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Complete List of Authors:	Calderone, Alicia; St. Vincent's Hospital Melbourne, Rheumatology Stevens, Wendy; St. Vincent\'s Hospital Melbourne, Rheumatology Prior, David; The University of Melbourne, Medicine; St. Vincent\'s Hospital Melbourne, Cardiology Nandurkar, Harshal; The University of Melbourne, Medicine; Monash University, Australian Centre for Blood Diseases Gabbay, Eli; The University of Notre Dame; Sir Charles Gairdner Hospital, Institute for Respiratory Health Proudman, Susanna; University of Adelaide, Medicine; Royal Adelaide Hospital, Rheumatology Williams, Trevor; Monash University, Allergy, Immunology and Respiratory Medicine at Alfred Hospital Celermajer, David; University of Sydney, Cardiology Sahhar, Joanne; Monash Health and Monash Universiy, Rheumatology Wong, Peter; Mid-North Coast Arthritis Clinic; University of New South Wales, Rural Clinical School Thakkar, Vivek ; Liverpool Hospital, Rheumatology; University of Western Sydney, School of Medicine Dwyer, Nathan; Royal Hobart Hospital, Cardiology Wrobel, Jeremy; Fiona Stanley Hospital, Advanced Lung Disease Unit Chin, Weng; Sir Charles Gairdner Hospital, Institute for Respiratory Health Liew, Danny; Monash University, Epidemiology and Preventive Medicine Staples, Margaret; Monash University, Epidemiology at Cabrini Health Buchbinder, Rachelle; Monash University, Epidemiology and Preventive Medicine; Monash University, Epidemiology at Cabrini Health Nikpour, Mandana; The University of Melbourne, Medicine; St. Vincent\'s Hospital Melbourne, Rheumatology
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TITLE

A multi-centre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol.

Full name of authors

Alicia Calderone[1], Wendy Stevens[1], David Prior[2,3], Harshal Nandurkar[3,4], Eli Gabbay[5,6], Susanna M. Proudman[7,8], Trevor Williams[9], David Celermajer[10], Joanne Sahhar[11], Peter K. K. Wong[12,13], Vivek Thakkar[14,15], Nathan Dwyer[16], Jeremy Wrobel[17], Weng Chin[6], Danny Liew[18], Margaret Staples[18,19], Rachelle Buchbinder[18,19] and Mandana Nikpour[1,3].

Institutional addresses

[1]Departments of Rheumatology, [2]Cardiology and [3]The University of Melbourne Department of Medicine at St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia. [4]Australian Centre for Blood Diseases, Central Clinical School, Monash University, The Alfred, Commercial Road, Melbourne, VIC 3004, Australia. [5]The University of Notre Dame, 19 Mouat Street, Fremantle, WA 6959, Australia. [6]Institute for Respiratory Health, Ground Floor, E Block, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia. [7]Department of Rheumatology and [8]University of Adelaide Discipline of Medicine at Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia. [9]Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Monash University, PO Box 315, Prahran, VIC 3181, Australia. [10]Department of Cardiology, Sydney Medical School, University of Sydney, NSW 2006, Australia. [11]Department of Rheumatology, Monash Health and Monash University, 246 Clayton Road, Clayton, VIC 3168, Australia. [12]Mid-North Coast Arthritis Clinic, PO Box 6307, Coffs Harbour, NSW, 2450, Australia. [13]Rural Clinical School, Faculty of Medicine, University of New South Wales, Locked Bag 812, Coffs Harbour, NSW, 2450, Australia. [14]Department of Rheumatology, Liverpool Hospital, Elizabeth Street, Liverpool, NSW 2170, Australia. [15]School of Medicine, University of Western Sydney, Locked bag 1797, Penrith, NSW 2751, Australia. [16]Department of Cardiology, Royal Hobart Hospital, 48 Liverpool Street, Hobart, TAS 7000, Australia.

[17]Advanced Lung Disease Unit, Fiona Stanley Hospital, Murdoch, WA 6150, Australia. [18]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia. [19]Monash Department of Clinical Epidemiology, Cabrini Institute, Cabrini Health, Suite 41 Cabrini Medical Centre, 183 Wattletree Rd, Malvern, VIC 3144, Australia.

Corresponding author

Dr Mandana Nikpour, Departments of Rheumatology and Medicine, The University of Melbourne, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia. Tel: + 61 3 9231 2211, Fax: + 61 3 9417 0822, Email: m.nikpour@unimelb.edu.au

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a multi-organ autoimmune connective tissue disease characterised by vasculopathy and fibrosis. It is one of the most severe and costly rheumatic diseases. One of the major causes of SSc-related death is pulmonary arterial hypertension (PAH), which develops in 12-15% of patients with SSc and accounts for 30-40% of deaths.

Thrombotic arteriopathy has been implicated in the complex pathophysiology of SSc-related PAH (SSc-PAH), with international clinical guidelines recommending the use of anticoagulants for some types of PAH, such as idiopathic PAH. However, anticoagulation has not become part of standard clinical care for patients with SSc-PAH as only observational evidence exists to support its use. Therefore, we present the rationale and methodology of a Phase III randomized controlled trial (RCT) to evaluate the safety, efficacy and cost-effectiveness of anticoagulation in SSc-PAH.

Methods and analysis: This Australian multi-centre RCT, will compare 2.5mg apixaban with placebo, in parallel treatment groups randomized in a 1:1 ratio, both administered twice daily for 3 years as adjunct therapy to stable oral PAH therapy. The composite primary outcome measure will be the time to death or clinical worsening of PAH. Secondary outcomes will include functional capacity, health-related quality of life measures and adverse events. A cost-effectiveness analysis of anticoagulation versus placebo will also be undertaken.

Ethics and dissemination: Ethical approval for this RCT has been granted by the human research ethics committees of all participating centres. An independent data safety monitoring board will review safety and tolerability data for the duration of the trial. The findings of this RCT are to be published in open access journals. We hypothesise that anticoagulation prolongs survival, increases functional capacity and overall wellbeing, and reduces hospitalisation compared to placebo in patients with SSc-PAH, a lethal and costly disease.

Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN12614000418673.

Strengths and limitations of this study

- This is the first clinical trial ever to evaluate the the efficacy, safety and cost-effectiveness of anticoagulation as adjunct treatment in systemic sclerosis-related pulmonary arterial hypertension.
- The blinded randomised placebo-controlled design of this trial is intended to minimise bias.
- The choice of apixaban 2.5 mg bid as the anticoagulant treatment is intended to optimise the risk to benefit ratio in systemic sclerosis-related pulmonary arterial hypertension.
- However, this study is not designed to specifically evaluate the the efficacy, safety and cost-effectiveness of other anticoagulant doses or drugs in this condition.

INTRODUCTION

Scleroderma or systemic sclerosis (SSc), is a multi-organ autoimmune connective tissue disease (CTD) characterised by vasculopathy and fibrosis, that is estimated to affect over two million people worldwide, with some studies indicating a rising incidence.[1-3] Due to the multi-organ nature and chronicity of the disease, SSc is associated with significant morbidity and is one of the most costly rheumatic diseases.[4-7] SSc is also a life-threatening condition that carries the greatest burden of case-based mortality among the rheumatic diseases, reducing life expectancy by an average of 16 years per male and 34.1 years per female patient.[8] It is now well established that pulmonary arterial hypertension (PAH), a condition of increased resistance in the pulmonary vasculature, is one of the leading causes of death in SSc, accounting for 30-40% of deaths in this disease.[9-13] Untreated, SSc-related PAH (SSc-PAH) may follow a rapidly fatal course, with death resulting from right ventricular failure and arrhythmias.[9]

So called 'advanced' PAH therapies target mediators of the complex pathophysiology underlying PAH (Figure 1), predominantly molecules responsible for vascular remodelling, that result in an imbalance between endogenous pulmonary vasoconstriction and vasodilation.[14, 15] In SSc-PAH, these advanced PAH therapies demonstrate improved survival, exercise capacity as measured by 6-minute walk distance (6MWD), and health-related quality of life (HRQoL) outcomes, compared with placebo.[14-16] Prior to the advent of advanced PAH therapies in the early 2000s, the one-year survival of patients with SSc-PAH was 45%.[17] Subsequently, a systematic review of all randomised controlled trials (RCTs) of advanced PAH therapies, including patients with primary 'idiopathic' PAH (iPAH) and PAH secondary to CTD (CTD-PAH), reported an absolute reduction in mortality of 39% (p=0.04) with specific PAH treatment compared with placebo.[18] Further, two Australian observational studies have shown improved survival with combination PAH therapy compared with monotherapy in patients with iPAH and CTD-PAH (three-year survival 85% with combination therapy versus 60% with monotherapy in CTD-PAH).[19, 20] Thus, survival has improved dramatically since

the introduction of advanced therapies. However, PAH still carries a high burden of morbidity and mortality.[10, 15] Importantly, SSc-PAH continues to display the poorest prognosis compared with iPAH and other CTD-PAH subgroups.[21, 22]

In situ thrombosis is a likely contributor to the pathophysiology of SSc-PAH, with pulmonary vascular (venous and arterial) thrombosis appearing as a common histological feature in both iPAH and CTD-PAH tissue specimens.[23-25] While several observational studies, including the Australian Scleroderma Cohort Study, have suggested a survival benefit with anticoagulation in PAH, other observational studies have not supported this finding.[19, 26-29] However, many of the patients included in these studies were not on advanced PAH therapy, and the majority had iPAH.[28, 29] In contrast, the Australian Scleroderma Cohort Study data revealed a substantial survival benefit attributable to anticoagulation when administered in conjunction with advanced PAH therapy.[19] In this CTD-PAH cohort (95% of whom were SSc-PAH patients), exhibiting a median survival of only five years, an estimated 5-fold reduction in mortality was observed with warfarin treatment, prescribed at physician discretion, over an average 2.6 ± 1.8 years follow-up.[19] Furthermore, in contrast to the support for anticoagulation in European and American guidelines for treatment of iPAH, due to absence of RCT data, recommendations for anticoagulation in SSc-PAH are based on weak evidence and reflect a state of clinical equipoise among experts.[30-34] Although pulmonary vascular pathobiology may be similar to that seen in iPAH, SSc-PAH patients have other clinical features which may impact the risk to benefit ratio of anticoagulation. Hence, there is great variability in beliefs and prescribing habits regarding anticoagulation as adjunct therapy in SSc-PAH.[26, 35] The weight of preliminary evidence, societal costs and high morbidity of SSc-PAH, demand an urgent resolution of this contentious issue through an RCT.

In design of this RCT, several considerations favour the use of novel oral anticoagulants as safer, more effective and more convenient than warfarin for SSc-PAH patients. Factor Xa is a pivotal component of the coagulation cascade, and oral factor Xa inhibitors such as apixaban and

rivaroxaban, which are hypothesised to have antiplatelet and endothelial effects, may target multiple pathways critical to SSc-PAH pathogenesis.[36-39] Oral factor Xa inhibitors may offer more stable blood levels than warfarin, assuming full compliance. These agents are administered at fixed doses, have fewer diet or drug interactions, are eliminated through multiple pathways and do not require routine international normalised ratio (INR) monitoring.[36, 37] The predictable bioavailability of the factor Xa inhibitors is particularly advantageous in patients with SSc, many of whom have gut hypomotility and bacterial overgrowth, which may affect warfarin and vitamin K absorption, resulting in erratic INRs.[40] With up to 6% of SSc patients exhibiting intestinal telangiectasiae or gastric antral vascular ectasiae (GAVE) which may bleed,[41] the lower risk of gastrointestinal bleeding with apixaban, observed in large clinical trials of other patient groups, is reassuring.[42-44] Finally, patients with SSc often have difficult venous access due to skin fibrosis and subcutaneous joint contractures.[26] Such patients are typically reluctant to have the multiple venesections required for INR monitoring. As oral factor Xa inhibitors do not require monitoring of blood levels and dose adjustment,[36, 37] there is potential to blind treatment assignment for RCTs and participant retention in clinical trials could possibly increase.

Objective:

The *aim* of this study is to evaluate the efficacy, safety and cost-effectiveness of treatment over three years with the novel oral anticoagulant apixaban (a factor Xa inhibitor) in SSc-PAH, by undertaking a multi-centre, double-blind, placebo-controlled RCT. The intervention will occur on a background of advanced PAH therapy prescribed as standard of care for participants assigned to both treatment and placebo arms.

The *hypothesis* is that anticoagulation prolongs survival, increases functional capacity and overall wellbeing, and is safe and cost effective in patients with SSc-PAH.

METHODS AND ANALYSIS

Study design

The study is designed as a multi-centre, participant- and investigator-blinded, placebo-controlled, Phase III clinical trial to compare the efficacy, safety and cost-effectiveness of apixaban 2.5 mg twice daily (bid) versus placebo, randomised in a 1:1 ratio, over a treatment period of 3 years, as additional therapy in patients with SSc-PAH who are already on advanced pulmonary vasodilators. The study design and assessment timeline is illustrated in Figure 2.

Study population

Study participants will be identified by cardiologists, rheumatologists and respirologists, during the course of routine care at 13 Australian PAH treatment centres across six states (New South Wales, Queensland, South Australia, Tasmania, Victoria and Western Australia). Recruitment will take place over 24 months until sample size requirements are met and participants will be treated for 36 months. Participants will be adult males and females with symptomatic SSc-PAH as defined by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 classification criteria for SSc[45] and international guidelines for diagnosis of PAH.[33, 46] Inclusion and exclusion criteria are listed in Table 1 and Table 2, respectively. Many of the exclusion criteria focus on reducing the risk of adverse bleeding events in the study population.[47, 48] All eligible participants will sign informed consent prior to study enrolment, following adequate explanation of the aims, methods, objectives, and potential hazards of the trial by the responsible investigator.

Table 1: The SPHInX Study Inclusion Criteria

Item	Characteristics of eligible participants*
1.	Male and female patients aged from 18 to 75 years inclusive.
2.	Scleroderma defined by the ACR/EULAR 2013 classification criteria.
3.	RHC at any time prior to Baseline demonstrating the following haemodynamic characteristics in line with current international guidelines for diagnosis of PAH: i. resting mPAP ≥25 mmHg, and ii. resting PVR ≥3 woods units, and iii. resting PCWP or LVEDP ≤15 mmHg, or iv. if PVR cannot or has not been measured, then mPAP ≥30 mmHg with PCWP or LVEDP ≤15 mmHg.
4.	6-minute walk distance greater than 50 meters at Screening and/or Baseline.
5.	Other causes of PAH, in particular CTEPH must have been previously excluded by either a V/Q scan or CTPA.
6.	Currently taking at least one of the ETRA or PDE-5 inhibitor medications in a stable dose for the 2 months prior to Baseline (either bosentan, ambrisentan or macitentan, and/or sildenafil or tadalafil).
7.	Female participants of childbearing potential must test negative for pregnancy.
8.	Male and female participants of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of the study drug. A participant is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
9.	Female participants who are not of childbearing potential must meet at least one of the following criteria: i. have undergone documented hysterectomy and/or bilateral oophorectomy, ii. have medically confirmed ovarian failure, or iii. achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone level within the laboratory's reference range for post-menopausal females.

*All items must be present for eligibility into the clinical trial. *Abbreviations:* RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; CTEPH, chronic thromboembolic pulmonary hypertension; V/Q, ventilation/perfusion; CTPA, computed tomography pulmonary angiogram.

Table 2: The SPHInX Study Exclusion Criteria

Item	Characteristics of ineligible participants**
1.	Pulmonary hypertension due to any other cause than SSc.
2.	Moderate or severe obstructive lung disease, ie. FEV1/FVC ratio <70% and FEV1 <65% of predicted value after bronchodilator administration.
3.	Moderate or severe restrictive lung disease, ie. FVC <70% of predicted value, provided that HRCT scan demonstrates moderate to severe changes of ILD, or FVC <60% of predicted value, regardless of HRCT result.
4.	Moderate or severe hepatic impairment (ie. Child-Pugh class B or C).
5.	Documented left ventricular dysfunction (i.e. ejection fraction <45%).
6.	Severe renal insufficiency (estimated creatinine clearance <25 mL/min, or serum creatinine >200 µmol/L).
7.	Receiving any investigational drugs within 1 month prior to, or at Baseline.
8.	Receiving continuous intravenous epoprostenol or iloprost at Baseline or have planned to initiate this therapy within the next 3 months.
9.	Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements.
10.	Life expectancy due to another condition of less than 12 months.
11.	Females who are breastfeeding or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study.
12.	Known hypersensitivity to drugs of the same class as the study drug, or any of the excipients of the drug formulations.
13.	Gastrointestinal tract bleeding in the last 12 months due to GAVE or unexplained iron deficiency anemia (in the last 12 months).
14.	Hemoglobin <100 g/L at Screening.
15.	Participants with significant falls risk in whom anticoagulation would be inappropriate.
16.	Participants who have received any oral or subcutaneous anticoagulants (e.g. warfarin, apixaban, rivaroxaban, dabigatran, enoxaparin, dalteparin or heparin) for more than 3 months since the diagnosis of PAH.
17.	Participants with a prosthetic valve who require long term oral anticoagulation.
18.	Participants who are currently in atrial fibrillation.
19.	Participants with PAH not on either an ETRA or PDE-5 inhibitor.
20.	Participants with known bleeding disorders and/or platelet count <100 at screening and/or INR>1.2 at screening.
21.	Brain, spinal or eye surgery within the last one month.
22.	Uncontrolled systemic hypertension defined as either systolic blood pressure >179mmHg or diastolic blood pressure >109 mmHg at Screening.
23.	Documented episode of either pulmonary embolus or deep venous thrombosis since diagnosis of PAH.
24.	Participants with a current, or active in the last one month, major bleed that is life threatening, causes chronic sequelae or consumes major health care resources, as defined by the International Society on Thrombosis and Haemostasis.

