean±SD Under Poverty Line Under National Average Above National Average				
Urban/Rural Metro Manila Cebu Negros Occidental				
Smoking Yes No Ex-Smoker				

Table 2. Clinical Characteristics of TB by treatment success

	Treatment Success n=x (%)	**Adverse Treatment Outcome** n=y (%)	**P-value**	**All** n=x+y (%)
Diagnosis				
Clinically Diagnosed				
Smear-Positive				
Xpert Positive				
Drug Susceptibility				
DS-TB				
DR-TB				
TB Registration				
New				
Relapse				
Treatment After Failure				
TALF				
PTOU				
HIV				
Positive				
Negative				
Unknown				
TB Regimen				
Category I				
Category Ia				
MDR-shorter regimen				

Table 3. Clinical characteristics of Anthropometry & Diabetes by treatment success[7]

	Treatment Success n=x (%)	**Adverse Treatment Outcome** n=y (%)	**P-value**	**All** n=x+y (%)
BMI ≦17.0 >17.0				
BMI Mean±SD				
MUAC Mean±SD				
Body Fat & Muscle Mean±SD (Body Fat) Mean±SD (Body Muscle)				
Haemoglobin Level Normal Mild and moderate Severe				
Blood Pressure Mean±SD				
Diabetes Diagnosis Normal Pre-Diabetic Diabetic				
Diabetes Treatment None Mono Therapy Dual Therapy or More without Insulin Dual Therapy or More with Insulin Other				
Diabetes Complication/Disability Yes No				

Stratification by Urban/rural and DS/DR TB will be investigated

[7] Basic tables only shown for primary outcome. Analysis will likely include multiple level models of time-varying co-variates, e.g. multiple measures of nutritional status as a risk factor for the primary outcome of adverse treatment outcome

Table 4. Characteristics of Anthropometry & Diabetes in HHC compared to TB index cases – *analysis adjusting for clustering within households, may be stratified by urban/rural, DS-DR-TB status, Household income level***.**

	HHC n=x (%)	**TB index case** n=y (%)	**P-value**	**All** n=x+y (%)
BMI ≦17.0 >17.0				
MUAC Mean±SD				
Body Fat & Muscle Mean±SD (Body Fat) Mean±SD (Body Muscle)				
Haemoglobin Level Normal Mild or moderate severe				
Blood pressure Mean±SD				

Table 5. Total Patient Costs ***** *may be stratified by DM vs non-DM, urban vs rural and association with treatment outcome assessed.*

	DS-TB Mean (%)	DR-TB Mean (%)	P-value
Total Patient Cost			
Direct Cost			
Direct Medical Cost			
Outpatient Service Cost			
Diagnosis/Laboratory Cost			
Dispensing Cost			
Drug Cost			
Supplement/Herbal Remedies Cost			
Hospitalization Cost			
Other Service Cost			
Expenditure at Other Facilities			
Direct Non-Medical Cost			
Transportation Cost			
Accommodation Cost			
Special Meal/Drink Cost			
Informal/Traditional Care Cost at home & outside of home			
Cost of Facilities/Equipment at home			
Cost of Time Loss to Visit for Patient			
Cost of Time Loss to Visit for Accompanies			
Payment to paid caregivers			
Other Expenses			

Indirect Cost			
Indirect Non-Medical Cost Income Loss due to Work Absence for Patient Income Loss due to Work Absence for Family Cost of Permanent Disability Payment of Interest due to Loan			

Table 6. Patient Costs as a Proportion of Household Income

	DS-TB Mean (%)	**DR-TB Mean (%)**	**P-value**
Monthly Household Income			
TB Diagnosis Intensive Phase Continuation Phase			

Table 7. Proportion of households with catastrophic costs by DM and malnutrition status – may be stratified by DS/DR-TB status.

	Catastophic TB total costs # (%)	Non-catastrophic TB total costs # (%)	P-value
Diabetes Diabetic on treatment Diabetic not on treatment Non diabetic			
Malnutrition ≦17.0 >17.0			

Table 8. Patient Coping Strategy for TB Patient

	DS-TB # (%)	DR-TB # (%)	P-value
Total Number of Patients			
Coping Strategy Using cash/mobilizing savings sales of assets Taking loans Support from relatives or community Income Diversification by Using Leisure Time Working as a Wage-Labor Drop out of child's schooling			

Table 9. prevalence of adherence among TB patients with and without malnutrition and DM

	Adherence # (%)	Non-adherence # (%)	P-value
Diabetic			
Non diabetic			
Malnutrition BMI ≦17.0 BMI >17.0			

Table 10. The effect of risk factors on adherence

	Adherence # (%)	Non-adherence # (%)	P-value
Depression			
Social & family support			
Self-esteem			
Stigma			