Low Dose Corticosteroids and Theophylline in the Treatment of Chronic Obstructive Pulmonary Disease – the TASCS Study (Theophylline and Steroids in COPD Study)

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Chief Investigators are members of the Steering Committee.

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Prof Christine Jenkins
Prof Peter Barnes
Prof Bartolome Celli
Prof John Seale

Responsibilities:

The Chief Investigators are responsible for implementing the study protocol. The Steering Committee is responsible for ensuring that study implementation is consistent with the stated objectives, procedures and outcomes for a study conducted according to ICH GCP (Good Clinical Practice).

2. Sponsor and Contacts

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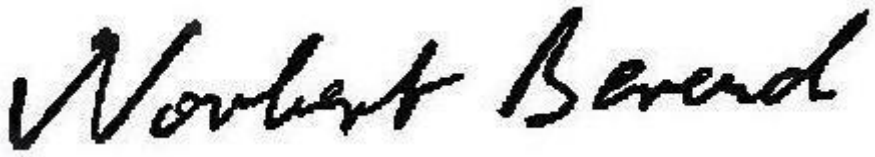
1. Chief Investigator's Signature

I have read and approve this protocol. I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Name (print):	Professor Norbert Berend
Signature:	
Date of Signature:	27th May 2015

2. Participating Centre Investigator Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make all reasonable efforts to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the study Steering Committee to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study. I understand that the study may be terminated or enrolment suspended at any time by the Steering Committee, with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Investigator's Name (print):	
Signature:	
Date of Signature:	

3. List of Abbreviations

Abbreviation	Term
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ATS	American Thoracic Society
BSQ	Brief screening questionnaire
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
DSMC	Data Safety Monitoring Committee
e-CRF	Electronic Case Report Form
FBC	Full Blood Count
FDA	Food and Drugs Administration
FEV1	Forced expiratory volume in 1 second (L)
FVC	Forced Vital Capacity (L)
GCP	Good Clinical Practice
GGT	Gamma - glutamyl transferase
GOLD	Global Initiative for Obstructive Lung Disease
HRU	Health Resource Use
ICC	International Coordinating Centre
ICH	The International Conference on Harmonization
ICS	Inhaled Corticosteroids
ITT	Intention To Treat Trial
LABA	Long acting beta-2 agonist
LAMA	Long acting anti-muscarinic antagonist
PCA	Participating Centre Agreement
RCT	Randomised Controlled Trial
SABA	Short acting beta-2 agonist
SAE	Serious Adverse Event
SGRQ	St George's Respiratory Questionnaire
TGA	Therapeutic Goods Administration

4. Synopsis

Study Title	Low dose corticosteroids and theophylline in the treatment of COPD – the TASCS Study (Theophylline and Steroids in COPD Study)
Clinical Phase	IV
Study Rationale	This trial aims to assess the effect of low dose theophylline, singly or in combination with low dose oral prednisone, on COPD exacerbations, quality of life, and secondary clinical outcomes compared with placebo over 48 weeks. The study has been designed with clinically important outcomes, in order to be feasible in multiple centres in China. The inclusion criteria ensure that the results are generalisable to the majority of symptomatic patients with COPD.
Trial Design	This is a multi-centre, double blind, randomised, controlled trial comparing low dose theophyline alone or in combination with low dose prednisone, versus placebo over 48 weeks in patients with COPD.
Study Intervention	This is a trial with a 3-arm blinded, double dummy comparison: 1. placebo and placebo 2. low-dose theophylline and placebo 3. low-dose theophylline and low dose oral prednisone.
Study Medications & Dose	Prednisone 5 mg daily, slow release theophylline 100mg bd and matched placebos
Intervention Duration	48 weeks
Rationale for Number of Participants	1650 patients are required to detect 20% relative risk reduction (80%power, 2-tailed alpha) for comparison of low dose theophylline and low dose prednisone versus placebo (arm 3 vs arm1) for the primary outcome, number of COPD exacerbations per patient over 48 weeks, annualised to 12 months in a 3-arm trial. A 20% risk reduction, with baseline of 1 exacerbation per year, 15% drop out, 12 months follow up and 80% power would require 550 patients per arm. In addition, low dose theophylline administered alone will be compared with placebo (arm 2 vs arm 1).
Study Endpoints	<u>Primary Outcome</u> The primary outcome for this study is the difference between the three treatment groups in • COPD exacerbation rate <u>Secondary Outcomes</u> • Time to first severe exacerbation requiring hospitalisation or death • Quality of Life using the St George's Respiratory Questionnaire

	• COPD Assessment Test (CAT), score out of total 40 • Pre-bronchodilator spirometry • Post-bronchodilator spirometry Analyses will include difference in exacerbation rates between the two groups at 12-, 24 and 48 weeks. Quality of life will be assessed by the change in quality of life between randomisation and 48-weeks visit measured by the SGRQ. Study specific Adverse Events and Serious Adverse Events assessments will be recorded including those recorded in the participant diary, phone visits and at 12 weekly study visits, serum theophylline levels collected at baseline, 12- and 48-weeks in a subgroup of 100 participants will be stored and analysed at the end of the participant follow up. In addition, the ACTH stimulation test will be performed at and 50-weeks in another subgroup of 100 participants. Symptoms attributable to corticosteroid and theophylline toxicity will be recorded at each patient visit.
Medication Adherence	Medication compliance will be assessed by residual tablet count at each study visit. Good compliance is defined as taking > 80% of study medication.
Inclusion Criteria	Patients will be eligible for inclusion if they • Are current or former smokers (> 10 pack years) • 40-80 years of age • Have a clinical diagnosis of COPD • Have a post-bronchodilator FEV1 < 70% predicted • Have FEV1/FVC ratio < 70% after bronchodilator
Exclusion criteria	Patients will be excluded if, in the opinion or knowledge of the responsible clinician: • Life expectancy of less than 12 months • Exacerbation or respiratory infection within 4 weeks prior to randomisation • Patient is taking and requires maintenance oral corticosteroids • Patient is on domiciliary oxygen • There has been previous pulmonary resection • Previous sensitivity to, or intolerance of theophylline • Coexistent illness precluding participation in the study (epilepsy, chronic liver disease, unstable cardiovascular disease, diabetes, active malignancy) • Inability to complete quality of life questionnaire • Concomitant major illness that would interfere with visits, assessments and follow-up