**Participants must not meet any of the exclusion criteria for eligibility into the clinical trial. *Abbreviations:* FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease.

Randomisation and allocation concealment

Ethical considerations mandate background treatment with advanced PAH therapies as standard of care in all study participants.[33, 34] As sites differ in rates of use of PAH specific therapies, including combination therapy, randomisation will be stratified according to site, with the effect of various PAH therapies subsequently adjusted for in multiple regression analysis.

Randomisation to placebo or study drug in a 1:1 ratio will be performed by a statistician who is not associated with any study site, using computer generated block randomisation, stratified according to study site. After the investigator obtains informed consent and confirms eligibility, patients who meet all inclusion criteria and none of the exclusion criteria will be assigned to study treatment by the site pharmacist at Baseline visit, according to the site randomisation schedule.

Participants, healthcare providers, investigators, data collectors and outcome assessors will be blinded to treatment assignment. To ensure allocation concealment, the appearance of the investigational drug [apixaban, BMS-562247, Bristol-Myers Squibb Limited (BMS), New Jersey, USA] and its packaging will be indistinguishable from the matching placebo, both manufactured by BMS. The labelling and packaging of apixaban and matching placebo will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and national regulatory requirements, coordinated by the study lead pharmacy.

A password-protected limited access electronic database of all randomisation codes will be kept for emergency unblinding purposes. If any participant experiences a medical emergency wherein management would be improved by knowledge of the blinded treatment assignment, unblinding will be available 24 hours per day. A set of tamper-proof sealed envelopes containing the blinding code for each participant will be kept at each site in case contact with the database server fails. The integrity of these sealed envelopes will be periodically checked. A log of every access to the unblinding codes will be kept and all requests for unblinding must be clearly justified.

Treatment exposure and compliance

The study drug will be administered orally, twice daily as 2.5mg tablets of apixaban or matching placebo, with a dose interval of approximately 12 hours. Participants will be asked to return all unused study drug at follow-up visits and to self-report any missed doses of therapy. Study drug adherence will be assessed by recording quantities of returned study drug at each follow-up visit. Participants will cease study drug 36 months after initiation at baseline visit.

The study design mandates the concomitant use of at least one advanced pulmonary vasodilator, such as an endothelin-1 receptor antagonist (ETRA) and/or a phosphodiesterase type-5 (PDE-5) inhibitor. However, these therapies must be at a stable dose for at least two months prior to baseline. Permissible concomitant medication includes diuretic therapy, provided that a stable dose was maintained for at least one month prior to baseline; one antiplatelet agent will be allowed at physician discretion. However, the combination of clopidogrel or ticagrelor and aspirin is not allowed due to increased risk of bleeding.[49] Prohibited concomitant medications from one month prior to baseline until study drug cessation include any investigational drug other than the study drug; oral or subcutaneous anticoagulation with warfarin, apixaban, rivaroxaban, dabigatran, enoxaparin, dalteparin or heparin. Participants must not be receiving continuous intravenous infusion of epoprostenol or iloprost for PAH at baseline or be planned to initiate this therapy within the next three months. However, the following exceptions may apply following study commencement: (1) study drug may be temporarily suspended to receive prophylactic anticoagulation during a therapeutic or surgical procedure if this is deemed in the participant's best interest; and (2) addition of intravenous epoprostenol to oral advanced PAH therapy for participants in modified New York Heart Association/World Health Organisation (NYHA/WHO) functional class (FC) IV failing ETRAs and PDE-5 inhibitors.[33]

Concomitant medications will be monitored closely from one month following baseline visit. Participants will be required to self-report all changes to therapy throughout the study treatment

period using a health care utilisation diary. Commencement of any new PAH-specific treatment or a dose increase of such a drug without adjudicated clinical worsening of PAH is strongly discouraged during the study period. If continued administration of the study drug is believed to be contrary to the best interests of the participant (i.e. adverse event, diagnostic or therapeutic procedure, laboratory abnormalities, pregnancy, unblinding, or withdrawal of consent), interruption or permanent discontinuation of the study drug is mandated. Participants will resume study drug as long as the investigator feels it is safe for them to do so and no more than eight weeks of study treatment has been missed. Participants who prematurely discontinue the study drug for any reason will not be replaced and unless they withdraw consent, will continue to be followed up 6-monthly until 36 months from Baseline.

Study assessments

The study assessment schedule is illustrated in Figure 2, commencing with screening and ending with follow-up 30 days after the permanent cessation of study drug. Additional visits may also take place at any time during the treatment period in case of a suspected clinical worsening event (CWE). Screening assessments to confirm study eligibility may occur at any time prior to randomization, or be completed on the same day as the baseline visit. Adverse event surveillance is prioritised at follow-up assessments. With reference to their health care utilisation diary, participants will be required to self-report all health care utilisation (i.e. visits to health care/allied health practitioners and hospitalisations), side effects and pregnancy test results if applicable. Data collection requirements over the duration of the study are described in Table 3.

Table 3: Data collection requirements over the duration of the study

Screening	Baseline	Follow-up Visits	Telephone Follow-up
Participant demographics	Physical examination	Physical examination	Concomitant medications
Previous and ongoing medical history	Height and weight	Weight	Adverse event reporting
Medications history	Vital signsϕ	Vital signsϕ	Results of urine pregnancy test §§
Criteria for scleroderma classification	Electrocardiogramϕϕ	Electrocardiogramϕϕ	
RHC hemodynamic parameters that confirm PAH diagnosis	NYHA/WHO functional class	NYHA/WHO functional class	
V/Q scan or CTPA results that exclude CTEPH as a cause of the PAH	Concomitant medications	Concomitant medications and adverse event reporting	
HRCT results that exclude ILD	6MWT and Borg dyspnea index	6MWT and Borg dyspnea index	
Echocardiography results*	HRQoL questionnaires	HRQoL questionnaires	
Laboratory results**	Echocardiography results*	Echocardiography results*	
6MWT and Borg dyspnea index	Specimen collection§	Specimen collection§	

*Echocardiogram images will be collected where available, and data must be obtained within two months of Baseline, 6 and 24 month visits. **Laboratory samples must be taken within two weeks of Baseline including full blood count, liver function, renal function, INR, and serum pregnancy test or follicle-stimulating hormone levels for female participants only. ϕVital signs comprise heart rate and blood pressure (standing and supine). ϕϕA standard 12-lead electrocardiogram will be performed at Baseline, 6 month, 24 month, clinical worsening event and end of study visits. §Serum and platelet-free plasma samples will be stored for biomarker testing; §§monthly urine pregnancy tests are required for women of childbearing potential.

The 6-minute walk test (6MWT) will be performed in a standardised, non-encouraged fashion, measuring the walking distance covered by the patient during a 6-minute period followed immediately by the Borg dyspnea index, which rates dyspnea severity on a visual analogue scale from '0' to '10'.[50] The following validated HRQoL questionnaires will be completed by the patient: The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36),[51] the scleroderma-modified Stanford Health Assessment Questionnaire (sHAQ)[52, 53] and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[54] The 6MWT and HRQoL questionnaires will be omitted from visit 2 (1 month post-randomization), which will serve as an abridged safety assessment only, unless there is a suspected CWE.

Serum and platelet-free plasma samples collected at Baseline, 6 and 24 month follow-up visits, will be stored at -80˚ Celcius for N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) assay and exploratory biomarker testing.[55, 56] Factor Xa levels in platelet-free plasma specimens will also be compared between Baseline and 6 months to reflect bioavailability of apixaban in the treatment group.[57] Anti-factor Xa assays and biomarker assays will be performed for all samples in triplicate, in a single laboratory at the conclusion of the study.

Outcome measures

In line with the Task Force on Endpoints and Clinical Trial design recommendation for Phase III trials at the 4th World Symposium on pulmonary hypertension in Dana Point, California,[58] a composite primary endpoint will be employed, providing measurable parameters to support an independent adjudication of "time to clinical worsening (TtCW)". The primary endpoint will be time from randomisation up to 36 months to the first adjudicated clinical worsening event from the composite parameters listed in Table 4. CWEs will be adjudicated in a blinded fashion by an endpoint adjudication committee consisting of at least three investigators who are not the treating physician of the given participant. Study drug will be continued in a blinded fashion after a CWE is adjudicated, to enable quantification of the total number of CWEs during the study period as a secondary endpoint.

Table 4: Definition of measurable composite primary endpoint parameters

Item	Possible clinical worsening events
1.	Death (all-cause mortality).
2.	Hospitalization for worsening of PAH due to either: i. Need for lung transplantation or balloon atrial septostomy, or ii. Initiation of parenteral (subcutaneous and intravenous) prostanoid therapy or chronic oxygen therapy.
3.	Disease progression defined by the combination of at least two of the following components: i. Reduction from baseline in 6MWD by 15%, confirmed by two consecutive 6MWTs done on different days, ideally within 2 weeks of one another. ii. Worsening of PAH symptoms included at least one of the following parameters: a) either an increase from baseline in NYHA/WHO functional class (except for participants already in functional class IV), or b) appearance/worsening of signs/symptoms of right heart failure. iii. Need for additional PAH specific therapy that may include inhaled prostanoids, PDE-5 inhibitors, ETRAs or intravenous diuretics.

Any of the above singular events, or combinations of events, may be adjudicated as clinical worsening events within the composite primary endpoint for the first such event, or as a secondary efficacy endpoint for subsequent events.

Selection of secondary endpoints was informed by Expert Panel recommendations for a 'core set' of outcome measures to be used in clinical trials of new therapies in SSc-PAH.[59] Secondary efficacy endpoints include all-cause mortality; absence of worsening in NYHA/WHO functional class; change in 6MWD and Borg dyspnea index; change in the SF-36, sHAQ and CAMPHOR questionnaire sub-scales. Secondary endpoint comparisons will be evaluated from Baseline to each of 12, 24 and 36 month follow-up time-points, adjusted for time since diagnosis of PAH. The last valid post-baseline value will be carried forward to compensate for any missing values at each time-point.

Safety and tolerability endpoints will comprise treatment-emergent adverse events (serious and non-serious) including marked laboratory abnormalities up to 7 days after last study drug intake, adverse events leading to premature discontinuation of study drug, change from baseline to end of study in vital signs. Health economic endpoints will include number per year, and associated costs, of

all-cause and PAH-related hospitalisations and in-patient hospital days, general practitioner, specialist visits, allied health service utilisation and initiation of new medications.

Sample size estimation

Sample size was calculated based on a comparison of two survival curves for the primary outcome of clinical worsening over 3 years, applying the method of Rubinstein *et. al.*[60] This method uses median survival rather than event rate. The following variables were used to determine sample size: (i) alpha = 0.05, two-sided; (ii) beta=0.2 (power 80%); (iii) difference to be detected expressed as a hazard ratio of placebo:treatment = 2.0 based on previous Australian observational data, but reduced by 60% to provide a more conservative estimate for the purposes of an RCT;[19] (iv) control group median survival = 45.6 months also based on previous Australian observations;[19] (v) ratio of participants randomised to control and experimental groups = 1:1; (vi) block randomisation stratified according to 13 centres; (vii) duration of recruitment = 24 months; (viii) duration of follow-up = 36 months; (ix) expected attrition = 10%. However, substantial loss to follow-up is unlikely as trial participants are required to attend for regular review to continue receiving PAH therapy subsidised under the Pharmaceutical Benefit Scheme. Based on these assumptions, it is expected that 65 events will be observed in this study and a total sample size of 170 participants (85 per arm) is required.

Statistical analyses

The hypothesis to be tested is: Null hypothesis (H0) = the distribution of the primary endpoint is the same in the treatment groups; Alternative hypothesis (H1) = the distribution of the primary endpoint in the placebo group differs from the distribution in the active group. The ratio of the hazards of a clinical worsening event in the two groups is not expected to change over time. Therefore, the use of methods requiring proportional hazards is considered appropriate. The main analyses for the primary and secondary end points will test the null hypothesis by means of the log-rank and Wilcoxon tests, performed in the intention-to-treat population, which includes all participants

randomised. No adjustment for covariates is planned for the primary analysis. However, in order to evaluate the robustness of results, the primary endpoint will also be analysed on the per-protocol set, with 80% used as the cut-off to define an adherent patient. Supportive analyses will be conducted using appropriate covariates (e.g., the date PAH was first diagnosed by RHC, the start date of concomitant PAH medications and combination PAH therapy) in a Cox regression model.

The time to occurrence of the first clinical worsening event up to 30 days after the last study drug intake will be described by Kaplan-Meier survival curves. The hazard ratio of placebo:treatment with two-sided 95% confidence intervals of the event-free proportion estimates at relevant time-points will be presented for each treatment group in graphical and tabular form, in addition to descriptive statistics to summarise patient and disease characteristics. No imputation method will be used for the primary endpoint and if there is a missing assessment (e.g., no confirmatory 6MWT or NYHA/WHO FC) for a clinical worsening event; the endpoint adjudication committee will be responsible for qualifying or disqualifying such events before primary endpoint analysis. Patients without a clinical worsening event permanently discontinuing treatment will be censored 30 days after study treatment discontinuation or date of last contact for time to death.

Differences in baseline characteristics of patients in the apixaban and control arms will be compared using univariate methods (chi-square, t-tests and Mann-Whitney tests). Univariate and multivariable methods (logistic and linear regression) will be used to compare differences in echocardiographic parameters, 6MWD, NYHA/WHO FC, NT-proBNP level and HRQoL in the apixaban and control arms at 1, 2 and 3 years. Covariates included in multivariable analyses will include specific PAH therapy, cardiovascular medications and immunosuppressives. Sensitivity analyses will be performed to evaluate the effect of poor treatment adherence and loss to follow-up in patients whose fate is unknown at the end of the study. There will be no interim efficacy analyses and all analyses for efficacy will be undertaken at the end of the study. However, a planned re-estimation of the sample size may be performed prior to the expected closure of recruitment, based on observed blinded

event rate in the composite endpoint. All statistical analyses will be performed using STATA software (Version 13).

Cost-effectiveness analysis

On completion of the RCT, a health economic analysis will be undertaken to determine the incremental cost-effectiveness ratio, in terms of 'net costs' per unit of 'health gain'. Net costs will comprise the costs of treatment with apixaban and advanced PAH therapies for the duration of life-years gained, minus costs saved from hospitalisation and health service utilisation in the same 3-year time period. In order to enable this type of analysis, we will collect detailed usage and cost data for medications, primary care, outpatient consultations, emergency department and elective hospitalisations, through participant health service utilisation diaries, questionnaires administered at study contact, and source databases of the participating hospitals. Collection of time-to-event data and HRQoL data will enable calculation of quality-adjusted life years (QALYs) gained by the inclusion of anticoagulation therapy. Depending on the findings of the initial cost-effectiveness analysis, further economic modelling beyond three years may be required.

ETHICS AND DISSEMINATION

Ethical approval for this trial has been granted by the Human Research Ethics Committees of St Vincent's Hospital (Melbourne), the Royal Perth Hospital, the University of Western Australia, the Menzies Research Institute of Tasmania and acknowledged by the Governance offices of all hospitals involved in the trial (Fiona Stanley Hospital, Gold Coast University Hospital, Liverpool Hospital, Monash Health, Royal Adelaide Hospital, Royal Hobart Hospital, Royal Prince Alfred Hospital, The Alfred Hospital and The Queen Elizabeth Hospital). The findings of this RCT are to be published in open access journals, with none of the participants identifiable.

An independent Data and Safety Monitoring Board, comprising a rheumatologist, haematologist, cardiologist and gastroenterologist, will review unblinded safety and tolerability data at 3-monthly intervals, to ensure safety of participants for the duration of the study. The randomisation code will

not be broken and made available to investigators, including the study statistician, until after data analysis is complete.

DISCUSSION

The design of this clinical trial was not without its challenges. Numerous studies have demonstrated that survival in SSc-PAH declines precipitously over the first three years following diagnosis and thereafter plateaus, with an overall median survival of five years.[19, 21, 22, 40, 61] Furthermore, registry studies have shown that prevalent cohorts of patients with PAH have better overall survival than incident cohorts, suggesting there may be survivor bias in patients with long standing PAH.[19] Therefore, in an RCT of a novel therapy for SSc-PAH wherein the endpoint is a combination of mortality and clinical worsening, it would be ideal to limit enrolment to those with less than three years' duration since diagnosis of PAH on RHC. However, given the low disease prevalence, this restriction could limit enrolment of an appropriate sample size in a timely manner.

As the novel oral anticoagulants are unable to be readily reversed, safety considerations were of utmost importance to study design. The overall drug safety profile indicates apixaban is generally well tolerated with an elimination half-life of 12 hours.[37] For stroke prevention in atrial fibrillation, apixaban administered in a 'full-dose' (5 mg bid) has been demonstrated to be superior to warfarin for stroke prevention ($p=0.01$), with lower risk of bleeding ($p<0.001$).[44] Similarly, there is emerging evidence that apixaban administered in 'low-dose' (2.5 mg bid), may yield comparable efficacy to full-dose apixaban in certain clinical settings, such as thromboprophylaxis post arthroplasty or treatment of venous thromboembolism, with no increased risk of bleeding.[42, 43, 62] Furthermore, in acute coronary syndromes, full-dose apixaban demonstrated a 2.45 fold increased risk of bleeding compared with placebo ($p=0.005$), whereas an increased risk of bleeding was not observed with low-dose treatment ($p=0.09$).[63] Therefore, our study treatment comprising 'low-dose' apixaban should offer safety comparable to placebo, without compromising efficacy.

The clinical impact of this study is likely to be realised in the near term and the scope for cost savings from reduced need for hospitalisations is considerable. Due to the high cost of pharmacotherapy in SSc-PAH, it was important to build a health economic analysis into this study to determine cost-effectiveness of adjunct anticoagulation. If anticoagulant therapy is successful at prolonging life in SSc-PAH, patients will spend a greater period of time on costly advanced PAH specific therapies (typically approaching AUD$40,000 per drug, per patient year).[64, 65] Therefore, HRQoL outcomes must be balanced against these costs.

This study seeks to determine the efficacy of a novel therapy with the goal of improving survival in a disease with very high short-term mortality. To date, there have been no published RCTs of anticoagulation in SSc-PAH and there are no other trials currently registered in the WHO trials portal. Blinding of treatment assignment is an innovative feature of our study design as the majority of oral anticoagulation studies have been open-label. Positive findings in this study may provide a rationale for further studies of Factor Xa inhibition in other pulmonary vascular diseases, including iPAH. Thus, positive findings may have far-reaching implications beyond SSc. If the findings are negative, patients will be spared the potential risk, inconvenience and cost of anticoagulation. As 30% of patients with SSc-PAH are being anticoagulated at present in clinical practice,[19] this presents a unique situation where a negative study may be as important in terms of changing practice, as a positive study. Regardless of outcome, our study has the potential to re-define the standard of care in a disease entity where there is much uncertainty.

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AUTHORS' CONTRIBUTIONS

AC participated in design of the study and coordinated drafting of the manuscript. WS, DP, HN, EG, SP, TW, DC, PY, JS, MR, PW, VT, ND, JW, WC, MS and RB made substantial contributions to conception and design of the study. MN conceived of the study, coordinated its design and drafted the manuscript. All authors read and were involved in critically reviewing and revising important intellectual content of the manuscript. All authors approved the final manuscript prior to submission.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

FIGURE LEGENDS

Figure 1: The pathophysiological targets of advanced pulmonary arterial hypertension therapies. Pulmonary artery endothelial cell dysfunction impacts on vascular smooth muscle cell tone and remodelling in the following ways, targeted by the three main classes of advanced PAH therapy to prevent (–) or promote (+) the physiological mechanisms described in the centre of the diagram: (+++) Over-expression of endothelin-1 (ET-1) has a potent vasoconstrictor effect. Thus ET-1 receptor antagonists (ETRAs) such as bosentan and ambrisentan, block vasoconstriction of pulmonary artery smooth muscle cells. (ϕϕϕ) Impaired production of nitric oxide (NO) is remedied by phosphodiesterase type-5 (PDE-5) inhibitors such as sildenafil, that enhance NO-mediated vasodilation. (---) Prostacyclin is a vasodilator with anti-proliferative effects that is deficient in the setting of PAH. Prostacyclin analogues such as epoprostenol, treprostinil and iloprost, therefore promote vasodilation in pulmonary smooth muscle cells and prevent vascular remodelling which may involve numerous cells, including platelets and fibroblasts.

Figure 2: Study design and assessment timeline. During the initial stages of Screening, scleroderma-related pulmonary arterial hypertension (SSc-PAH) patients will be identified via review of medical records at the multidisciplinary study sites. Formal screening assessments to confirm eligibility for the study will occur after the patient has provided informed consent. Patients who meet all inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio, stratified by study site, to receive double-blinded treatment with either 2.5mg apixaban or placebo, twice daily for 36 months. Over the course of study treatment, participants will visit study sites at the following times post-randomization: 1, 3, 6, 12, 18, 24, 30 and 36 months (* = end of study visit, performed on the day of permanent cessation of study drug, sooner than 36 months in exceptional circumstances). Telephone follow-up will occur monthly in the first 12 months, then third-monthly thereafter, between scheduled visits until 30 days after the end of study visit (ϕ = 37 months post-randomisation at the latest), to ensure no adverse events have occurred and to capture all health care utilisation, including changes to concomitant medication.

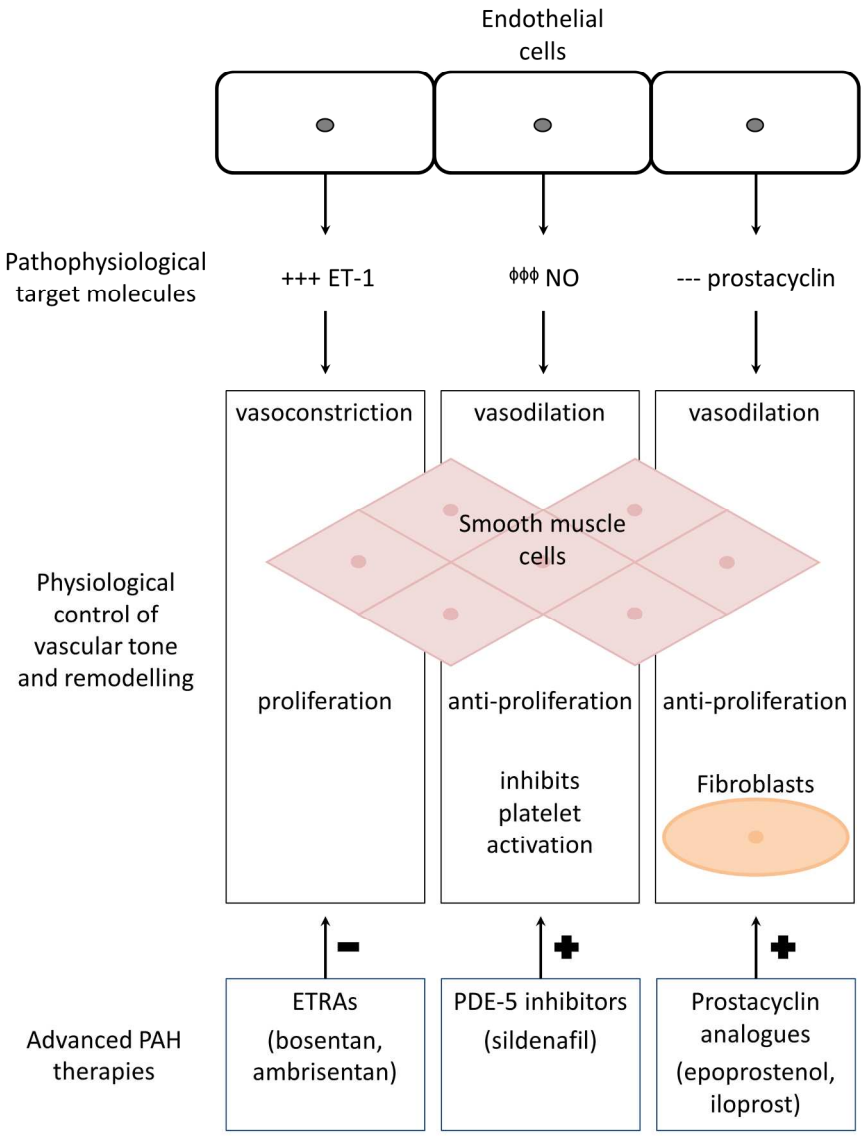

Figure 1: The pathophysiological targets of advanced pulmonary arterial hypertension therapies.

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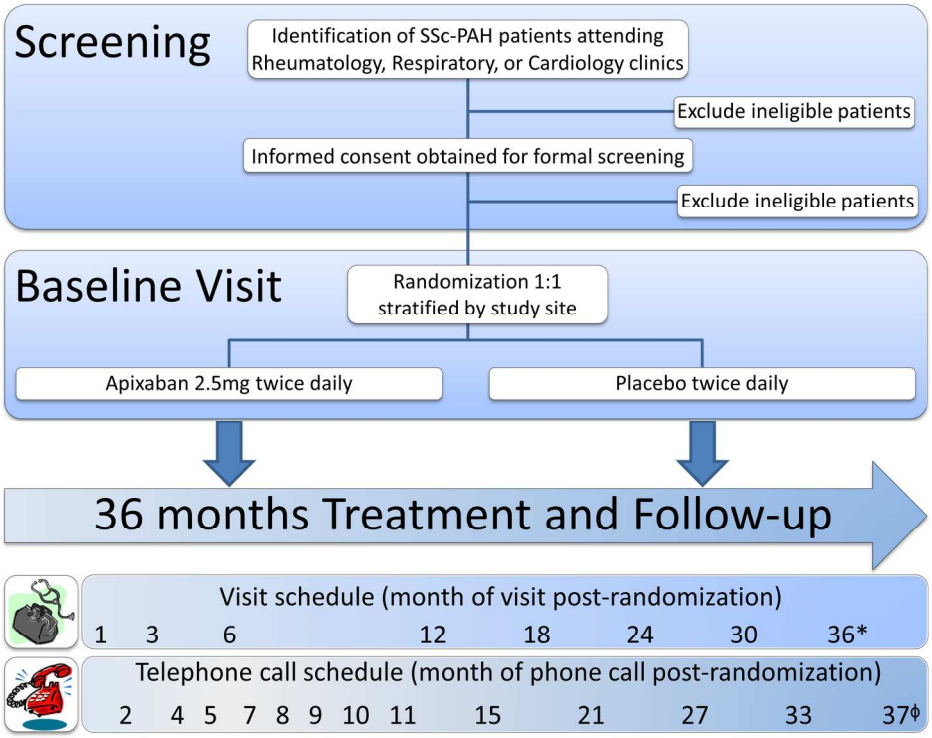

Figure 2: Study design and assessment timeline.

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A multi-centre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol.

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Complete List of Authors:	Calderone, Alicia; St. Vincent's Hospital Melbourne, Rheumatology Stevens, Wendy; St. Vincent\'s Hospital Melbourne, Rheumatology Prior, David; The University of Melbourne, Medicine; St. Vincent\'s Hospital Melbourne, Cardiology Nandurkar, Harshal; The University of Melbourne, Medicine; Monash University, Australian Centre for Blood Diseases Gabbay, Eli; The University of Notre Dame; Sir Charles Gairdner Hospital, Institute for Respiratory Health Proudman, Susanna; University of Adelaide, Medicine; Royal Adelaide Hospital, Rheumatology Williams, Trevor; Monash University, Allergy, Immunology and Respiratory Medicine at Alfred Hospital Celermajer, David; University of Sydney, Cardiology Sahhar, Joanne; Monash Health and Monash Universiy, Rheumatology Wong, Peter; Mid-North Coast Arthritis Clinic; University of New South Wales, Rural Clinical School Thakkar, Vivek ; Liverpool Hospital, Rheumatology; University of Western Sydney, School of Medicine Dwyer, Nathan; Royal Hobart Hospital, Cardiology Wrobel, Jeremy; Fiona Stanley Hospital, Advanced Lung Disease Unit Chin, Weng; Sir Charles Gairdner Hospital, Institute for Respiratory Health Liew, Danny; Monash University, Epidemiology and Preventive Medicine Staples, Margaret; Monash University, Epidemiology at Cabrini Health Buchbinder, Rachelle; Monash University, Epidemiology and Preventive Medicine; Monash University, Epidemiology at Cabrini Health Nikpour, Mandana; The University of Melbourne, Medicine; St. Vincent\'s Hospital Melbourne, Rheumatology
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TITLE

A multi-centre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol.

Full name of authors

Alicia Calderone[1], Wendy Stevens[1], David Prior[2,3], Harshal Nandurkar[3,4], Eli Gabbay[5,6], Susanna M. Proudman[7,8], Trevor Williams[9], David Celermajer[10], Joanne Sahhar[11], Peter K. K. Wong[12,13], Vivek Thakkar[14,15], Nathan Dwyer[16], Jeremy Wrobel[17], Weng Chin[6], Danny Liew[18], Margaret Staples[18,19], Rachelle Buchbinder[18,19] and Mandana Nikpour[1,3].

Institutional addresses

[1]Departments of Rheumatology, [2]Cardiology and [3]The University of Melbourne Department of Medicine at St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia. [4]Australian Centre for Blood Diseases, Central Clinical School, Monash University, The Alfred, Commercial Road, Melbourne, VIC 3004, Australia. [5]The University of Notre Dame, 19 Mouat Street, Fremantle, WA 6959, Australia. [6]Institute for Respiratory Health, Ground Floor, E Block, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia. [7]Department of Rheumatology and [8]University of Adelaide Discipline of Medicine at Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia. [9]Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Monash University, PO Box 315, Prahran, VIC 3181, Australia. [10]Department of Cardiology, Sydney Medical School, University of Sydney, NSW 2006, Australia. [11]Department of Rheumatology, Monash Health and Monash University, 246 Clayton Road, Clayton, VIC 3168, Australia. [12]Mid-North Coast Arthritis Clinic, PO Box 6307, Coffs Harbour, NSW, 2450, Australia. [13]Rural Clinical School, Faculty of Medicine, University of New South Wales, Locked Bag 812, Coffs Harbour, NSW, 2450, Australia. [14]Department of Rheumatology, Liverpool Hospital, Elizabeth Street, Liverpool, NSW 2170, Australia. [15]School of Medicine, University of Western Sydney, Locked bag 1797, Penrith, NSW 2751, Australia. [16]Department of Cardiology, Royal Hobart Hospital, 48 Liverpool Street, Hobart, TAS 7000, Australia.

[17]Advanced Lung Disease Unit, Fiona Stanley Hospital, Murdoch, WA 6150, Australia. [18]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia. [19]Monash Department of Clinical Epidemiology, Cabrini Institute, Cabrini Health, Suite 41 Cabrini Medical Centre, 183 Wattletree Rd, Malvern, VIC 3144, Australia.

Corresponding author

Dr Mandana Nikpour, Departments of Rheumatology and Medicine, The University of Melbourne, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia. Tel: + 61 3 9231 2211, Fax: + 61 3 9417 0822, Email: m.nikpour@unimelb.edu.au

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a severe and costly multi-organ autoimmune connective tissue disease characterised by vasculopathy and fibrosis. One of the major causes of SSc-related death is pulmonary arterial hypertension (PAH), which develops in 12-15% of patients with SSc and accounts for 30-40% of deaths.

In situ thrombosis in the small calibre peripheral pulmonary vessels resulting from endothelial dysfunction and an imbalance of anticoagulant and prothrombotic mediators has been implicated in the complex pathophysiology of SSc-related PAH (SSc-PAH), with international clinical guidelines recommending the use of anticoagulants for some types of PAH, such as idiopathic PAH. However, anticoagulation has not become part of standard clinical care for patients with SSc-PAH as only observational evidence exists to support its use. Therefore, we present the rationale and methodology of a Phase III randomized controlled trial (RCT) to evaluate the efficacy, safety and cost-effectiveness of anticoagulation in SSc-PAH.