	• Have evidence of chronic liver disease, or transaminase or GGT elevation > 1.5 x ULN • Random blood glucose level > 8 mmol/L • High chance in the view of the treating physician that the patient will not adhere to study treatment and follow up • Current asthma • Pregnancy or breast feeding
Number of Participants	1650 participants
Centres	Centres will be recruited in China
Treatment Administration	Patients will be randomized to receive either theophylline and placebo 2 tabs twice a day or prednisone and theophylline 2 tabs twice a day or placebo and placebo 2 tabs twice a day for 48 weeks. Randomisation will be stratified by smoking status and centre. Returned by participant tablets will be counted at study visit.
Safety Evaluation	Safety for individual participants will be assessed on an ongoing basis by physical examination including vital signs, laboratory assessments, and monitoring of adverse events. Symptoms attributable to corticosteroid and theophylline toxicity will be sought and specifically recorded at each patient visit. A subgroup of 100 participants, will have serum theophylline measured at baseline, 12- and 48- weeks. Another subgroup of 100 participants, , will have the ACTH stimulation test performed at 48 weeks.
Efficacy Evaluation	Data will be collected from participant visits at baseline, 12, 24, 36, and 48 weeks.
DSMC Analysis	Safety data will be reviewed at 6-12 month intervals and/ or when 25%, 50 %, 75% and 100 % participants have been randomised. Thereafter safety data review will be at the discretion of the DSMC and/or the Steering Committee.
Ethical Approval	Application for ethical approval for the conduct of the study will be submitted to the Human Research Ethics Committee (HREC) of the University of Sydney, followed by submission to either HREC at each participating hospital or to a central ethics committee (or equivalent) as appropriate in accordance with the national and local regulatory and research ethics guidelines applicable in China.

5. Schedule of Study Tests, Procedure and Visits

Table 1 Schedule of Study Tests, Procedures and Visits

Assessment Description	Screening 2--4 weeks prior to randomisation	Baseline/ Randomisation (Week 0)	6,18,30, 42 weeks (phone)	12 weeks	24 weeks	36 weeks	48 weeks	50 weeks
Informed Consent	X							
Physical Examination incl. blood pressure	X							
Spirometry	X	X		X	X	X	X	
CAT score		X		X	X	X	X	
Medications	X	X		X	X	X	X	
Demographics, Medical History, Vital signs	X							
SGRQ		X					X	
Routine pathology as listed below[1]	X							
ACTH stimulation test[3] (100 participants)								X
Serum theophylline levels (100 participants)		X		X			X	
Plasma storage for subsequent analysis[4]		X					X	
Study Medication Dispense and Compliance		X		X	X	X	X	
Adverse Events/Serious Adverse Events[2]		X	X	X	X	X	X	
Participant Diary review			X	X	X	X	X	
Vital status		X	X	X	X	X	X	

[1] Routine pathology collected at screening:
Haemoglobin, White cell count, Platelets, Potassium, Sodium, Chloride , SGOT, SGPT, LDH, GGT (Gamma Glutamic Transpeptidase), neutrophils, lymphocytes, monocytes, eosinophils, basophils, Bicarbonate, Blood Urea Nitrogen, Creatinine

[2] Study Specific AEs and all SAEs will be collected from randomisation until completing the study or withdrawal from the study. This includes the records in the participant diary.

[3] The ACTH stimulation test will be performed 2 weeks after completion of 48 weeks study treatment. A visit window is not applicable for this test.

[4]Plasma is collected at selected sites with suitable storage facilities
Study visits window is ± 2 weeks.

6. Administrative Structure

6.1 International Coordinating Centre

The International Coordinating Centre (ICC) is based at The George Institute for Global Health. The ICC has responsibility for the overall management of the study including the following: assistance with HREC applications, management of study budget, liaison with funding bodies; funding applications; liaison with Coordinating Centre staff, Steering Committee and Data Safety Monitoring Committee (DSMC), case report form design; preparation and completion of Investigator contracts; management of regulatory affairs; study set up, monitoring and study close out at the participating centre; training of Investigators and Study Coordinators; organisation of Investigator meetings; liaison with Independent Data and Safety Monitoring Committee; data analysis and collaboration on publications.

6.2 Data Management

Data management will be provided by The George Institute for Global Health and the principle means of data collection and data processing will be electronic via the Internet. All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date. Quality control of spirometry will be managed using software standardized for EasyOne spirometers used in the Burden of Obstructive Lung Disease Study, and overseen by Professor Norbert Berend, Chief Investigator.

6.3 Clinical Centres

Individual clinical centres will manage the study at their own centre in accordance with the study protocol. Additionally, the individual centres will manage:

- protocol education of staff members involved in the study,
- participant recruitment,
- data collection, storage and data transfer
- spirometry training, documentation and quality
- data query resolution at their centre
- liaison with local ethics committee regarding adherence to local ethics committee guidelines and reporting requirements,
- adverse event reporting to ethics committee and the international/regional coordinating centre.

7. Funding and Insurance

The study is funded by a National Health and Medical Research Council of Australia Project Grant and by seeding grants from The George Institute for Global Health and the George Foundation.

The study was designed by the Principal Investigators, and initiated at the George Institute for Global Health. The study design, protocol and procedures have been finalised in collaboration with The George Institute for Global Health.

The George Institute for Global Health certifies that it has taken out a liability insurance policy. This insurance policy is in accordance with local laws and requirements. The insurance of The George Institute for Global Health does not relieve the Investigator or manufacturers of the study interventions of any obligation to maintain their own liability insurance policy as required by applicable law. Liability and insurance provisions for this study are given in separate clinical trial agreements.

8. Study Background

8.1 Burden of Disease

Chronic obstructive pulmonary disease (COPD) accounts for a large proportion of the global burden of death and disability and is projected to rise even further over the next few decades. Strategies for the prevention of COPD, such as tobacco control and reduction in indoor smoke pollution, are critical components of the necessary public health response. However, in the short to medium term, prevention alone will not be enough to deal with the huge burden of largely irreversible lung disease that is now unavoidable. Therefore affordable treatment strategies that improve symptoms and quality of life are also an essential component of the public health response. In combination, anti-inflammatory drugs and long acting bronchodilators, while having a doubtful effect on progression of disease or reducing mortality, are effective in reducing exacerbations, improving lung function and quality of life. However, these medications are expensive and unaffordable for many patients, particularly in low-income countries, where the prevalence of COPD is particularly high and is increasing most rapidly. Oral corticosteroids and theophylline are available at much lower cost and there is compelling new evidence that suggests that when given at low doses in combination, they will act synergistically to confer worthwhile benefits. If proven effective, such therapy will offer the first affordable treatment option for many patients with COPD in resource-poor settings around the world. Furthermore, oral drugs are easier to administer and may have an advantage over inhaled medication in targeting the peripheral lung which is the main site of disease activity.