Methods and analysis: This Australian multi-centre RCT will compare 2.5mg apixaban with placebo, in parallel treatment groups randomized in a 1:1 ratio, both administered twice daily for 3 years as adjunct therapy to stable oral PAH therapy. The composite primary outcome measure will be the time to death or clinical worsening of PAH. Secondary outcomes will include functional capacity, health-related quality of life measures and adverse events. A cost-effectiveness analysis of anticoagulation *versus* placebo will also be undertaken.

Ethics and dissemination: Ethical approval for this RCT has been granted by the human research ethics committees of all participating centres. An independent data safety monitoring board will review safety and tolerability data for the duration of the trial. The findings of this RCT are to be published in open access journals.

Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN12614000418673.

Strengths and limitations of this study

- This is the first clinical trial ever to evaluate the efficacy, safety and cost-effectiveness of anticoagulation as adjunct treatment in systemic sclerosis-related pulmonary arterial hypertension.
- The blinded randomised placebo-controlled design of this trial is intended to minimise bias.
- The choice of apixaban 2.5 mg bid as the anticoagulant treatment is based on consideration of the risk to benefit ratio in systemic sclerosis-related pulmonary arterial hypertension.
- However, this study is not intended to specifically evaluate the efficacy, safety and cost-effectiveness of other anticoagulant doses or drugs in this condition.
- The use of a composite clinical worsening primary end-point and health-related quality of life as a secondary endpoint is in line with the most recent expert taskforce recommendations.
- Among the limitations of this study is the inclusion of patients with PAH of varying durations and not exclusively incident cases, and the use of self-reported health service utilisation in cost-effectiveness analysis. In addition, indirect costs are not quantified.

INTRODUCTION

Scleroderma or systemic sclerosis (SSc), is a multi-organ autoimmune connective tissue disease (CTD) characterised by vasculopathy and fibrosis, that is estimated to affect over two million people worldwide, with some studies indicating a rising incidence.[1-3] Due to the multi-organ nature and chronicity of the disease, SSc is associated with significant morbidity and is one of the most costly rheumatic diseases.[4-7] SSc is also a life-threatening condition that carries the greatest burden of case-based mortality among the rheumatic diseases, reducing life expectancy by an average of 16 years per male and 34.1 years per female patient.[8] It is now well established that pulmonary arterial hypertension (PAH), a condition of increased resistance in the pulmonary vasculature, is one of the leading causes of death in SSc, accounting for 30-40% of deaths in this disease.[9-13] Untreated, SSc-related PAH (SSc-PAH) may follow a rapidly fatal course, with death resulting from right ventricular failure and arrhythmias.[9]

So called 'advanced' PAH therapies target mediators of the complex pathophysiology underlying PAH (Figure 1), predominantly molecules responsible for vascular remodelling, that result in an imbalance between endogenous pulmonary vasoconstriction and vasodilation.[14, 15] In SSc-PAH, these advanced PAH therapies demonstrate improved survival, exercise capacity as measured by 6-minute walk distance (6MWD), and health-related quality of life (HRQoL) outcomes, compared with placebo.[14-16] Prior to the advent of advanced PAH therapies in the early 2000s, the one-year survival of patients with SSc-PAH was 45%.[17] Subsequently, a systematic review of all randomised controlled trials (RCTs) of advanced PAH therapies, including patients with primary 'idiopathic' PAH (iPAH) and PAH secondary to CTD (CTD-PAH), reported an absolute reduction in mortality of 39% (p=0.04) with specific PAH treatment compared with placebo.[18] Further, two Australian observational studies have shown improved survival with combination PAH therapy compared with monotherapy in patients with iPAH and CTD-PAH (three-year survival 85% with combination therapy

versus 60% with monotherapy in CTD-PAH).[19, 20] Thus, survival has improved dramatically since the introduction of advanced therapies. However, PAH still carries a high burden of morbidity and mortality.[10, 15] Importantly, SSc-PAH continues to display the poorest prognosis compared with iPAH and other CTD-PAH subgroups.[21, 22]

In situ thrombosis is a likely contributor to the pathophysiology of SSc-PAH, with pulmonary vascular (venous and arterial) thrombosis in the small caliber peripheral pulmonary vessels appearing as a common histological feature in both iPAH and CTD-PAH tissue specimens (Figure 2).[23-25] While several observational studies, including the Australian Scleroderma Cohort Study, have suggested a survival benefit with anticoagulation in PAH, other observational studies have not supported this finding.[19, 26-31] However, many of the patients included in these studies were not on advanced PAH therapy, and the majority had iPAH.[28, 31] In contrast, the Australian Scleroderma Cohort Study data revealed a substantial survival benefit with anticoagulation when administered in conjunction with advanced PAH therapy.[19] In this CTD-PAH cohort (95% of whom were SSc-PAH patients), exhibiting a median survival of only five years, an estimated 5-fold reduction in mortality was observed with warfarin treatment, prescribed at physician discretion, over an average 2.6 ± 1.8 years follow-up.[19] Furthermore, in contrast to the support for anticoagulation in European and American guidelines for treatment of iPAH, due to absence of RCT data, recommendations for anticoagulation in SSc-PAH are based on weak evidence and reflect a state of clinical equipoise among experts.[32-36] Although pulmonary vascular pathobiology may be similar to that seen in iPAH, SSc-PAH patients have other clinical features which may impact the risk to benefit ratio of anticoagulation. Hence, there is great variability in beliefs and prescribing habits regarding anticoagulation as adjunct therapy in SSc-PAH.[26, 37] The weight of preliminary evidence, societal costs and high morbidity of SSc-PAH, demand an urgent resolution of this contentious issue through an RCT.

In design of this RCT, several considerations favour the use of novel oral anticoagulants as safer, more effective and more convenient than warfarin for SSc-PAH patients. Factor Xa is a pivotal component of the coagulation cascade, and oral factor Xa inhibitors such as apixaban and rivaroxaban, which are hypothesised to have antiplatelet and endothelial effects, may target multiple pathways critical to SSc-PAH pathogenesis.[38-41] Oral factor Xa inhibitors may offer more stable blood levels than warfarin, assuming full compliance. These agents are administered at fixed doses, have fewer diet or drug interactions, are eliminated through multiple pathways and do not require routine international normalised ratio (INR) monitoring.[38, 39] The reliable bioavailability of the factor Xa inhibitors is particularly advantageous in patients with SSc, many of whom have gut hypomotility and bacterial overgrowth, which may affect warfarin and vitamin K absorption, resulting in unstable INRs.[42] With up to 6% of SSc patients exhibiting intestinal telangiectasiae or gastric antral vascular ectasiae (GAVE) which may bleed,[43, 44] the lower risk of gastrointestinal bleeding with apixaban, observed in large clinical trials of other patient groups, is reassuring.[45-53] Finally, patients with SSc often have difficult venous access due to skin fibrosis and subcutaneous joint contractures.[26] Such patients are typically reluctant to have the multiple venesections required for INR monitoring. As oral factor Xa inhibitors do not require monitoring of blood levels and dose adjustment,[38,39] there is potential to blind treatment assignment for RCTs and participant retention in clinical trials could possibly increase.

Objective:

The *aim* of this study is to evaluate the efficacy, safety and cost-effectiveness of treatment over three years with the novel oral anticoagulant apixaban (a factor Xa inhibitor) in SSc-PAH, by undertaking a multi-centre, double-blind, placebo-controlled RCT. The intervention will occur on a background of advanced PAH therapy prescribed as standard of care for participants assigned to both treatment and placebo arms.

METHODS AND ANALYSIS

Study design

The study is designed as a multi-centre, participant- and investigator-blinded, placebo-controlled, Phase III clinical trial to compare the efficacy, safety and cost-effectiveness of apixaban 2.5 mg twice daily (bid) versus placebo, randomised in a 1:1 ratio, over a treatment period of 3 years, as additional therapy in patients with SSc-PAH who are already on advanced pulmonary vasodilators. The study design and assessment timeline is illustrated in Figure 3.

Study population

Study participants will be identified by cardiologists, rheumatologists and respirologists, during the course of routine care at 13 Australian PAH treatment centres across six states (New South Wales, Queensland, South Australia, Tasmania, Victoria and Western Australia). Recruitment will take place over 24 months or until sample size requirements are met and participants will be treated for 36 months. Participants will be adult males and females with symptomatic SSc-PAH as defined by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 classification criteria for SSc[54] and international guidelines for diagnosis of PAH.[35, 54] Inclusion and exclusion criteria are listed in Table 1 and Table 2, respectively. Many of the exclusion criteria focus on reducing the risk of adverse bleeding events in the study population.[44, 50] All eligible participants will sign informed consent prior to study enrolment, following adequate explanation of the aims, methods, objectives, and potential hazards of the trial by the responsible investigator.

Table 1: The SPHInX Study Inclusion Criteria

Item	Characteristics of eligible participants*
1.	Male and female patients aged from 18 to 75 years inclusive.
2.	Scleroderma defined by the ACR/EULAR 2013 classification criteria.
3.	RHC at any time prior to Baseline demonstrating the following haemodynamic characteristics in line with current international guidelines for diagnosis of PAH: i. resting mPAP ≥25 mmHg, and ii. resting PVR ≥3 woods units, and iii. resting PCWP or LVEDP ≤15 mmHg, or iv. if PVR cannot or has not been measured, then mPAP ≥30 mmHg with PCWP or LVEDP ≤15 mmHg.
4.	6-minute walk distance greater than 50 meters at screening and/or baseline.
5.	Other causes of PAH, in particular CTEPH must have been previously excluded by either a V/Q scan or CTPA.
6.	Currently taking at least one of the ETRA or PDE-5 inhibitor medications in a stable dose for the 2 months prior to Baseline (either bosentan, ambrisentan or macitentan, and/or sildenafil or tadalafil).
7.	Female participants of childbearing potential must test negative for pregnancy.
8.	Male and female participants of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of the study drug. A participant is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
9.	Female participants who are not of childbearing potential must meet at least one of the following criteria: i. have undergone documented hysterectomy and/or bilateral oophorectomy, ii. have medically confirmed ovarian failure, or iii. achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone level within the laboratory's reference range for post-menopausal females.

*All items must be present for eligibility into the clinical trial. *Abbreviations:* RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; CTEPH, chronic thromboembolic pulmonary hypertension; V/Q, ventilation/perfusion; CTPA, computed tomography pulmonary angiogram.

Table 2: The SPHInX Study Exclusion Criteria

Item	Characteristics of ineligible participants**
1.	Pulmonary hypertension due to any other cause than SSc.
2.	Moderate or severe obstructive lung disease, i.e. FEV1/FVC ratio <70% and FEV1 <65% of predicted value after bronchodilator administration.
3.	Moderate or severe restrictive lung disease, i.e. FVC <70% of predicted value, provided that HRCT scan demonstrates moderate to severe changes of ILD, or FVC <60% of predicted value, regardless of HRCT result.
4.	Moderate or severe hepatic impairment (i.e. Child-Pugh class B or C).
5.	Documented left ventricular dysfunction (i.e. ejection fraction <45%).
6.	Severe renal insufficiency (estimated creatinine clearance <25 mL/min, or serum creatinine >200 µmol/L).
7.	Receiving any investigational drugs within 1 month prior to, or at Baseline.
8.	Receiving continuous intravenous epoprostenol or iloprost at Baseline or have planned to initiate this therapy within the next 3 months.
9.	Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements.
10.	Life expectancy due to another condition of less than 12 months.
11.	Females who are breastfeeding or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study.
12.	Known hypersensitivity to drugs of the same class as the study drug, or any of the excipients of the drug formulations.
13.	Gastrointestinal tract bleeding in the last 12 months due to GAVE or unexplained iron deficiency anemia (in the last 12 months).
14.	Hemoglobin <100 g/L at Screening.
15.	Participants at risk of falls in whom anticoagulation would be inappropriate.
16.	Participants who have received any oral or subcutaneous anticoagulants (e.g. warfarin, apixaban, rivaroxaban, dabigatran, enoxaparin, dalteparin or heparin) for more than 3 months since the diagnosis of PAH.
17.	Participants with a prosthetic valve who require long term oral anticoagulation.
18.	Participants who are currently in atrial fibrillation.
19.	Participants with PAH not on either an ETRA or PDE-5 inhibitor.
20.	Participants with known bleeding disorders and/or platelet count <100 at screening and/or INR>1.2 at screening.
21.	Brain, spinal or eye surgery within the last one month.
22.	Uncontrolled systemic hypertension defined as either systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at Screening.
23.	Documented episode of either pulmonary embolus or deep venous thrombosis since diagnosis of PAH.
24.	Participants with a current, or active in the last one month, major bleed that is life threatening, causes chronic sequelae or consumes major health care resources, as defined by the International Society on Thrombosis and Haemostasis.

**Participants must not meet any of the exclusion criteria for eligibility into the clinical trial. *Abbreviations:*

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HRCT, high resolution computed

tomography; ILD, interstitial lung disease.

Randomisation and allocation concealment

Ethical considerations mandate background treatment with advanced PAH therapies as standard of care in all study participants.[35, 36] As sites differ in rates of use of PAH specific therapies, including combination therapy, randomisation will be stratified according to site, with the effect of various PAH therapies subsequently adjusted for in multiple regression analysis.

Randomisation to placebo or study drug in a 1:1 ratio will be performed by a statistician who is not associated with any study site, using computer generated block randomisation, stratified according to study site. After the investigator obtains informed consent and confirms eligibility, patients who meet all inclusion criteria and none of the exclusion criteria will be assigned to study treatment by the site pharmacist at baseline visit, according to the site randomisation schedule.

Participants, healthcare providers, investigators, data collectors and outcome assessors will be blinded to treatment assignment. To ensure allocation concealment, the appearance of the investigational drug [apixaban, BMS-562247, Bristol-Myers Squibb Limited (BMS), New Jersey, USA] and its packaging will be indistinguishable from the matching placebo, both manufactured by BMS. The labelling and packaging of apixaban and matching placebo will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and national regulatory requirements, coordinated by the study lead pharmacy.

A password-protected restricted access electronic database of all randomisation codes will be kept for emergency unblinding purposes. If any participant experiences a medical emergency wherein management would be improved by knowledge of the blinded treatment assignment, unblinding will be available 24 hours per day. A set of tamper-proof sealed envelopes containing the blinding code for each participant will be kept at each site in case contact with the database server fails. The integrity of these sealed envelopes will be periodically checked. A log of every access to the unblinding codes will be kept and all requests for unblinding must be clearly justified.

Treatment exposure and compliance

The study drug will be administered orally, twice daily as 2.5mg tablets of apixaban or matching placebo, with a dose interval of approximately 12 hours. Participants will be asked to return all unused study drug at follow-up visits and to self-report any missed doses of therapy. Study drug adherence will be assessed by recording quantities of returned study drug at each follow-up visit. Participants will cease study drug 36 months after initiation at baseline visit.

The study design mandates the concomitant use of at least one advanced pulmonary vasodilator, such as an endothelin-1 receptor antagonist (ETRA) and/or a phosphodiesterase type-5 (PDE-5) inhibitor. However, these therapies must be at a stable dose for at least two months prior to baseline. Permissible concomitant medication includes diuretic therapy, provided that a stable dose was maintained for at least one month prior to baseline; one antiplatelet agent will be allowed at physician discretion. However, the combination of clopidogrel or ticagrelor and aspirin is not allowed due to increased risk of bleeding.[51] Prohibited concomitant medications from one month prior to baseline until study drug cessation include any investigational drug other than the study drug; oral or subcutaneous anticoagulation with warfarin, apixaban, rivaroxaban, dabigatran, enoxaparin, dalteparin or heparin. Participants must not be receiving continuous intravenous infusion of epoprostenol or iloprost for PAH at baseline or be planned to initiate this therapy within the next three months. However, the following exceptions may apply following study commencement: (1) study drug may be temporarily suspended to receive prophylactic anticoagulation during a therapeutic or surgical procedure if this is deemed in the participant's best interest; and (2) addition of intravenous epoprostenol to oral advanced PAH therapy for participants in modified New York Heart Association/World Health Organisation (NYHA/WHO) functional class (FC) IV failing ETRAs and PDE-5 inhibitors.[35] Short term treatment with IV prostacyclin for severe Raynaud's phenomenon or digital ulcers, may be administered at any time during the study without constituting a clinical worsening event (CWE).

Concomitant medications will be monitored closely from one month following baseline visit. Participants will be required to self-report all changes to therapy throughout the study treatment period using a health care utilisation diary. Commencement of any new PAH-specific treatment or a dose increase of such a drug without adjudicated clinical worsening of PAH is strongly discouraged during the study period. If continued administration of the study drug is believed to be contrary to the best interests of the participant (i.e. adverse event, diagnostic or therapeutic procedure, laboratory abnormalities, pregnancy, unblinding, or withdrawal of consent), interruption or permanent discontinuation of the study drug is mandated. Participants will resume study drug as long as the investigator feels it is safe for them to do so and no more than eight weeks of study treatment has been missed. Participants who prematurely discontinue the study drug for any reason will not be replaced and unless they withdraw consent, will continue to be followed up 6-monthly until 36 months from baseline.