8.2 The Global Burden of COPD

In recent studies using standardised methodology including spirometry, the prevalence rates across the world for Global Initiative for Obstructive Lung Disease (GOLD) stage II to IV ranged from 6-19% of the population [2-3]. The morbidity of COPD is considerable. Estimates of the years of living with disability (YLD) for COPD of 1.7 YLD per thousand represents about 1.8% of all YLDs. The economic cost of COPD is huge. A telling figure is that the annual cost of healthcare per capita in the United States for people with COPD is approximately 2.5 times the expenditure for people without COPD [2]. The social burden of COPD as measured by Disability-Adjusted Life Years (DALYs) ranked 12th in the world in 1990 and is estimated to become the 5th leading cause of DALYs by 2020 [3]. The mortality of COPD is increasing with deaths attributed to COPD ranking sixth in 1990 and COPD projected to be the third leading cause of death by 2020 [3] . Reasons for the increase include greater longevity of the

population, allowing people to develop COPD later in life, and continuing exposure to noxious agents which cause COPD.

8.3 Risk Factors for COPD

Cigarette smoking and exposure to smoke from combustion of biomass fuels are the most common causes of COPD. While cigarette smoking is the most common cause in Western countries, both causes are common in Asia and the developing world[4]. Whilst the prevalence of smoking in women in most Asian countries is < 5% [5], women and children have significant exposure to indoor air pollution due to combustion of unprocessed biomass (wood, dung, coal and crop residues) for cooking, heating and lighting in developing countries. It has been estimated that up to 3 billion people world-wide and 90% of rural households are exposed to open fires or poorly functioning and unflued stoves and heaters[6], including China and India [7,8]. Women are at particularly high risk because of longer periods of exposure in the home [9, 8]. One study in China has demonstrated a greater prevalence of COPD in rural women exposed to biomass smoke than in cigarette smoking city women [8]. In China the prevalence of COPD in men is 12.4% whereas in women it is 5.1% [10]. Therefore, although the main cause of COPD in women in China appears to be biomass smoke exposure, passive smoking is also an important cause of COPD amongst non-smokers in China. The overall prevalence of COPD in Chinese non-smokers is 5.2%[11]. In summary, throughout the Asia Pacific region and in other developing parts of the world, cigarette smoking is much more prevalent in men than in women and most of the COPD in women appears to be caused by biomass smoke exposure.

8.4 Treatment for COPD

Treatment for COPD involves a number of modalities including pharmacological treatment (bronchodilators and anti-inflammatory agents), pulmonary rehabilitation, vaccination against influenza, and domiciliary oxygen and lung volume reduction surgery for severe and end-stage disease [1].

8.4.1 Currently Recommended Pharmacological Treatment for COPD

The mainstay of pharmacological treatment is the early and sustained use of bronchodilators, and the later introduction of inhaled corticosteroids. The current GOLD evidence -based guidelines for COPD[1] recommend short and long acting bronchodilators (beta agonists and muscarinic antagonists) alone or in combination for symptomatic mild to moderate COPD (GOLD stage 1 and 2). Theophylline is also of benefit but due to its potential toxicity when used in bronchodilating doses is regarded as a second-line drug. The addition of inhaled corticosteroids (ICS) is recommended for severe to very severe COPD (FEV1 ≤ 50% pred, GOLD stage 3 and 4) with frequent exacerbations[12,13]. Combination ICS and long acting bronchodilator is usually given as ICS/LABA combination in a single inhaler. There is emerging evidence that the addition of a long acting antimuscarinic (LAMA) to the ICS/LABA combination offers additional benefit[14] .

8.4.1.1 Limitations of Current Pharmacological Treatment

Short-acting beta agonists, LABAs and LAMAs are effective in reducing airway smooth muscle tone and offer relief of breathlessness, improve quality of life and reduce exacerbations. However, COPD is an inflammatory disease of the lungs with extra-pulmonary inflammatory manifestations[15-18]. The anti-inflammatory agents used in COPD are ICS but, in contrast to asthma where they have potent anti-inflammatory effects and markedly reduce clinical morbidity, they have disappointingly limited efficacy in improving inflammation in COPD [19,20].

8.4.1.2 The High Cost of Current Pharmacological Treatment

Tiotropium and combination therapies of ICS and LABAs are expensive and impose a large financial burden on patients in low-income countries and on governments in countries which provide full or partial cover for the cost of medications. In Australia, the total cost of COPD is estimated to be ~$A8.8 billion 6, with the health system shouldering ~$0.9billion of this cost. After the cost of hospitalisation ($473M or 63%), pharmaceuticals make up the next highest share ($147M or 20%). In China the annual cost for a patient with COPD treated with tiotropium is RMB 6132 ($A907) and with high dose Seretide RMB 5076 ($A 761). There is therefore an urgent need for an effective low-cost treatment option.

8.5 Rationale for the Proposed Study

ICS have very limited efficacy in COPD and hence there is a large effort by the pharmaceutical industry to find more effective agents. Even if these efforts bear fruit it is highly likely that the new agents will be expensive and will continue to impose a large financial burden and, in the worst case, will totally deny patients access to these drugs. There is now a large body of evidence from studies carried out in vitro and in vivo that corticosteroids and theophylline, both in low dosage, have synergistic and clinically useful anti-inflammatory effects in COPD [21-29]. The molecular mechanisms for this effect have been elucidated and a proof of concept clinical study has been published. A large clinical trial is now required to more clearly define the magnitude of the clinical benefit. Such a study will not be funded by the pharmaceutical industry as these drugs are off patent and cheap. The impact of a positive study outcome will be immense throughout the developing world. In China, the annual cost to a patient of low dose prednisone (RMB 11, $A 1.70) in addition to theophylline (RMB 146, $A 22) is approximately 1.4% of the cost of the inhaler combination of fluticasone and salmeterol (Seretide™).

Apart from the efficacy and cost advantage of the proposed regimen and lack of increased systemic steroid exposure, other compelling arguments can be made in favour of oral therapy in COPD. Although both fluticasone and budesonide have high topical activity, when given by inhalation they may not be distributed uniformly to the small airways where the functionally important airway inflammatory and fibrotic changes are located in COPD[30,31]. The most severely affected airways are minimally ventilated and will receive little drug [31]. Giving both prednisone and theophylline orally will ensure good penetration to the peripheral airways via the systemic and pulmonary circulation [32]. In addition, oral therapy will abolish the risk of laryngeal side-effects seen with ICS [33,34]. This is particularly the case in older patients in whom

difficulties with co-ordination and correct device use can markedly affect pulmonary deposition[35].

Adherence to prescribed medication is problematic in chronic disease. In COPD the causes of low adherence have been investigated and are found to be complex and include race/ethnic and cultural differences [35]. There is evidence that adherence to inhaled medication is lower than to oral therapy of the same class of drug [36, 37]. Cost-related non-adherence is highly prevalent in asthma and COPD (31% in a recent study) even in the United States. Similarly, cost was a cause of non-adherence in the Asia-Pacific region in 37% of surveyed patients [37]. In addition, correct inhaler use is a major issue whereby even adherent patients may receive inadequate dosing unless adequate instruction is given initially with repeated follow-up. Even in developed countries inadequate inhaler technique is seen in nearly half of all patients [38,39].

8.6 Intervention Plan

This study will assess the efficacy of two relatively inexpensive treatment options already widely available around the world: oral theophylline and oral corticosteroids (prednisone). The study will test low dose theophylline administered in combination with low dose prednisone, compared to placebo over 48 weeks.

The study has been designed with clinically important endpoints in order to be feasible in centres in China. The wide inclusion criteria ensure that the results are generalisable to the majority of symptomatic patients with COPD.

This randomised clinical trial will be conducted with a 3-arm blinded, double dummy comparison:
Arm 1. Placebo (1 tablet twice a day) + placebo (1 tablet once a day)
Arm 2. Low-dose theophylline (100mg slow release) (1 tablet twice a day) + placebo (1 tablet once a day)
Arm 3. Low-dose theophylline (100mg slow release) (1 tablet twice a day) + low dose oral prednisone (5mg) (1 tablet once a day)

9. Study Design

9.1 Hypothesis and Aims

We hypothesise that patients with COPD will have beneficial responses to combination of low dose theophylline and low dose prednisone, superior to placebo reflected by a range of clinically important outcomes.
Further we hypothesise that there will be no significant increase in serious adverse events and study specific adverse events in patients receiving both prednisone and theophylline, compared to placebo.
The primary efficacy comparison aims to demonstrate that treatment with low dose oral prednisone and low dose, slow release theophylline compared to placebo will reduce COPD exacerbations over 48 weeks.

9.2 Study Treatments

This randomised clinical trial will be conducted with a 3-arm blinded, double dummy comparison:

Arm 1. Placebo (twice a day) + placebo (once a day)
Arm 2. Theophylline 100mgs (twice a day) and placebo (once a day)
Arm 3. Theophylline 100mgs (twice a day) and prednisone 5 mgs (once a day)

9.2.1 Permitted Concurrent Therapy

Patients may continue on the following:

- regular inhaled LAMA or LABA therapy
- short acting anticholinergic inhaled medication
- short acting beta agonist (SABA) inhaled rescue medication

9.2.2 Non-Permitted Concurrent Therapy

The following maintenance medications are not permitted during the study:

- Inhaled corticosteroids, except at exacerbation for maximum seven (7) days
- Daily oral corticosteroids in addition to study medication
- Parenteral corticosteroids
- Oral syrups or other formulations containing theophylline

9.3 Study Outcomes

9.3.1 Primary Outcome

Number of COPD exacerbations per participant in 48 weeks

Definition of a severe COPD exacerbation – symptomatic deterioration in COPD symptoms (cough, sputum production or dyspnea) requiring treatment with antibiotics, increase in the dose of oral corticosteroids, hospitalisation or a combination of these.

9.3.2 Secondary Outcomes

- Time to first severe exacerbation leading to hospitalisation or death
- Quality of Life using the St George's Respiratory Questionnaire
- COPD Assessment Test (CAT), score out of total 40
- Pre-bronchodilator spirometry: FEV1, FVC, FEV1/FVC
- Post-bronchodilator spirometry: FEV1, FVC, FEV1/FVC

- Mild, moderate and severe exacerbations. Exacerbations are defined as worsening for at least two consecutive days of two or more of the major symptoms (dyspnoea, sputum volume or sputum purulence) or worsening of any one major symptom together with any one minor symptom (sore throat, colds (nasal discharge or nasal congestion), fever without other cause, cough or wheeze). **Severity grades:**
  - **Mild** : exacerbations requiring symptomatic treatment with inhaled bronchodilators only
  - **Moderate** exacerbations are those managed with antibiotics and/or oral corticosteroids**;**
  - **Severe** exacerbations are those that resulted in emergency department presentation hospitalization**.**

9.3.3 Study Duration

48 weeks of study treatment

9.3.4 Number of Participants

Total of 1650 randomised participants, with 550 in each treatment arm

10. Study Population

10.1 Participant Recruitment

10.1.1 Study Population

The definition of COPD adopted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] is generally accepted world-wide. COPD is a preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways or lung to noxious inhaled particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production and /or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this context. A post-bronchodilator FEV1/FVC ratio < 0.7 confirms the presence of airflow limitation and thus the diagnosis of COPD.

This is the definition that will define the patient population in this trial. GOLD defines severity of COPD in terms of post-bronchodilator spirometry, performed according to ATS standards after administration of 400mcgs salbutamol. Four stages are recognised:

GOLD 1 - Mild - FEV1/FVC< 0.7, FEV1≥ 80% predicted
GOLD 2 - Moderate - FEV1/FVC < 0.7, 50% ≤ FEV1 < 80% predicted
GOLD 3 – Severe - FEV1/FVC< 0.7, 30% ≤ FEV1 < 50% predicted
GOLD 4 – Very severe – FEV1/FVC < 0.7, FEV1 < 30% predicted

Although there is imperfect correlation between classification of severity by spirometry and symptoms, using inclusion criteria of FEV1/FVC < 0.7 and FEV1< 70% predicted will include most patients with symptomatic COPD.