Study assessments

The study assessment schedule is illustrated in Figure 2, commencing with screening and ending with follow-up 30 days after the permanent cessation of study drug. Additional visits may also take place at any time during the treatment period in case of a suspected clinical worsening event (CWE). Screening assessments to confirm study eligibility may occur at any time prior to randomization, or be completed on the same day as the baseline visit. Adverse event surveillance is prioritised at follow-up assessments. With reference to their health care utilisation diary, participants will be required to self-report all health care utilisation (i.e. visits to health care/allied health practitioners and hospitalisations), side effects and pregnancy test results if applicable. Data collection requirements over the duration of the study are described in Table 3. All data collected will be entered de-identified into a customised electronic case report form, created on the REDCap platform, that is password protected and stored securely on the central server at St. Vincent's Hospital Melbourne. Hard copies of source documents will be retained for 5 years following the end of the study.

Table 3: Data collection requirements over the duration of the study

Participant demographics	Physical examination	Physical examination	Concomitant medications
Previous and ongoing medical history	Height and weight	Weight	Adverse event reporting
Medications history	Vital signs$^{\phi}$	Vital signs$^{\phi}$	Results of urine pregnancy test §§
Criteria for scleroderma classification	Electrocardiogram$^{\phi\phi}$	Electrocardiogram$^{\phi\phi}$	
RHC hemodynamic parameters that confirm PAH diagnosis	NYHA/WHO functional class	NYHA/WHO functional class	
V/Q scan or CTPA results that exclude CTEPH as a cause of the PAH	Concomitant medications	Concomitant medications and adverse event reporting	
HRCT results that exclude ILD	6MWT and Borg dyspnea index	6MWT and Borg dyspnea index	
Echocardiography results*	HRQoL questionnaires	HRQoL questionnaires	
Laboratory results**	Echocardiography results*	Echocardiography results*	
6MWT and Borg dyspnea index	Specimen collection§	Specimen collection§	

*Echocardiogram images will be collected where available, and data must be obtained within two months of Baseline, 6 and 24 month visits. **Laboratory samples must be taken within two weeks of baseline including full blood count, liver function, renal function, INR, and serum pregnancy test or follicle-stimulating hormone levels for female participants only. $^{\phi}$Vital signs comprise heart rate and blood pressure (standing and supine). $^{\phi\phi}$A standard 12-lead electrocardiogram will be performed at baseline, 6 month, 24 month, clinical worsening event and end of study visits. §Serum and platelet-free plasma samples will be stored for biomarker testing; §§monthly urine pregnancy tests are required for women of childbearing potential.

Abbreviations: RHC, right heart catheterisation; V/Q scan, ventilation perfusion scan; CTPA, CT pulmonary angiogram; CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease; 6MWT, 6-minute walk test, NHYA/WHO, New York heart Association / World Health Organisation;

HRQoL, health related quality of life.

The 6-minute walk test (6MWT) will be performed in a standardised, non-encouraged fashion, measuring the walking distance covered by the patient during a 6-minute period followed immediately by the Borg dyspnea index, which rates dyspnea severity on a visual analogue scale from '0' to '10'.[55] The following validated HRQoL questionnaires will be completed by the patient: The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36),[56] the scleroderma-modified Stanford Health Assessment Questionnaire (sHAQ)[57, 58] and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[59] The 6MWT and HRQoL questionnaires will be omitted from visit 2 (1 month post-randomisation), which will serve as an abridged safety assessment only, unless there is a suspected CWE.

Serum and platelet-free plasma samples collected at baseline, 6 and 24 month follow-up visits, will be stored at -80˚ Celcius for N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) assay and exploratory biomarker testing.[60, 61] Factor Xa levels in platelet-free plasma specimens will also be compared between baseline and 6 months to reflect bioavailability of apixaban in the treatment group.[62] Anti-factor Xa assays and biomarker assays will be performed for all samples in triplicate, in a single laboratory at the conclusion of the study.

Outcome measures

In line with the Task Force on Endpoints and Clinical Trial design recommendation for Phase III trials at the 4th World Symposium on pulmonary hypertension in Dana Point, California,[63] a composite primary endpoint will be employed, providing measurable parameters to support an independent adjudication of "time to clinical worsening (TtCW)". The primary endpoint will be time from randomisation up to 36 months to the first adjudicated clinical worsening event from the composite parameters listed in Table 4. CWEs will be adjudicated in a blinded fashion by an endpoint adjudication committee consisting of four of the investigators (MN, WS, DP, SP) who will adjudicate each event independently and then meet to discuss any that were not unanimously agreed upon. Study drug will be continued in a blinded fashion after a CWE is adjudicated, to enable quantification of the total number of CWEs during the study period as a secondary endpoint.

Table 4: Definition of measurable composite primary endpoint parameters

Item	Possible clinical worsening events
1.	Death (all-cause mortality).
2.	Hospitalisation for worsening of PAH due to either: i. Need for lung transplantation or balloon atrial septostomy, or ii. Initiation of parenteral (subcutaneous and intravenous) prostanoid therapy or chronic oxygen therapy.
3.	Disease progression defined by the combination of at least two of the following components: i. Reduction from baseline in 6MWD by 15%, confirmed by two consecutive 6MWTs done on different days, ideally within 2 weeks of one another. ii. Worsening of PAH symptoms included at least one of the following parameters: a) either an increase from baseline in NYHA/WHO functional class (except for participants already in functional class IV), or b) appearance/worsening of signs/symptoms of right heart failure. iii. Need for additional PAH specific therapy that may include inhaled prostanoids, PDE-5 inhibitors, ETRAs or intravenous diuretics.

Any of the above singular events, or combinations of events, may be adjudicated as clinical worsening events within the composite primary endpoint for the first such event, or as a secondary efficacy endpoint for subsequent events.

Selection of secondary endpoints was informed by Expert Panel recommendations for a 'core set' of outcome measures to be used in clinical trials of new therapies in SSc-PAH.[64] Secondary efficacy endpoints include all-cause mortality; absence of worsening in NYHA/WHO functional class; change in 6MWD and Borg dyspnea index; change in the SF-36, sHAQ and CAMPHOR questionnaire sub-scales. Secondary endpoint comparisons will be evaluated from baseline to each of 12, 24 and 36 month follow-up time-points, adjusted for time since diagnosis of PAH. The last valid post-baseline value will be carried forward to compensate for any missing values at each time-point.

Safety and tolerability endpoints will comprise treatment-emergent adverse events (serious and non-serious) including marked laboratory abnormalities up to 7 days after last study drug intake, adverse events leading to premature discontinuation of study drug, change from baseline to end of

study in vital signs. Health economic endpoints will include number per year, and associated costs, of all-cause and PAH-related hospitalisations and in-patient hospital days, general practitioner, specialist visits, allied health service utilisation and initiation of new medications.

In participants who discontinue the study, where possible, CWE will be captured every 6 months to the end of 36 weeks from enrolment.

Sample size estimation

Sample size was calculated based on a comparison of two survival curves for the primary outcome of clinical worsening over 3 years, applying the method of Rubinstein *et. al.*[65] This method uses median survival rather than event rate. The following variables were used to determine sample size: (i) alpha = 0.05, two-sided; (ii) beta=0.2 (power 80%); (iii) difference to be detected expressed as a hazard ratio of placebo:treatment = 2.0, based on previous Australian observational data, but reduced by 60% to provide a more conservative estimate for the purposes of an RCT;[19] (iv) control group median survival = 45.6 months also based on previous Australian observations;[19] (v) ratio of participants randomised to control and experimental groups = 1:1; (vi) block randomisation stratified according to 13 centres; (vii) duration of recruitment = 24 months; (viii) duration of follow-up = 36 months; (ix) expected attrition = 10%. However, substantial loss to follow-up is unlikely as trial participants are required to attend for regular review to continue receiving PAH therapy subsidised under the Pharmaceutical Benefit Scheme (PBS). Based on these assumptions, it is expected that 65 events will be observed in this study and a total sample size of 170 participants (85 per arm) is required.

Statistical analyses

The hypothesis to be tested is: Null hypothesis (H0) = the distribution of the primary endpoint is the same in the treatment groups; Alternative hypothesis (H1) = the distribution of the primary endpoint in the placebo group differs from the distribution in the active group. The ratio of the hazards of a clinical worsening event in the two groups is not expected to change over time. Therefore, the use of

methods requiring proportional hazards is considered appropriate. The main analyses for the primary and secondary end points will test the null hypothesis by means of the log-rank and Wilcoxon tests, performed in the intention-to-treat population, which includes all participants randomised. No adjustment for covariates is planned for the primary analysis. However, in order to evaluate the robustness of results, the primary endpoint will also be analysed on the per-protocol set, with 80% used as the cut-off to define an adherent patient. Supportive analyses will be conducted using appropriate covariates (e.g., the date PAH was first diagnosed by RHC, the start date of concomitant PAH medications and combination PAH therapy) in a Cox regression model.

The time to occurrence of the first clinical worsening event up to 30 days after the last study drug intake will be described by Kaplan-Meier survival curves. The hazard ratio of placebo:treatment with two-sided 95% confidence intervals of the event-free proportion estimates at relevant time-points will be presented for each treatment group in graphical and tabular form, in addition to descriptive statistics to summarise patient and disease characteristics. No imputation method will be used for the primary endpoint and if there is a missing assessment (e.g., no confirmatory 6MWT or NYHA/WHO FC) for a clinical worsening event; the endpoint adjudication committee will be responsible for qualifying or disqualifying such events before primary endpoint analysis. Patients without a clinical worsening event permanently discontinuing treatment will be censored 30 days after study treatment discontinuation or date of last contact.

Differences in baseline characteristics of patients in the apixaban and control arms will be compared using univariate methods (chi-square, t-tests and Mann-Whitney tests). Univariate and multivariable methods (logistic and linear regression) will be used to compare differences in echocardiographic parameters, 6MWD, NYHA/WHO FC, NT-proBNP level and HRQoL in the apixaban and control arms at 1, 2 and 3 years. Covariates included in multivariable analyses will include specific PAH therapy, cardiovascular medications and immunosuppressives. Sensitivity analyses will be performed to evaluate the effect of poor treatment adherence and loss to follow-up in patients whose fate is

unknown at the end of the study. No interim efficacy analyses are planned at this stage. However, a planned re-estimation of the sample size may be performed prior to the expected closure of recruitment, based on observed blinded event rate in the composite endpoint.

Predefined subgroup analyses include a comparison of efficacy and safety in incident *versus* prevalent PAH, limited *versus* diffuse SSc disease subtypes and according to autoantibody profile (anti-centromere anti-nuclear antibody *versus* anti-topoisomerase antibody). All statistical analyses will be performed by a biostatistician using STATA software.

Cost-effectiveness analysis

On completion of the RCT, a health economic analysis will be undertaken to determine the incremental cost-effectiveness ratio, in terms of 'net costs' per unit of 'health gain'. Net costs will comprise the costs of treatment with apixaban and advanced PAH therapies for the duration of life-years gained, minus costs saved from hospitalisation and health service utilisation in the same 3-year time period. In order to enable this type of analysis, we will collect detailed usage data for medications, primary care, outpatient consultations, emergency department and elective hospitalisations, through participant health service utilisation diaries, questionnaires administered at study contact, and source databases of the participating hospitals. As actual costs of health service utilisation are not recorded, in cost-effectiveness analysis, we are making the assumption that the unit cost assigned to each service in the Medicare Benefits Schedule (MBS) is an accurate estimate of true costs.

Collection of time-to-event data and HRQoL data will enable calculation of quality-adjusted life years (QALYs) gained by the inclusion of anticoagulation therapy. Depending on the findings of the initial cost-effectiveness analysis, further economic modelling beyond three years, using the Markov approach, may be required.

Ethics, safety monitoring, auditing and access to data

Ethical approval for this trial has been granted by the Human Research Ethics Committees of St Vincent's Hospital (Melbourne), the Royal Perth Hospital, the University of Western Australia, the Menzies Research Institute of Tasmania and acknowledged by the Governance offices of all hospitals involved in the trial (Fiona Stanley Hospital, Gold Coast University Hospital, Liverpool Hospital, Monash Health, Royal Adelaide Hospital, Royal Hobart Hospital, Royal Prince Alfred Hospital, The Alfred Hospital and The Queen Elizabeth Hospital). The findings of this RCT are to be published in open access journals, with none of the participants identifiable.

An independent Data and Safety Monitoring Board (DSMB), comprising a rheumatologist, haematologist, cardiologist and gastroenterologist, will review unblinded safety and tolerability data at 3-monthly intervals, to ensure safety of participants for the duration of the study. Members of the DSMB are independent of the study investigators and are free of competing interests. A formal DSMB charter has been produced for this study.

The randomisation code will not be broken and made available to investigators, including the study statistician, until after data analysis is complete.

The project coordinator based at St. Vincent's Hospital Melbourne will audit trial conduct and data entry every 3 to 4 months and will undertake site visits. At this stage no independent audit of trial conduct is planned but would occur at the request of the DSMB or regulatory bodies.

Only the lead chief investigator, trial coordinator and biostatistician will have access to the final unblinded trial data set for the purpose of analysis and dissemination of the findings from this study. None of these team members will have access to unblinded trial data prior to the completion of the study.

Communication with investigators and dissemination of findings

Any protocol modifications such as changes to eligibility criteria and analysis plans will be communicated by the lead chief investigator (MN) to the principal and associated investigators, and

affected trial participants, through personal communication including emails and teleconferences and circulation of written documents including an amended study protocol. Authorship of papers arising from this study will be based on contribution to the study including intellectual content.

Study limitations

Limitations of this study include the inclusion of patients with PAH of varying durations and not exclusively incident cases, and the use of self-reported health service utilisation in cost-effectiveness analysis. In addition, in this study, indirect costs are not quantified.

DISCUSSION

The design of this clinical trial was not without its challenges. Numerous studies have demonstrated that survival in SSc-PAH declines precipitously over the first three years following diagnosis and thereafter plateaus, with an overall median survival of five years.[19, 21, 22, 42, 66] Furthermore, registry studies have shown that prevalent cohorts of patients with PAH have better overall survival than incident cohorts, suggesting there may be survivor bias in patients with long standing PAH.[19] Therefore, in an RCT of a novel therapy for SSc-PAH wherein the endpoint is a combination of mortality and clinical worsening, it would be ideal to limit enrolment to those with less than three years' duration since diagnosis of PAH on RHC. However, given the low disease prevalence, this restriction could limit enrolment of an appropriate sample size in a timely manner. Despite these more generous inclusion criteria, the recruitment of a sufficient number of patients to power this clinical trial remains the biggest challenge to its timely completion. The investigators are currently in the process of enlisting more recruitment sites to meet sample size requirements.

As the novel oral anticoagulants are unable to be readily reversed, safety considerations were of utmost importance to study design. The overall drug safety profile indicates apixaban is generally well tolerated with an elimination half-life of 12 hours.[39] For stroke prevention in atrial fibrillation, apixaban administered in a 'full-dose' (5 mg bid) has been demonstrated to be superior to warfarin for stroke prevention ($p=0.01$), with lower risk of bleeding ($p<0.001$).[47] Similarly, there is emerging

evidence that apixaban administered in 'low-dose' (2.5 mg bid), may yield comparable efficacy to full-dose apixaban in certain clinical settings, such as thromboprophylaxis post arthroplasty or treatment of venous thromboembolism, with no increased risk of bleeding.[45, 46, 52] Furthermore, in acute coronary syndromes, full-dose apixaban demonstrated a 2.45 fold increased risk of bleeding compared with placebo (p=0.005), whereas an increased risk of bleeding was not observed with low-dose treatment (p=0.09).[53] Therefore, in our study treatment comprising 'low-dose' apixaban should offer safety comparable to placebo, without compromising efficacy.

The clinical impact of this study is likely to be realised in the near term and the scope for cost savings from reduced need for hospitalisations is considerable. Due to the high cost of pharmacotherapy in SSc-PAH, it was important to build a health economic analysis into this study to determine cost-effectiveness of adjunct anticoagulation. If anticoagulant therapy is successful at prolonging life in SSc-PAH, patients will spend a greater period of time on costly advanced PAH specific therapies (typically approaching AUD$40,000 per drug, per patient year).[67, 68] Therefore, HRQoL outcomes must be balanced against these costs.