10.1.2 Participant Inclusion Criteria

Participants are eligible for INCLUSION in the study if ALL the following criteria are met:

- Current or former smokers (> 10 pack years) or biomass exposure
- 40 – 80 years of age
- Clinical diagnosis of COPD
- Post-bronchodilator FEV1 < 70% predicted
- Post bronchodilator FEV1/FVC ratio < 70%

10.1.3 Participant Exclusion Criteria

- Patients will be EXCLUDED from the study if, in the opinion or knowledge of the responsible clinician any of the following criterion is present:
- Life expectancy of less than 12 months
- Exacerbation or respiratory infection within 4 weeks prior to randomisation
- Patient is taking and requires maintenance oral corticosteroids
- Patient is on domiciliary oxygen
- There has been previous pulmonary resection
- Previous sensitivity to, or intolerance of theophylline
- Coexistent illness precluding participation in the study (epilepsy, chronic liver disease, unstable cardiovascular disease, diabetes, active malignancy)
- Inability to complete quality of life questionnaire
- Concomitant major illness that would interfere with visits, assessments and follow-up
- Have evidence of chronic liver disease, or transaminase or GGT elevation > 1.5 x ULN
- Random blood glucose level > 8mmol/L
- High chance in the view of the treating physician that the patient will not adhere to study treatment and follow up.
- Current asthma
- Pregnancy or breast feeding

11. Assessments and Study Visits

11.1 Brief Study Visits Outline

Patients with COPD and considered eligible will undertake a screening visit, two to four weeks before the randomisation visit (Baseline, Week 0). During the four week run-in, all prohibited medications, specifically any theophylline containing medications and ICS will be ceased. LABA, LAMA and SABA may be continued. The patient's usual supply of SABA will be used as rescue medication throughout the study.
Spirometry before and after bronchodilator, according to ATS criteria will be performed at the screening visit to confirm eligibility. Patients will be randomised to treatment groups and provided with blinded medication at the baseline visit. The study visits will take place at 12 week intervals for 48 weeks. At each visit study medication will be dispensed to the participant to ensure supply for the following 12 weeks. In summary, the information that will be sought

from all the participants is outlined in Table 1 - Schedule of Study Tests, Procedures and Visits. All visits have a window is 2 ± week.

11.2 Participant Consent

Prior to any study related procedures being performed informed consent is to be obtained from each participant.

11.3 Study Visits

11.3.1 Screening Visit

The purposes of the screening evaluation are to identify patients for study enrolment, provide potentially eligible patients with information regarding the study, obtaining the informed consent for participation in this study. Assessment at this visit will include spirometry and gathering information on the type of medication a potential participant is using for their COPD treatment. If a participant wishes to participate they will be asked to withdraw the inhaled corticosteroids or theophylline before being randomised to one of the three study groups. Study staff at the centre will also estimate patient's ability to adhere to study treatment and clinic visits, and also their capacity to complete participant diary. Participants who smoke will be encouraged to stop smoking.

11.3.2 Baseline Visit & Randomisation

At baseline visit the following baseline characteristics and clinical assessments will be made: vital signs, spirometry, CAT score, medical history including bone fracture, medication, demographics, routine pathology, SGRQ. In addition, blood will be collected for the plasma storage (selected sites only), and also for the theophylline levels in 100 randomly selected participants. Adverse Events will be recorded and study medication will be dispensed. Participants will also be provided with the Participant Diary to record all events that occur between study visits.

11.3.3 6, 18, 30 and 42-Weeks Phone Visit

Participants will be phoned up in between clinic visits to review the Participants Diary card, vital status and record any Adverse Events. All information will be recorded directly into the eCRF.

11.3.4 12-Weeks Visit

The following assessments will be performed during this visit: spirometry, CAT score, medication, if applicable, blood collection for the theophylline levels in 100 randomly selected participants. Adverse Events will be recorded, Participant's Diary will be reviewed and study

medication will be dispensed. Accountability for the returned study medication will be performed.

11.3.5 24-Weeks and 36-Weeks Visits

The following will be performed during this visit: spirometry, CAT score and medication, if applicable. Adverse Events will be recorded, Participant's Diary will be reviewed and study medication will be dispensed. Accountability for the returned study medication will be performed.

11.3.6 48-Weeks Visit

The following assessments will be performed during this visit: spirometry,CAT score and medication, if applicable, and SGRQ, In addition, blood will be collected for the plasma storage (selected sites only), for the theophylline levels in 100 randomly selected participants. Adverse Events will be recorded and Participant's Diary will be reviewed. Accountability for the returned study medication will be performed.

11.3.7 50-Weeks Visit

The ACTH stimulation test to be undertaken 2 weeks after completion of 48 weeks' study treatment in 100 randomly selected participants.

11.4 Safety Assessments

Symptoms attributable to corticosteroid and theophylline toxicity will be sought and specifically recorded at each patient visit. These will be classified as:

Severe – convulsions
Moderate – stomach discomfort, headache, insomnia, palpitations, weight gain, bruising
Routine adverse event data will be collected according to ICH GCP.
Participants will be specifically asked about respiratory tract infections in the previous 12 weeks and whether bone fractures have occurred.
In a subgroup of 100 patients blood samples will be taken at 12 and 48 weeks, serum theophylline will be analysed in a central laboratory, investigators will be informed of the results after the participant has completed the study follow up. Serum cortisol and ACTH suppression tests will be performed in a subgroup of 100 patients at 50 weeks. The 50 week time point (2 weeks following completion of the 48 week study drug administration) was chosen to assess the safety of long term administration[40]. The 250mg ACTH stimulation test will specifically assess adrenal suppression and recovery two weeks after completion of 48 weeks' administration of low dose prednisone and theophylline. All adverse event data will be reviewed by the Data Safety Monitoring Committee (DSMC). The DSMC will include 6 members with experience in clinical trials conduct and oversight, not associated with the conduct of the trial.

11.5 Losses to Follow-up

Efforts will be made to follow all randomised subjects for 48 weeks, irrespective of their adherence to the randomised therapy. All losses to follow-up with reason will be reported to the ICC and reviewed by the Steering Committee.

11.6 Non-adherence and Deviations from the Protocol

All participants will be strongly encouraged throughout the study to adhere to the randomised therapy. Participants will continue to be followed for all data collection, irrespective of their adherence to the randomised therapy (intent to treat analysis).

11.7 Duration of Subject Participation

Individual participants will participate in the 48 weeks treatment phase of the study until the earliest of:

- completion of the intervention period at 48 weeks,
- withdrawal of consent, by the participant or
- participant death

All participants will attend all scheduled three-monthly follow-up visits for 48 weeks.

11.8 Duration of the Study

The expected timelines for the study:

June 2014	TASCS first patient randomised
December 2016	Recruitment complete (n=1650)
December 2017	TASCS last patient visit
Jan – March 2018	Site close out activities
April – May 2018	Statistical analyses and publication preparation

11.9 Screening and Recruitment log

The screening and randomisation logs are designed to monitor patient recruitment at the individual study centre.

11.10 Data Collection

Streamlined data collection instruments and procedures will be used to minimise the work in collaborating centres. The George Institute for Global Health will take responsibility for the randomisation and data management of the study. This includes programming and data management support of the randomisation system and the database during the study.

12. Statistics

12.1 Power Calculations and Statistical Analysis

All analyses will be performed on an intention to treat basis (ITT). The primary endpoint of this study is the event rate of exacerbations of COPD. Randomisation of 1650 participants (550 in each arm) will provide 80% power (alpha=0.05) to detect a 20% relative risk reduction in the primary endpoint in each intervention group compared with the control group. The assumptions inherent in this calculation are: (a) event rates of 1 per person per year for the primary endpoint in control group; (b) 15% drop out - but all patients will be followed up even if they drop out of treatment; (c) assuming the exacerbation event rates follow negative binomial distribution which is robust to handle the problem of over-dispersion. Number of exacerbations will vary with severity of disease from about 0.6 to 1.6 but an overall baseline exacerbation rate of 1 is conservative. [41,42]. A comparison of the theophylline and placebo arms will also be undertaken for the primary outcome, number of exacerbations, although the study is not powered for this probably smaller effect [43].

This is a multi-centre, randomized, three-arm blinded clinical trial to investigate the clinical benefit of combination of low-dose theophylline plus low dose oral prednisone for patients with COPD. The full Statistical Analysis Plan (SAP) will be developed separately. This will be finalized prior to locking the trial database. The SAP will give a detailed description of the data summaries and analyses that will be performed.

12.1.1 Baseline characteristics

All analyses will be performed on an intention-to-treat basis. Baseline comparability of the intervention and control groups will be assessed via descriptive analyses in terms of age, gender, medical history, etc. Descriptive demographic and baseline clinical characteristics statistics will be used for the total population.

12.1.2 Effects of treatment

For the primary efficacy analysis, the events rate of exacerbations of COPD will be analysed using Negative Binomial regression. Time to first severe exacerbation will be analysed using a Cox models Kaplan-Meier plot. Analysis of other secondary outcomes will be conducted using standard statistical procedures applicable to categorical or continuous data as appropriate.

12.2 Randomisation and Allocation of Treatment

Treatment randomisation will be stratified by smoking status and centre. The randomisation process will be centrally administered. . Details of the randomisation schedule will remain confidential and known by a limited number of persons including the unblinded statistician working on the study. This will be done in agreement with the GI standard operating procedures (SOP) on randomisation. Randomisation will occur using a secure web based randomisation system developed and maintained by The George Institute for Global Health.

Randomisation will be achieved using a minimisation algorithm stratified by study centre via a password-protected encrypted website interface.

12.3 Missing Data

Efforts to minimise missing data will be made and will include data monitoring and feedback, the collection of data from individuals after termination of randomised therapy and rescheduling visits if a participant is hospitalised or unavailable. Methods for handling missing data at the analysis stage will be detailed in the statistical analysis plan.

12.4 Blinding

Key clinical endpoints will be collected in a fashion that will allow bias to be minimised as much as possible. Both, participants and investigators will be fully blinded to the treatment allocation. Similarly, the endpoints will be collected by study personnel unaware of treatment allocation. The only personnel with access to the randomisation during the study conduct will be the IT person(s) who will have an access to the secure web-based randomisation module and the unblinded statistician(s) responsible for providing the reports to the DSMC. The GI SOP on blinding/unblinding will be followed by personnel involved in these procedures.

12.5 Final Analysis

Enrolment will be terminated when 1650 participants have been randomised into the study. When all participants have completed their 48 weeks assessment the main analysis will be conducted for all endpoints and safety.

13. Termination of Study Treatment

Study treatment prior to 48 weeks will cease if or when any of the following criteria are met:

- Participant withdraws consent for study treatment, *or*
- Participant dies, *or*
- The treating clinicians consider it is clearly in the participant's best interest to receive treatment other than the randomised therapy, *or*
- The DSMC advises study termination

Following completion of the study further treatment will be prescribed at the discretion of the caring physician.

Participants withdrawn from the randomised treatment for any reason will be followed up and analysed according to the intention-to-treat-principle.

14. Human Research Ethics Committee Approvals

An application requesting approval to conduct this study will be submitted to the Human Research Ethics Committee (HREC) of the University of Sydney (central HREC), followed by the HREC application at each of the participating regional centres or hospitals and/or at a central ethics committee where applicable. Each application will be submitted according to

the requirements of each hospital ethics committee, all of which have been formed and are conducted in accordance with the national and local guidelines applicable in China. The content and format of the Participant Information Statements and Consent Forms will be approved by each ethics committee and formatted in accordance with their own guidelines and requirements notwithstanding the requirements of the central Ethics Committee.

Each Principal Investigator will be responsible for preparation of annual status reports, serious adverse event reports, and any other required documentation to the local HREC in accordance with their guidelines. Any amendments or additions to the study protocol and material will be notified to the HREC by the Chief Investigator.

It is the responsibility of the Principal Investigator at each participating hospital or study centre to maintain up to date records of all correspondence and applicable documentation with the local HREC and the regulatory authorities. The Template of the Informed Consent Form and Participant Information Statements that are to be used at each hospital or study centre, together with a copy of all signed Informed Consent Forms and any other consent related correspondence will also be kept in a separate file for audit purposes. All study records and documents will be stored for a minimum of 15 years from the end of the study or for a period as required by the individual HREC or central Ethics Committee.

15. Informed Consent

A copy of each participating centre's proposed informed consent document should be submitted to the George Institute for Global Health for review and comment before submission to the relevant ethics committee. The study should not begin until the document has been approved by the ethics committee. Copies of the regulations relating to informed consent and the protection of human subjects in clinical studies are available from the George Institute for Global Health. Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. The participant information sheet will be provided to the participant, to make an informed decision concerning continued participation in the study.