This study seeks to determine the efficacy of a novel therapy with the goal of improving survival in a disease with very high short-term mortality. To date, there have been no published RCTs of anticoagulation in SSc-PAH and there are no other trials currently registered in the WHO trials portal. Blinding of treatment assignment is an innovative feature of our study design as the majority of oral anticoagulation studies have been open-label. Positive findings in this study may provide a rationale for further studies of Factor Xa inhibition in other pulmonary vascular diseases, including iPAH. Thus, positive findings may have far-reaching implications beyond SSc. If the findings are negative, patients will be spared the potential risk, inconvenience and cost of anticoagulation. As 30% of patients with SSc-PAH are being anticoagulated at present in clinical practice,[19] this presents a unique situation where a negative study may be as important in terms of changing practice, as a positive study. Regardless of outcome, our study has the potential to re-define the standard of care in a disease

entity where there is much uncertainty.

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AUTHORS' CONTRIBUTIONS

AC participated in design of the study and coordinated drafting of the manuscript. WS, DP, HN, EG, SP, TW, DC, PY, JS, MR, PW, VT, ND, JW, WC, MS and RB made substantial contributions to conception and design of the study. MN conceived of the study, coordinated its design and drafted the manuscript. All authors read and were involved in critically reviewing and revising important intellectual content of the manuscript. All authors approved the final manuscript prior to submission.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

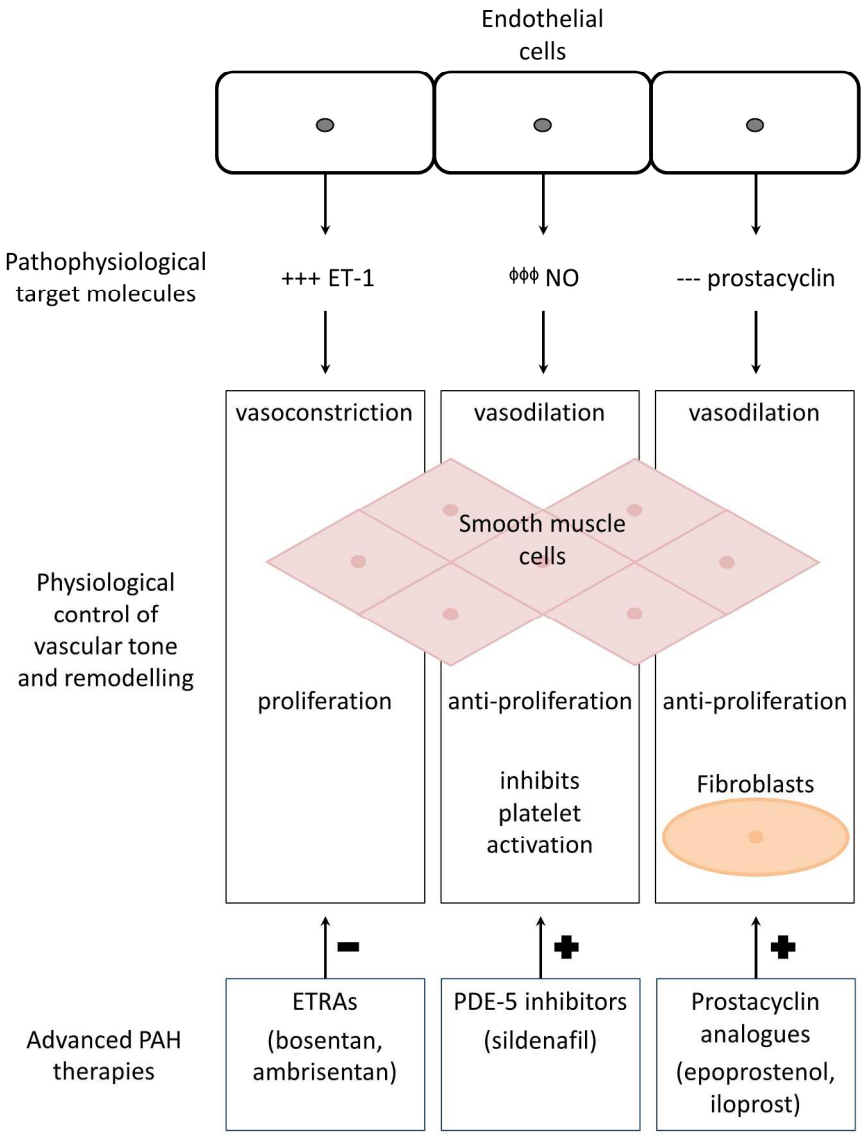
FIGURE LEGENDS

Figure 1: The pathophysiological targets of advanced pulmonary arterial hypertension therapies. Pulmonary artery endothelial cell dysfunction impacts on vascular smooth muscle cell tone and remodelling in the following ways, targeted by the three main classes of advanced PAH therapy to prevent (–) or promote (+) the physiological mechanisms described in the centre of the diagram: (+++) Over-expression of endothelin-1 (ET-1) has a potent vasoconstrictor effect. Thus ET-1 receptor antagonists (ETRAs) such as bosentan and ambrisentan, block vasoconstriction of pulmonary artery smooth muscle cells. (ϕϕϕ) Impaired production of nitric oxide (NO) is remedied by phosphodiesterase type-5 (PDE-5) inhibitors such as sildenafil, that enhance NO-mediated vasodilation. (---) Prostacyclin is a vasodilator with anti-proliferative effects that is deficient in the setting of PAH. Prostacyclin analogues such as epoprostenol, treprostinil and iloprost, therefore promote vasodilation in pulmonary smooth muscle cells and prevent vascular remodelling which may involve numerous cells, including platelets and fibroblasts.

Figure 2: The pathogenic triad of systemic sclerosis related pulmonary arterial hypertension. Vasoconstriction, vascular remodelling and thrombosis constitute the pathogenic 'triad' of pulmonary arterial hypertension in systemic sclerosis (SSc-PAH). The endothelin receptor antagonists (ETRAs), phosphodiesterase type-5 (PDE-5) inhibitors and prostacyclin promote vasodilation and prevent vascular remodelling, while anticoagulants may have a beneficial effect in SSc-PAH by preventing thrombosis.

Figure 3: Study design and assessment timeline. During the initial stages of Screening, scleroderma-related pulmonary arterial hypertension (SSc-PAH) patients will be identified via review of medical records at the multidisciplinary study sites. Formal screening assessments to confirm eligibility for the study will occur after the patient has provided informed consent. Patients who meet all inclusion

criteria and none of the exclusion criteria will be randomized in a 1:1 ratio, stratified by study site, to receive double-blinded treatment with either 2.5mg apixaban or placebo, twice daily for 36 months. Over the course of study treatment, participants will visit study sites at the following times post-randomization: 1, 3, 6, 12, 18, 24, 30 and 36 months (* = end of study visit, performed on the day of permanent cessation of study drug, sooner than 36 months in exceptional circumstances). Telephone follow-up will occur monthly in the first 12 months, then third-monthly thereafter, between scheduled visits until 30 days after the end of study visit (ϕ = 37 months post-randomisation at the latest), to ensure no adverse events have occurred and to capture all health care utilisation, including changes to concomitant medication.



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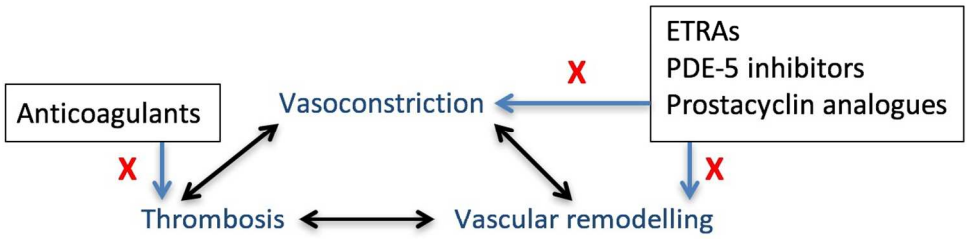

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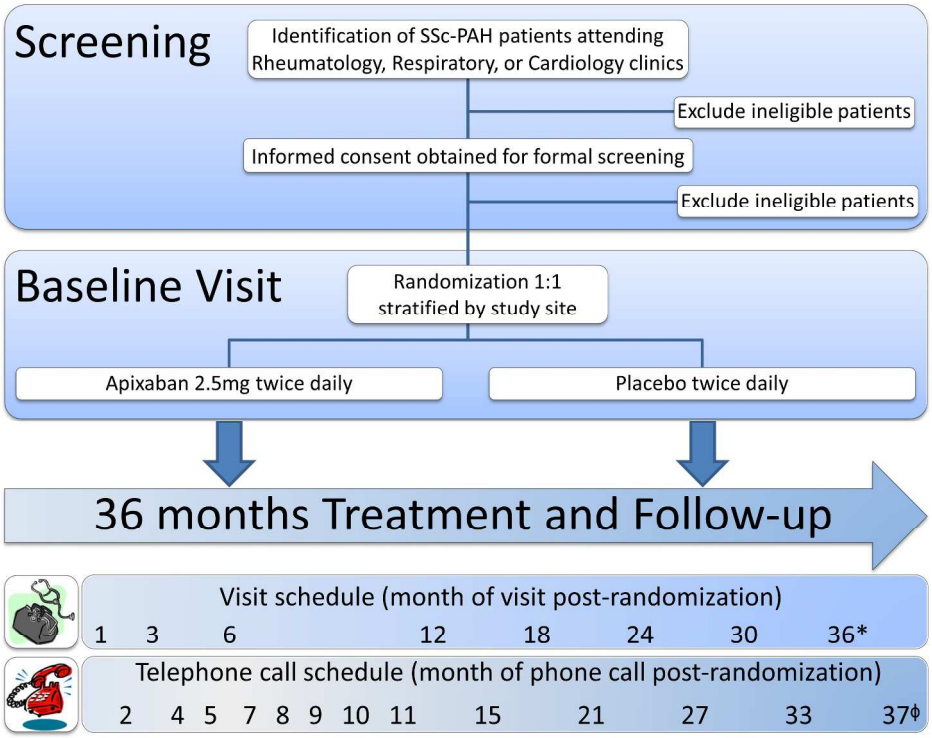

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____NA_____
Protocol version	3	Date and version identifier	_____NA_____
Funding	4	Sources and types of financial, material, and other support	_____31_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1, 2 and 31__
	5b	Name and contact information for the trial sponsor	_____2_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____31_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_8, 11, 13, 16, 21_

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-7, 22-23 and Figures 1 & 2
	6b	Explanation for choice of comparators	5-6, 12-13 & 22-23
Objectives	7	Specific objectives or hypotheses	_____7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3, 7 & Figure 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-10, Table 1 & 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____12-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____12-13____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___12 & 16_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_9-10, 12-13___
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____16-18_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____Figure 3___

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____18_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8 & 18____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____11_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___13-16_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_13, 16-18___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__11-13_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___18-20_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____18-20_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___18-20_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___21_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___17, 21_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____21_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___20_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____21_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	31
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

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

BMJ Open

A multi-centre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol.

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Systemic sclerosis, Pulmonary arterial hypertension, Anticoagulation < HAEMATOLOGY, Apixaban, Randomised controlled trial

TITLE

A multi-centre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol.

Full name of authors

Alicia Calderone[1], Wendy Stevens[1], David Prior[2,3], Harshal Nandurkar[3,4], Eli Gabbay[5,6], Susanna M. Proudman[7,8], Trevor Williams[9], David Celermajer[10], Joanne Sahhar[11], Peter K. K. Wong[12,13], Vivek Thakkar[14,15], Nathan Dwyer[16], Jeremy Wrobel[17], Weng Chin[6], Danny Liew[18], Margaret Staples[18,19], Rachelle Buchbinder[18,19] and Mandana Nikpour[1,3].

Institutional addresses

[1]Departments of Rheumatology, [2]Cardiology and [3]The University of Melbourne Department of Medicine at St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia. [4]Australian Centre for Blood Diseases, Central Clinical School, Monash University, The Alfred, Commercial Road, Melbourne, VIC 3004, Australia. [5]The University of Notre Dame, 19 Mouat Street, Fremantle, WA 6959, Australia. [6]Institute for Respiratory Health, Ground Floor, E Block, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia. [7]Department of Rheumatology and [8]University of Adelaide Discipline of Medicine at Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia. [9]Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Monash University, PO Box 315, Prahran, VIC 3181, Australia. [10]Department of Cardiology, Sydney Medical School, University of Sydney, NSW 2006, Australia. [11]Department of Rheumatology, Monash Health and Monash University, 246 Clayton Road, Clayton, VIC 3168, Australia. [12]Mid-North Coast Arthritis Clinic, PO Box 6307, Coffs Harbour, NSW, 2450, Australia. [13]Rural Clinical School, Faculty of Medicine, University of New South Wales, Locked Bag 812, Coffs Harbour, NSW, 2450, Australia. [14]Department of Rheumatology, Liverpool Hospital, Elizabeth Street, Liverpool, NSW 2170, Australia. [15]School of Medicine, University of Western Sydney, Locked bag 1797, Penrith, NSW 2751, Australia. [16]Department of Cardiology, Royal Hobart Hospital, 48 Liverpool Street, Hobart, TAS 7000, Australia.

[17]Advanced Lung Disease Unit, Fiona Stanley Hospital, Murdoch, WA 6150, Australia. [18]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia. [19]Monash Department of Clinical Epidemiology, Cabrini Institute, Cabrini Health, Suite 41 Cabrini Medical Centre, 183 Wattletree Rd, Malvern, VIC 3144, Australia.

Corresponding author

Dr Mandana Nikpour, Departments of Rheumatology and Medicine, The University of Melbourne, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia. Tel: + 61 3 9231 2211, Fax: + 61 3 9417 0822, Email: m.nikpour@unimelb.edu.au

Keywords: Systemic sclerosis, pulmonary arterial hypertension, anticoagulation, apixaban, randomised controlled trial.

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a severe and costly multi-organ autoimmune connective tissue disease characterised by vasculopathy and fibrosis. One of the major causes of SSc-related death is pulmonary arterial hypertension (PAH), which develops in 12-15% of patients with SSc and accounts for 30-40% of deaths.

In situ thrombosis in the small calibre peripheral pulmonary vessels resulting from endothelial dysfunction and an imbalance of anticoagulant and prothrombotic mediators has been implicated in the complex pathophysiology of SSc-related PAH (SSc-PAH), with international clinical guidelines recommending the use of anticoagulants for some types of PAH, such as idiopathic PAH. However, anticoagulation has not become part of standard clinical care for patients with SSc-PAH as only observational evidence exists to support its use. Therefore, we present the rationale and methodology of a Phase III randomized controlled trial (RCT) to evaluate the efficacy, safety and cost-effectiveness of anticoagulation in SSc-PAH.

Methods and analysis: This Australian multi-centre RCT will compare 2.5mg apixaban with placebo, in parallel treatment groups randomized in a 1:1 ratio, both administered twice daily for 3 years as adjunct therapy to stable oral PAH therapy. The composite primary outcome measure will be the time to death or clinical worsening of PAH. Secondary outcomes will include functional capacity, health-related quality of life measures and adverse events. A cost-effectiveness analysis of anticoagulation *versus* placebo will also be undertaken.

Ethics and dissemination: Ethical approval for this RCT has been granted by the human research ethics committees of all participating centres. An independent data safety monitoring board will review safety and tolerability data for the duration of the trial. The findings of this RCT are to be published in open access journals.

Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN12614000418673.

Strengths and limitations of this study

- This is the first clinical trial ever to evaluate the efficacy, safety and cost-effectiveness of anticoagulation as adjunct treatment in systemic sclerosis-related pulmonary arterial hypertension.
- The blinded randomised placebo-controlled design of this trial is intended to minimise bias.
- The choice of apixaban 2.5 mg bid as the anticoagulant treatment is based on consideration of the risk to benefit ratio in systemic sclerosis-related pulmonary arterial hypertension.
- However, this study is not intended to specifically evaluate the efficacy, safety and cost-effectiveness of other anticoagulant doses or drugs in this condition.
- The use of a composite clinical worsening primary end-point and health-related quality of life as a secondary endpoint is in line with the most recent expert taskforce recommendations.
- Among the limitations of this study is the inclusion of patients with PAH of varying durations and not exclusively incident cases, and the use of self-reported health service utilisation in cost-effectiveness analysis. In addition, indirect costs are not quantified.

INTRODUCTION

Scleroderma or systemic sclerosis (SSc), is a multi-organ autoimmune connective tissue disease (CTD) characterised by vasculopathy and fibrosis, that is estimated to affect over two million people worldwide, with some studies indicating a rising incidence.[1-3] Due to the multi-organ nature and chronicity of the disease, SSc is associated with significant morbidity and is one of the most costly rheumatic diseases.[4-7] SSc is also a life-threatening condition that carries the greatest burden of case-based mortality among the rheumatic diseases, reducing life expectancy by an average of 16 years per male and 34.1 years per female patient.[8] It is now well established that pulmonary arterial hypertension (PAH), a condition of increased resistance in the pulmonary vasculature, is one of the leading causes of death in SSc, accounting for 30-40% of deaths in this disease.[9-13] Untreated, SSc-related PAH (SSc-PAH) may follow a rapidly fatal course, with death resulting from right ventricular failure and arrhythmias.[9]

So called 'advanced' PAH therapies target mediators of the complex pathophysiology underlying PAH (Figure 1), predominantly molecules responsible for vascular remodelling, that result in an imbalance between endogenous pulmonary vasoconstriction and vasodilation.[14, 15] In SSc-PAH, these advanced PAH therapies demonstrate improved survival, exercise capacity as measured by 6-minute walk distance (6MWD), and health-related quality of life (HRQoL) outcomes, compared with placebo.[14-16] Prior to the advent of advanced PAH therapies in the early 2000s, the one-year survival of patients with SSc-PAH was 45%.[17] Subsequently, a systematic review of all randomised controlled trials (RCTs) of advanced PAH therapies, including patients with primary 'idiopathic' PAH (iPAH) and PAH secondary to CTD (CTD-PAH), reported an absolute reduction in mortality of 39% (p=0.04) with specific PAH treatment compared with placebo.[18] Further, two Australian observational studies have shown improved survival with combination PAH therapy compared with monotherapy in patients with iPAH and CTD-PAH (three-year survival 85% with combination therapy

versus 60% with monotherapy in CTD-PAH).[19, 20] Thus, survival has improved dramatically since the introduction of advanced therapies. However, PAH still carries a high burden of morbidity and mortality.[10, 15] Importantly, SSc-PAH continues to display the poorest prognosis compared with iPAH and other CTD-PAH subgroups.[21, 22]

In situ thrombosis is a likely contributor to the pathophysiology of SSc-PAH, with pulmonary vascular (venous and arterial) thrombosis in the small caliber peripheral pulmonary vessels appearing as a common histological feature in both iPAH and CTD-PAH tissue specimens (Figure 2).[23-25] While several observational studies, including the Australian Scleroderma Cohort Study, have suggested a survival benefit with anticoagulation in PAH, other observational studies have not supported this finding.[19, 26-31] However, many of the patients included in these studies were not on advanced PAH therapy, and the majority had iPAH.[28, 31] In contrast, the Australian Scleroderma Cohort Study data revealed a substantial survival benefit with anticoagulation when administered in conjunction with advanced PAH therapy.[19] In this CTD-PAH cohort (95% of whom were SSc-PAH patients), exhibiting a median survival of only five years, an estimated 5-fold reduction in mortality was observed with warfarin treatment, prescribed at physician discretion, over an average 2.6 ± 1.8 years follow-up.[19] Furthermore, in contrast to the support for anticoagulation in European and American guidelines for treatment of iPAH, due to absence of RCT data, recommendations for anticoagulation in SSc-PAH are based on weak evidence and reflect a state of clinical equipoise among experts.[32-36] Although pulmonary vascular pathobiology may be similar to that seen in iPAH, SSc-PAH patients have other clinical features which may impact the risk to benefit ratio of anticoagulation. Hence, there is great variability in beliefs and prescribing habits regarding anticoagulation as adjunct therapy in SSc-PAH.[26, 37] The weight of preliminary evidence, societal costs and high morbidity of SSc-PAH, demand an urgent resolution of this contentious issue through an RCT.

In design of this RCT, several considerations favour the use of novel oral anticoagulants as safer, more effective and more convenient than warfarin for SSc-PAH patients. Factor Xa is a pivotal component of the coagulation cascade, and oral factor Xa inhibitors such as apixaban and rivaroxaban, which are hypothesised to have antiplatelet and endothelial effects, may target multiple pathways critical to SSc-PAH pathogenesis.[38-41] Oral factor Xa inhibitors may offer more stable blood levels than warfarin, assuming full compliance. These agents are administered at fixed doses, have fewer diet or drug interactions, are eliminated through multiple pathways and do not require routine international normalised ratio (INR) monitoring.[38, 39] The reliable bioavailability of the factor Xa inhibitors is particularly advantageous in patients with SSc, many of whom have gut hypomotility and bacterial overgrowth, which may affect warfarin and vitamin K absorption, resulting in unstable INRs.[42] With up to 6% of SSc patients exhibiting intestinal telangiectasiae or gastric antral vascular ectasiae (GAVE) which may bleed,[43, 44] the lower risk of gastrointestinal bleeding with apixaban, observed in large clinical trials of other patient groups, is reassuring.[45-53] Finally, patients with SSc often have difficult venous access due to skin fibrosis and subcutaneous joint contractures.[26] Such patients are typically reluctant to have the multiple venesections required for INR monitoring. As oral factor Xa inhibitors do not require monitoring of blood levels and dose adjustment,[38,39] there is potential to blind treatment assignment for RCTs and participant retention in clinical trials could possibly increase.

Objective:

The *aim* of this study is to evaluate the efficacy, safety and cost-effectiveness of treatment over three years with the novel oral anticoagulant apixaban (a factor Xa inhibitor) in SSc-PAH, by undertaking a multi-centre, double-blind, placebo-controlled RCT. The intervention will occur on a background of advanced PAH therapy prescribed as standard of care for participants assigned to both treatment and placebo arms.

METHODS AND ANALYSIS

Study design

The study is designed as a multi-centre, participant- and investigator-blinded, placebo-controlled, Phase III clinical trial to compare the efficacy, safety and cost-effectiveness of apixaban 2.5 mg twice daily (bid) versus placebo, randomised in a 1:1 ratio, over a treatment period of 3 years, as additional therapy in patients with SSc-PAH who are already on advanced pulmonary vasodilators. The study design and assessment timeline is illustrated in Figure 3.

Study population

Study participants will be identified by cardiologists, rheumatologists and respirologists, during the course of routine care at 13 Australian PAH treatment centres across six states (New South Wales, Queensland, South Australia, Tasmania, Victoria and Western Australia). Recruitment will take place over 24 months or until sample size requirements are met and participants will be treated for 36 months. Participants will be adult males and females with symptomatic SSc-PAH as defined by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 classification criteria for SSc[54] and international guidelines for diagnosis of PAH.[35, 54] Inclusion and exclusion criteria are listed in Table 1 and Table 2, respectively. Many of the exclusion criteria focus on reducing the risk of adverse bleeding events in the study population.[44, 50] All eligible participants will sign informed consent prior to study enrolment, following adequate explanation of the aims, methods, objectives, and potential hazards of the trial by the responsible investigator.

Table 1: The SPHInX Study Inclusion Criteria

Item	Characteristics of eligible participants*
1.	Male and female patients aged from 18 to 75 years inclusive.
2.	Scleroderma defined by the ACR/EULAR 2013 classification criteria.
3.	RHC at any time prior to Baseline demonstrating the following haemodynamic characteristics in line with current international guidelines for diagnosis of PAH: i. resting mPAP ≥25 mmHg, and ii. resting PVR ≥3 woods units, and iii. resting PCWP or LVEDP ≤15 mmHg, or iv. if PVR cannot or has not been measured, then mPAP ≥30 mmHg with PCWP or LVEDP ≤15 mmHg.
4.	6-minute walk distance greater than 50 meters at screening and/or baseline.
5.	Other causes of PAH, in particular CTEPH must have been previously excluded by either a V/Q scan or CTPA.
6.	Currently taking at least one of the ETRA or PDE-5 inhibitor medications in a stable dose for the 2 months prior to Baseline (either bosentan, ambrisentan or macitentan, and/or sildenafil or tadalafil).
7.	Female participants of childbearing potential must test negative for pregnancy.
8.	Male and female participants of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of the study drug. A participant is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
9.	Female participants who are not of childbearing potential must meet at least one of the following criteria: i. have undergone documented hysterectomy and/or bilateral oophorectomy, ii. have medically confirmed ovarian failure, or iii. achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone level within the laboratory's reference range for post-menopausal females.

*All items must be present for eligibility into the clinical trial. *Abbreviations:* RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; CTEPH, chronic thromboembolic pulmonary hypertension; V/Q, ventilation/perfusion; CTPA, computed tomography pulmonary angiogram.

Table 2: The SPHInX Study Exclusion Criteria

Item	Characteristics of ineligible participants**
1.	Pulmonary hypertension due to any other cause than SSc.
2.	Moderate or severe obstructive lung disease, i.e. FEV1/FVC ratio <70% and FEV1 <65% of predicted value after bronchodilator administration.
3.	Moderate or severe restrictive lung disease, i.e. FVC <70% of predicted value, provided that HRCT scan demonstrates moderate to severe changes of ILD, or FVC <60% of predicted value, regardless of HRCT result.
4.	Moderate or severe hepatic impairment (i.e. Child-Pugh class B or C).
5.	Documented left ventricular dysfunction (i.e. ejection fraction <45%).
6.	Severe renal insufficiency (estimated creatinine clearance <25 mL/min, or serum creatinine >200 µmol/L).
7.	Receiving any investigational drugs within 1 month prior to, or at Baseline.
8.	Receiving continuous intravenous epoprostenol or iloprost at Baseline or have planned to initiate this therapy within the next 3 months.
9.	Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements.
10.	Life expectancy due to another condition of less than 12 months.
11.	Females who are breastfeeding or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study.
12.	Known hypersensitivity to drugs of the same class as the study drug, or any of the excipients of the drug formulations.
13.	Gastrointestinal tract bleeding in the last 12 months due to GAVE or unexplained iron deficiency anemia (in the last 12 months).
14.	Hemoglobin <100 g/L at Screening.
15.	Participants at risk of falls in whom anticoagulation would be inappropriate.
16.	Participants who have received any oral or subcutaneous anticoagulants (e.g. warfarin, apixaban, rivaroxaban, dabigatran, enoxaparin, dalteparin or heparin) for more than 3 months since the diagnosis of PAH.
17.	Participants with a prosthetic valve who require long term oral anticoagulation.
18.	Participants who are currently in atrial fibrillation.
19.	Participants with PAH not on either an ETRA or PDE-5 inhibitor.
20.	Participants with known bleeding disorders and/or platelet count <100 at screening and/or INR>1.2 at screening.
21.	Brain, spinal or eye surgery within the last one month.
22.	Uncontrolled systemic hypertension defined as either systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at Screening.
23.	Documented episode of either pulmonary embolus or deep venous thrombosis since diagnosis of PAH.
24.	Participants with a current, or active in the last one month, major bleed that is life threatening, causes chronic sequelae or consumes major health care resources, as defined by the International Society on Thrombosis and Haemostasis.

**Participants must not meet any of the exclusion criteria for eligibility into the clinical trial. *Abbreviations:*

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HRCT, high resolution computed

tomography; ILD, interstitial lung disease.

Randomisation and allocation concealment

Ethical considerations mandate background treatment with advanced PAH therapies as standard of care in all study participants.[35, 36] As sites differ in rates of use of PAH specific therapies, including combination therapy, randomisation will be stratified according to site, with the effect of various PAH therapies subsequently adjusted for in multiple regression analysis.

Randomisation to placebo or study drug in a 1:1 ratio will be performed by a statistician who is not associated with any study site, using computer generated block randomisation, stratified according to study site. After the investigator obtains informed consent and confirms eligibility, patients who meet all inclusion criteria and none of the exclusion criteria will be assigned to study treatment by the site pharmacist at baseline visit, according to the site randomisation schedule.

Participants, healthcare providers, investigators, data collectors and outcome assessors will be blinded to treatment assignment. To ensure allocation concealment, the appearance of the investigational drug [apixaban, BMS-562247, Bristol-Myers Squibb Limited (BMS), New Jersey, USA] and its packaging will be indistinguishable from the matching placebo, both manufactured by BMS. The labelling and packaging of apixaban and matching placebo will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and national regulatory requirements, coordinated by the study lead pharmacy.

A password-protected restricted access electronic database of all randomisation codes will be kept for emergency unblinding purposes. If any participant experiences a medical emergency wherein management would be improved by knowledge of the blinded treatment assignment, unblinding will be available 24 hours per day. A set of tamper-proof sealed envelopes containing the blinding code for each participant will be kept at each site in case contact with the database server fails. The integrity of these sealed envelopes will be periodically checked. A log of every access to the unblinding codes will be kept and all requests for unblinding must be clearly justified.

Treatment exposure and compliance

The study drug will be administered orally, twice daily as 2.5mg tablets of apixaban or matching placebo, with a dose interval of approximately 12 hours. Participants will be asked to return all unused study drug at follow-up visits and to self-report any missed doses of therapy. Study drug adherence will be assessed by recording quantities of returned study drug at each follow-up visit. Participants will cease study drug 36 months after initiation at baseline visit.

The study design mandates the concomitant use of at least one advanced pulmonary vasodilator, such as an endothelin-1 receptor antagonist (ETRA) and/or a phosphodiesterase type-5 (PDE-5) inhibitor. However, these therapies must be at a stable dose for at least two months prior to baseline. Permissible concomitant medication includes diuretic therapy, provided that a stable dose was maintained for at least one month prior to baseline; one antiplatelet agent will be allowed at physician discretion. However, the combination of clopidogrel or ticagrelor and aspirin is not allowed due to increased risk of bleeding.[51] Prohibited concomitant medications from one month prior to baseline until study drug cessation include any investigational drug other than the study drug; oral or subcutaneous anticoagulation with warfarin, apixaban, rivaroxaban, dabigatran, enoxaparin, dalteparin or heparin. Participants must not be receiving continuous intravenous infusion of epoprostenol or iloprost for PAH at baseline or be planned to initiate this therapy within the next three months. However, the following exceptions may apply following study commencement: (1) study drug may be temporarily suspended to receive prophylactic anticoagulation during a therapeutic or surgical procedure if this is deemed in the participant's best interest; and (2) addition of intravenous epoprostenol to oral advanced PAH therapy for participants in modified New York Heart Association/World Health Organisation (NYHA/WHO) functional class (FC) IV failing ETRAs and PDE-5 inhibitors.[35] Short term treatment with IV prostacyclin for severe Raynaud's phenomenon or digital ulcers, may be administered at any time during the study without constituting a clinical worsening event (CWE).

Concomitant medications will be monitored closely from one month following baseline visit. Participants will be required to self-report all changes to therapy throughout the study treatment period using a health care utilisation diary. Commencement of any new PAH-specific treatment or a dose increase of such a drug without adjudicated clinical worsening of PAH is strongly discouraged during the study period. If continued administration of the study drug is believed to be contrary to the best interests of the participant (i.e. adverse event, diagnostic or therapeutic procedure, laboratory abnormalities, pregnancy, unblinding, or withdrawal of consent), interruption or permanent discontinuation of the study drug is mandated. Participants will resume study drug as long as the investigator feels it is safe for them to do so and no more than eight weeks of study treatment has been missed. Participants who prematurely discontinue the study drug for any reason will not be replaced and unless they withdraw consent, will continue to be followed up 6-monthly until 36 months from baseline.

Study assessments

The study assessment schedule is illustrated in Figure 2, commencing with screening and ending with follow-up 30 days after the permanent cessation of study drug. Additional visits may also take place at any time during the treatment period in case of a suspected clinical worsening event (CWE). Screening assessments to confirm study eligibility may occur at any time prior to randomization, or be completed on the same day as the baseline visit. Adverse event surveillance is prioritised at follow-up assessments. With reference to their health care utilisation diary, participants will be required to self-report all health care utilisation (i.e. visits to health care/allied health practitioners and hospitalisations), side effects and pregnancy test results if applicable. Data collection requirements over the duration of the study are described in Table 3. All data collected will be entered de-identified into a customised electronic case report form, created on the REDCap platform, that is password protected and stored securely on the central server at St. Vincent's Hospital Melbourne. Hard copies of source documents will be retained for 5 years following the end of the study.