15.1 Documentation of Consent

A copy of the signed participant consent and participant information statement will be given to the participant who has provided the informed consent. The original copy of the signed informed consent will be filed in the participant's study related records and kept in a locked room or cabinet in the centre research office.

15.2 Withdrawal of Consent

At any time during the study, the participant may withdraw consent to participate in the study. This is documented in the informed consent form and participant information statement.

16. Other therapies

All participants will receive routine care as delivered in their usual context of clinical care.

17. Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC), independent from the investigators participating in the study, will perform an ongoing review of predefined safety parameters and overall study conduct. The DSMC will be comprised of experts in clinical trials, bio-statistics and respiratory medicine. The committee will review unblinded data on participant characteristics and adverse events at regular intervals during the study. The committee will be charged with monitoring total mortality, serious adverse events and making recommendations based on other outcomes such as cause specific death or serious non-fatal adverse events. They will principally monitor safety and adverse events without including any formal testing of a treatment effect. In addition, the DSMC will monitor the operational progress of the study. The DSMC will autonomously determine the timing of their meetings, the information required from the nature of their analyses. The Steering Committee may request various analyses from the DSMC from time to time.

Safety analyses presented at DSMC meetings will include summary reports of frequency and differences between treatment groups for each of the following:

i. deaths
ii. hospitalizations
iii. exacerbations and other SAEs
iv. fractures

18. Assessment of Safety

The investigator agrees to record all study specific AEs. Furthermore, the investigator is responsible for ensuring that any co-investigator or sub-investigator brings SAEs to the attention of the investigator, and then the investigator notifies the national medical leader according to GCP – i.e. within 24 hours of any SAE onset or notification to the investigator. The investigator is also responsible for informing their local HREC of any SAE's.

18.1 Definitions

The term "adverse event," as used here, is synonymous with the term "adverse experience," which is used by the TGA**.**

18.1.1 Adverse Event

An **Adverse Event** (AE) is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with a sponsor treatment, regardless of causal relationship.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the informed consent form or is documented as part of the subject's medical history.

The active phase of the study begins at the time of the first commencement of study intervention.

18.1.1.1 Recording of Adverse Events

The collection of study specific adverse events should be limited to:

i. Weight gain (>5kgs since baseline)
ii. Fractures
iii. Pneumonia
iv. Other infections
v. A new diagnosis of diabetes or hypertension
vi. Stomach discomfort
vii. Epileptic fits

18.1.2 Serious Adverse Event

A **Serious Adverse Event** (SAE) is any AE that meets 1 or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect.
- Is a medically important event or reaction

A life threatening adverse event is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalisation is identified by an official admission. Hospitalisation or prolongation of a hospitalisation is a criterion for considering an AE to be serious. In the absence of an SAE, the participating investigator should not report hospitalisation or prolongation of hospitalisation. This is the case in the following situations:

- Hospitalisation or prolongation of hospitalisation is part of a routine procedure followed by the study centre. This should be recorded in the study file.
- Hospitalisation is for an elective, unrelated procedure and no SAE occurs
- Hospitalisation for survey visits or annual physicals fall in the same category.

In addition, a hospitalisation planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt whether the information constitutes the SAE, please report the event.

18.1.2.1 Recording of Serious Adverse events

At each required study visit, all SAEs that have occurred since the previous visit must be recorded. The following SAE information must be included (when applicable): the specific condition or event; the dates and times of occurrence; severity; causal relationship to treatment; action taken; and outcome.

The causal relationship between an SAE and the treatment will be determined by the investigator on the basis of his or her clinical judgment and the following definitions:

- Definitely related: Event can be fully explained by administration of the treatment.
- Probably related: Event is most likely to be explained by administration of the treatment rather than the subject's clinical state or other agents/therapies.
- Possibly related: Event may be explained by administration of the treatment or by the subject's clinical state or other agents/therapies.
- Probably not related: Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the treatment.
- Definitely not related: Event can be fully explained by the subject's clinical state or other agents/therapies.

When assessing the relationship between the protocol and/or administration of a treatment and an SAE, the following should be considered:

- Temporal relationship between the protocol and/or administration of the treatment and the SAE
- Biological plausibility of relationship
- Participant's underlying clinical state or concomitant agents and/or therapies
- When applicable, whether the SAE abates on discontinuation of the treatment (de-challenge)
- When applicable, whether the SAE reappears on repeat exposure to the treatment (rechallenge)

SAEs that are not treatment related may nevertheless be considered by the participating investigator or the medical monitor (or designee) to be related to the conduct of the clinical study, i.e. to a subject's participation in the study. For example, a protocol-related SAE may

be an event that occurs during a washout period or that is related to a procedure required by the protocol.

18.1.3 Timing for Reporting Serious Adverse Events

All SAEs should be reported using the eCRF within the required timeframe after the site staff becomes aware of the SAE. Compliance with this requirement is essential so that the study team is aware of any safety signals and thus complies with local regulatory obligations. Where applicable all follow-up information relating to an SAE must be reported, as detailed above, within 24 hours of receipt by the investigator via eCRF or by faxing a completed serious adverse event form. The participant should be observed and monitored carefully until the condition resolves or stabilises or its cause is identified.

18.1.4 Documentation of Adverse Events and Serious Adverse Events

Study specific AEs and all SAEs will be reported on the eCRFs after randomisation. The AEs and SAEs must be documented in the source documents. The study centre investigator has to follow up all SAEs until the event has subsided or values have returned to baseline, or in case of permanent impairment, until the condition stabilises. If requested, the investigator will provide all supporting documentation pertaining to the event (e.g., additional laboratory tests, consultation reports, post mortem reports, etc.) to the George Institute for Global Health in a timely manner. Reports relative to the participant's subsequent course must be submitted to the George Institute for Global Health until the event has subsided or, in case of permanent impairment, until the condition stabilises.

19. Data Quality Assurance

A qualified representative of the George Institute for Global Health will monitor the conduct of the study by visiting the centre and by contacting the centre by telephone and email. During the visits, information recorded on the CRFs will be verified against source documents. Quality control of spirometry will occur at each centre through a predetermined constant review, using standardised software, and will be overseen by the Chief Investigator, Professor Norbert Berend.

A random sample of patients will be phoned at various intervals through the study by an independent person under the supervision of Professor Fuqiang Wen from West China Hospital of Sichuan University hospital as a quality assurance measure to ascertain the complete collection of the exacerbation data.

19.1 Pre-study Documentation

The investigator must provide The George Institute for Global Health with the following documents BEFORE enrolling any participants:

- Current signed and dated curricula vitae for the investigator, sub-investigators, and all key personnel listed on the clinical study information form.
- Copy of the Institutional Ethics Committee (HREC) approval letter for the protocol.

- Copy of the Institutional Ethics Committee (HREC) approval letter for the informed consent(s).
- Copy of the Institutional Ethics Committee (HREC) approval letter for the participant diary
- Centre Investigator Signed Protocol page.
- Laboratory Normal / Reference Ranges
- Laboratory Certification / Accreditation
- Participating Centres Agreement, containing confidentiality and indemnity clauses.
- EC membership list or letter of assurance.

On an ongoing basis the investigator must provide The George Institute for Global Health with written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the HREC. The investigator must also promptly report any changes in this study or unanticipated problems involving risks to the participants to the HREC. An investigator must not make any changes in a study without HREC and Study Steering Committee approval from The George Institute for Global Health except when necessary to eliminate apparent immediate hazards to the participants in which case the HREC and The George Institute for Global Health are to be notified immediately. All protocol amendments must be submitted to the HREC and approved.

19.2 Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and the applicable local regulatory requirements.

19.3 Source Data Documentation

The purpose of source documents is to document the existence of the participant and substantiate the integrity of the study data collected. Adequate and accurate source documents allow the investigator and the centre monitor to verify the reliability and authenticity of data recorded on the electronic CRFs and ultimately to validate that the clinical study was carried out in accordance with the protocol. Source data documentation includes original documents related to the study, medical treatment, and to the medical history of the participant. Source data constitute the original documents, certified copies, data and records necessary for the reconstruction and evaluation of the study. Examples of source documents include hospital records, patient notes, participant diary, X-rays, electrocardiography (ECG) reports, magnetic resonance imaging (MRI) reports, laboratory reports, pharmacy dispensing records, letters, emails and electronic records. In case of electronic records the readable copies must be generated and validated.

19.4 Case Report Forms

All data will be recorded in the CRFs. Information recorded in the CRF should accurately reflect participant's medical/hospital notes. Information must be completed in the case report form as soon as it is made available for recording. The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the investigators on the progress of the data submitted and to enhance the ability to collect early safety information in a more timely fashion to fully comply with the intent of GCP requirements.

19.5 Review of Source Records

During and after this study qualified representatives of The George Institute for Global Health will conduct inspections, audit and review medical records pertinent to the clinical study as permitted by the regulations. Participants will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

Accordingly, the following statement (or similar statement) will be included in the informed consent document:

'Representatives of regulatory agencies, HRECs, The George Institute for Global Health, the study manager and your personal physician may review your medical records and information related to this study as permitted by law. Identifying information will not appear on any record other than the medical record. Your identity will remain confidential unless disclosure is required by law in accordance with the Privacy of Information act.'

19.6 Monitoring of the Study

This study will be monitored by a representative of The George Institute for Global Health. Centre monitoring visits will be performed in regular intervals. Communication by telephone and mail and e-mail may be used as needed to supplement centre visits. The investigator and study personnel will assist the monitoring staff by providing all appropriate documentation, and being available to discuss the study. The purpose of the centre visits is to verify the following:

a. Adherence to the protocol. (The investigator should document and explain any deviation from the approved protocol.)

b. The completeness and accuracy of the CRFs and source documentation. (Adequate time and space for these visits should be allocated by the investigator.)

c. Compliance with regulations. The verification will require comparison of the source documents with the CRF data entry.

The source document verification (SDV) is to verify the data recorded in the electronic case report form (eCRF) against the source document. In other words, it is a process of checking the accuracy, consistency and completeness of data entered in the eCRF with the source data.

19.7 Protocol Amendments

Any significant change in the study protocol will require an amendment. The investigator and an appropriate representative of the Steering Committee will indicate their approval by signing the approval page of the amendment. Once the Steering Committee has approved a protocol amendment, the investigator will need to submit it to the HREC or centralised Ethics Committee for written approval. The approval letter, signed by the HREC chair, must refer specifically to the investigator, the protocol number, the protocol title, the protocol amendment number, and the date of the protocol amendment. The protocol amendment may be implemented only after it has been approved by the HREC. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, but the change must then be documented in an amendment, reported to the HREC and the International Coordinating Centre within 5 working days.

19.8 Change in Investigator

If any investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to The George Institute for Global Health, HREC, or other investigator. The George Institute for Global Health must be notified of and agree to the change. All associated documentation must also be updated.

19.9 Termination of the Study

19.9.1 Termination by the Study Steering Committee

The Study Steering Committee may terminate the entire study or terminate the study at a particular centre at any time for any of the following reasons:

- Failure to enroll participants.
- Protocol violations.
- Inaccurate or incomplete data.
- Unsafe or unethical practices.
- Questionable safety of the treatment.
- Suspected lack of efficacy of the treatment.
- Lack of treatment safety
- Administrative decision.

19.9.2 Termination by the Investigator

If the investigator terminates the study prematurely, the investigator will do the following:

- Return all study materials to The George Institute for Global Health.
- Provide the HREC and The George Institute for Global Health with a written statement describing why the study was terminated prematurely.

All discontinuations of therapy will be reviewed by the Steering Committee.

19.9.3 Notification of Study Closure

The investigator completes a report notifying the HREC of the conclusion of the clinical study. This report should be made within 3 months of completion or termination of the study. The final report sent to the HREC is also sent to The George Institute for Global Health.

20. Confidentiality

All unpublished information that The Steering Committee forwards to the investigator shall be kept confidential and should not be published or disclosed to a third party without the prior written consent of The Steering Committee.

21. Records Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those documents defined by GCP as essential documents, for 15 years following study closure. At the end of such period, the investigator shall notify in writing The International Coordinating Centre of its intent to destroy all such study material. The International Coordinating Centre shall have 30 days to respond to the investigator's notice, and The International Coordinating Centre shall have a further opportunity to retain such materials at The George Institute for Global Health's expense.

22. Organisation and Collaboration

The study will be conducted under the auspices of The George Institute for Global Health, University of Sydney. It will be overseen by the Steering Committee.

23. Publications and Presentations

The main reports from the study will be published in the name of "The TASCS Study Investigators" as requested by the publishing journal with credit assigned as determined by the Steering Committee to the appropriate investigators. Presentations of the study findings will be made at national and international meetings.

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