Table 3: Data collection requirements over the duration of the study

Participant demographics	Physical examination	Physical examination	Concomitant medications
Previous and ongoing medical history	Height and weight	Weight	Adverse event reporting
Medications history	Vital signs$^{\phi}$	Vital signs$^{\phi}$	Results of urine pregnancy test §§
Criteria for scleroderma classification	Electrocardiogram$^{\phi\phi}$	Electrocardiogram$^{\phi\phi}$	
RHC hemodynamic parameters that confirm PAH diagnosis	NYHA/WHO functional class	NYHA/WHO functional class	
V/Q scan or CTPA results that exclude CTEPH as a cause of the PAH	Concomitant medications	Concomitant medications and adverse event reporting	
HRCT results that exclude ILD	6MWT and Borg dyspnea index	6MWT and Borg dyspnea index	
Echocardiography results*	HRQoL questionnaires	HRQoL questionnaires	
Laboratory results**	Echocardiography results*	Echocardiography results*	
6MWT and Borg dyspnea index	Specimen collection§	Specimen collection§	

*Echocardiogram images will be collected where available, and data must be obtained within two months of Baseline, 6 and 24 month visits. **Laboratory samples must be taken within two weeks of baseline including full blood count, liver function, renal function, INR, and serum pregnancy test or follicle-stimulating hormone levels for female participants only. $^{\phi}$Vital signs comprise heart rate and blood pressure (standing and supine). $^{\phi\phi}$A standard 12-lead electrocardiogram will be performed at baseline, 6 month, 24 month, clinical worsening event and end of study visits. §Serum and platelet-free plasma samples will be stored for biomarker testing; §§monthly urine pregnancy tests are required for women of childbearing potential.

Abbreviations: RHC, right heart catheterisation; V/Q scan, ventilation perfusion scan; CTPA, CT pulmonary angiogram; CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease; 6MWT, 6-minute walk test, NHYA/WHO, New York heart Association / World Health Organisation; HRQoL, health related quality of life.

The 6-minute walk test (6MWT) will be performed in a standardised, non-encouraged fashion, measuring the walking distance covered by the patient during a 6-minute period followed immediately by the Borg dyspnea index, which rates dyspnea severity on a visual analogue scale from '0' to '10'.[55] The following validated HRQoL questionnaires will be completed by the patient: The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36),[56] the scleroderma-modified Stanford Health Assessment Questionnaire (sHAQ)[57, 58] and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[59] The 6MWT and HRQoL questionnaires will be omitted from visit 2 (1 month post-randomisation), which will serve as an abridged safety assessment only, unless there is a suspected CWE.

Serum and platelet-free plasma samples collected at baseline, 6 and 24 month follow-up visits, will be stored at -80˚ Celcius for N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) assay and exploratory biomarker testing.[60, 61] Factor Xa levels in platelet-free plasma specimens will also be compared between baseline and 6 months to reflect bioavailability of apixaban in the treatment group.[62] Anti-factor Xa assays and biomarker assays will be performed for all samples in triplicate, in a single laboratory at the conclusion of the study.

Outcome measures

In line with the Task Force on Endpoints and Clinical Trial design recommendation for Phase III trials at the 4th World Symposium on pulmonary hypertension in Dana Point, California,[63] a composite primary endpoint will be employed, providing measurable parameters to support an independent adjudication of "time to clinical worsening (TtCW)". The primary endpoint will be time from randomisation up to 36 months to the first adjudicated clinical worsening event from the composite parameters listed in Table 4. CWEs will be adjudicated in a blinded fashion by an endpoint adjudication committee consisting of four of the investigators (MN, WS, DP, SP) who will adjudicate each event independently and then meet to discuss any that were not unanimously agreed upon. Study drug will be continued in a blinded fashion after a CWE is adjudicated, to enable quantification of the total number of CWEs during the study period as a secondary endpoint.

Table 4: Definition of measurable composite primary endpoint parameters

Item	Possible clinical worsening events
1.	Death (all-cause mortality).
2.	Hospitalisation for worsening of PAH due to either: i. Need for lung transplantation or balloon atrial septostomy, or ii. Initiation of parenteral (subcutaneous and intravenous) prostanoid therapy or chronic oxygen therapy.
3.	Disease progression defined by the combination of at least two of the following components: i. Reduction from baseline in 6MWD by 15%, confirmed by two consecutive 6MWTs done on different days, ideally within 2 weeks of one another. ii. Worsening of PAH symptoms included at least one of the following parameters: a) either an increase from baseline in NYHA/WHO functional class (except for participants already in functional class IV), or b) appearance/worsening of signs/symptoms of right heart failure. iii. Need for additional PAH specific therapy that may include inhaled prostanoids, PDE-5 inhibitors, ETRAs or intravenous diuretics.

Any of the above singular events, or combinations of events, may be adjudicated as clinical worsening events within the composite primary endpoint for the first such event, or as a secondary efficacy endpoint for subsequent events.

Selection of secondary endpoints was informed by Expert Panel recommendations for a 'core set' of outcome measures to be used in clinical trials of new therapies in SSc-PAH.[64] Secondary efficacy endpoints include all-cause mortality; absence of worsening in NYHA/WHO functional class; change in 6MWD and Borg dyspnea index; change in the SF-36, sHAQ and CAMPHOR questionnaire sub-scales. Secondary endpoint comparisons will be evaluated from baseline to each of 12, 24 and 36 month follow-up time-points, adjusted for time since diagnosis of PAH. The last valid post-baseline value will be carried forward to compensate for any missing values at each time-point.

Safety and tolerability endpoints will comprise treatment-emergent adverse events (serious and non-serious) including marked laboratory abnormalities up to 7 days after last study drug intake, adverse events leading to premature discontinuation of study drug, change from baseline to end of

study in vital signs. Health economic endpoints will include number per year, and associated costs, of all-cause and PAH-related hospitalisations and in-patient hospital days, general practitioner, specialist visits, allied health service utilisation and initiation of new medications.

In participants who discontinue the study, where possible, CWE will be captured every 6 months to the end of 36 weeks from enrolment.

Sample size estimation

Sample size was calculated based on a comparison of two survival curves for the primary outcome of clinical worsening over 3 years, applying the method of Rubinstein *et. al.*[65] This method uses median survival rather than event rate. The following variables were used to determine sample size: (i) alpha = 0.05, two-sided; (ii) beta=0.2 (power 80%); (iii) difference to be detected expressed as a hazard ratio of placebo:treatment = 2.0, based on previous Australian observational data, but reduced by 60% to provide a more conservative estimate for the purposes of an RCT;[19] (iv) control group median survival = 45.6 months also based on previous Australian observations;[19] (v) ratio of participants randomised to control and experimental groups = 1:1; (vi) block randomisation stratified according to 13 centres; (vii) duration of recruitment = 24 months; (viii) duration of follow-up = 36 months; (ix) expected attrition = 10%. However, substantial loss to follow-up is unlikely as trial participants are required to attend for regular review to continue receiving PAH therapy subsidised under the Pharmaceutical Benefit Scheme (PBS). Based on these assumptions, it is expected that 65 events will be observed in this study and a total sample size of 170 participants (85 per arm) is required.

Statistical analyses

The hypothesis to be tested is: Null hypothesis (H0) = the distribution of the primary endpoint is the same in the treatment groups; Alternative hypothesis (H1) = the distribution of the primary endpoint in the placebo group differs from the distribution in the active group. The ratio of the hazards of a clinical worsening event in the two groups is not expected to change over time. Therefore, the use of

methods requiring proportional hazards is considered appropriate. The main analyses for the primary and secondary end points will test the null hypothesis by means of the log-rank and Wilcoxon tests, performed in the intention-to-treat population, which includes all participants randomised. No adjustment for covariates is planned for the primary analysis. However, in order to evaluate the robustness of results, the primary endpoint will also be analysed on the per-protocol set, with 80% used as the cut-off to define an adherent patient. Supportive analyses will be conducted using appropriate covariates (e.g., the date PAH was first diagnosed by RHC, the start date of concomitant PAH medications and combination PAH therapy) in a Cox regression model.

The time to occurrence of the first clinical worsening event up to 30 days after the last study drug intake will be described by Kaplan-Meier survival curves. The hazard ratio of placebo:treatment with two-sided 95% confidence intervals of the event-free proportion estimates at relevant time-points will be presented for each treatment group in graphical and tabular form, in addition to descriptive statistics to summarise patient and disease characteristics. No imputation method will be used for the primary endpoint and if there is a missing assessment (e.g., no confirmatory 6MWT or NYHA/WHO FC) for a clinical worsening event; the endpoint adjudication committee will be responsible for qualifying or disqualifying such events before primary endpoint analysis. Patients without a clinical worsening event permanently discontinuing treatment will be censored 30 days after study treatment discontinuation or date of last contact.

Differences in baseline characteristics of patients in the apixaban and control arms will be compared using univariate methods (chi-square, t-tests and Mann-Whitney tests). Univariate and multivariable methods (logistic and linear regression) will be used to compare differences in echocardiographic parameters, 6MWD, NYHA/WHO FC, NT-proBNP level and HRQoL in the apixaban and control arms at 1, 2 and 3 years. Covariates included in multivariable analyses will include specific PAH therapy, cardiovascular medications and immunosuppressives. Sensitivity analyses will be performed to evaluate the effect of poor treatment adherence and loss to follow-up in patients whose fate is

unknown at the end of the study. No interim efficacy analyses are planned at this stage. However, a planned re-estimation of the sample size may be performed prior to the expected closure of recruitment, based on observed blinded event rate in the composite endpoint.

Predefined subgroup analyses include a comparison of efficacy and safety in incident *versus* prevalent PAH, limited *versus* diffuse SSc disease subtypes and according to autoantibody profile (anti-centromere anti-nuclear antibody *versus* anti-topoisomerase antibody). All statistical analyses will be performed by a biostatistician using STATA software.

Cost-effectiveness analysis

On completion of the RCT, a health economic analysis will be undertaken to determine the incremental cost-effectiveness ratio, in terms of 'net costs' per unit of 'health gain'. Net costs will comprise the costs of treatment with apixaban and advanced PAH therapies for the duration of life-years gained, minus costs saved from hospitalisation and health service utilisation in the same 3-year time period. In order to enable this type of analysis, we will collect detailed usage data for medications, primary care, outpatient consultations, emergency department and elective hospitalisations, through participant health service utilisation diaries, questionnaires administered at study contact, and source databases of the participating hospitals. As actual costs of health service utilisation are not recorded, in cost-effectiveness analysis, we are making the assumption that the unit cost assigned to each service in the Medicare Benefits Schedule (MBS) is an accurate estimate of true costs.

Collection of time-to-event data and HRQoL data will enable calculation of quality-adjusted life years (QALYs) gained by the inclusion of anticoagulation therapy. Depending on the findings of the initial cost-effectiveness analysis, further economic modelling beyond three years, using the Markov approach, may be required.

We will be applying a 5% annual discount rate to projected future costs and benefits. We will

undertake sensitivity analyses to test the robustness of our cost-effectiveness results, and to identify key input parameters to which the results are most sensitive. Both 'one-way' sensitivity analyses, as well as 'multi-way' probabilistic sensitivity analyses will be undertaken.

Ethics, safety monitoring, auditing and access to data

Ethical approval for this trial has been granted by the Human Research Ethics Committees of St Vincent's Hospital (Melbourne), the Royal Perth Hospital, the University of Western Australia, the Menzies Research Institute of Tasmania and acknowledged by the Governance offices of all hospitals involved in the trial (Fiona Stanley Hospital, Gold Coast University Hospital, Liverpool Hospital, Monash Health, Royal Adelaide Hospital, Royal Hobart Hospital, Royal Prince Alfred Hospital, The Alfred Hospital and The Queen Elizabeth Hospital). The findings of this RCT are to be published in open access journals, with none of the participants identifiable.

An independent Data and Safety Monitoring Board (DSMB), comprising a rheumatologist, haematologist, cardiologist and gastroenterologist, will review unblinded safety and tolerability data at 3-monthly intervals, to ensure safety of participants for the duration of the study. Members of the DSMB are independent of the study investigators and are free of competing interests. A formal DSMB charter has been produced for this study.

The randomisation code will not be broken and made available to investigators, including the study statistician, until after data analysis is complete.

The project coordinator based at St. Vincent's Hospital Melbourne will audit trial conduct and data entry every 3 to 4 months and will undertake site visits. At this stage no independent audit of trial conduct is planned but would occur at the request of the DSMB or regulatory bodies.

Only the lead chief investigator, trial coordinator and biostatistician will have access to the final unblinded trial data set for the purpose of analysis and dissemination of the findings from this study. None of these team members will have access to unblinded trial data prior to the completion of the

study.

Communication with investigators and dissemination of findings

Any protocol modifications such as changes to eligibility criteria and analysis plans will be communicated by the lead chief investigator (MN) to the principal and associated investigators, and affected trial participants, through personal communication including emails and teleconferences and circulation of written documents including an amended study protocol. Authorship of papers arising from this study will be based on contribution to the study including intellectual content.

Study limitations

Limitations of this study include the inclusion of patients with PAH of varying durations and not exclusively incident cases, and the use of self-reported health service utilisation in cost-effectiveness analysis. In addition, in this study, indirect costs are not quantified.

DISCUSSION

The design of this clinical trial was not without its challenges. Numerous studies have demonstrated that survival in SSc-PAH declines precipitously over the first three years following diagnosis and thereafter plateaus, with an overall median survival of five years.[19, 21, 22, 42, 66] Furthermore, registry studies have shown that prevalent cohorts of patients with PAH have better overall survival than incident cohorts, suggesting there may be survivor bias in patients with long standing PAH.[19] Therefore, in an RCT of a novel therapy for SSc-PAH wherein the endpoint is a combination of mortality and clinical worsening, it would be ideal to limit enrolment to those with less than three years' duration since diagnosis of PAH on RHC. However, given the low disease prevalence, this restriction could limit enrolment of an appropriate sample size in a timely manner. Despite these more generous inclusion criteria, the recruitment of a sufficient number of patients to power this clinical trial remains the biggest challenge to its timely completion. The investigators are currently in the process of enlisting more recruitment sites to meet sample size requirements.

As the novel oral anticoagulants are unable to be readily reversed, safety considerations were of utmost importance to study design. The overall drug safety profile indicates apixaban is generally well tolerated with an elimination half-life of 12 hours.[39] For stroke prevention in atrial fibrillation, apixaban administered in a 'full-dose' (5 mg bid) has been demonstrated to be superior to warfarin for stroke prevention (p=0.01), with lower risk of bleeding (p<0.001).[47] Similarly, there is emerging evidence that apixaban administered in 'low-dose' (2.5 mg bid), may yield comparable efficacy to full-dose apixaban in certain clinical settings, such as thromboprophylaxis post arthroplasty or treatment of venous thromboembolism, with no increased risk of bleeding.[45, 46, 52] Furthermore, in acute coronary syndromes, full-dose apixaban demonstrated a 2.45 fold increased risk of bleeding compared with placebo (p=0.005), whereas an increased risk of bleeding was not observed with low-dose treatment (p=0.09).[53] Therefore, in our study treatment comprising 'low-dose' apixaban should offer safety comparable to placebo, without compromising efficacy.

While a comparison with warfarin would have been interesting, from a practical and safety point of view, this was not possible. Firstly, SSc-PAH is an infrequent condition and the addition of a third arm to the study would have increased sample size requirements, posing a serious threat to the feasibility of this study. Furthermore, two recently published studies have cast doubt over the safety of warfarin relative to its potential efficacy in SSc-PAH, suggesting that this treatment may in fact be harmful in this group of patients.[29-30] Possible reasons for this include the presence of SSc disease features such as gastrointestinal tract hypomotility and bacterial overgrowth affecting the absorption of warfarin, and the presence of gastric antral vascular ectasia and intestinal telangiectasia, which place patients at risk of gastrointestinal bleeding. For these reasons, as well as those discussed earlier, we have not included a warfarin arm in this trial.

Non-anticoagulant effects of heparins have been described. [67] The potential of such actions is currently being investigated for the novel anticoagulants, further supporting our choice of anticoagulant in this study.[68]

The clinical impact of this study is likely to be realised in the near term and the scope for cost savings from reduced need for hospitalisations is considerable. Due to the high cost of pharmacotherapy in SSc-PAH, it was important to build a health economic analysis into this study to determine cost-effectiveness of adjunct anticoagulation. If anticoagulant therapy is successful at prolonging life in SSc-PAH, patients will spend a greater period of time on costly advanced PAH specific therapies (typically approaching AUD$40,000 per drug, per patient year).[69-70] Therefore, HRQoL outcomes must be balanced against these costs. In Australia, there is no official threshold for incremental cost-effectiveness ratios, although AUD $50,000 per Quality Adjusted Life Years (QALY) saved is commonly used. The WHO recommends use of Gross Domestic Product per capita as a starting point to consider cost-effectiveness thresholds for a country, which for Australia at present is approximately AUD $88,000. [71]

This study seeks to determine the efficacy of a novel therapy with the goal of improving survival in a disease with very high short-term mortality. To date, there have been no published RCTs of anticoagulation in SSc-PAH and there are no other trials currently registered in the WHO trials portal. Blinding of treatment assignment is an innovative feature of our study design as the majority of oral anticoagulation studies have been open-label. Positive findings in this study may provide a rationale for further studies of Factor Xa inhibition in other pulmonary vascular diseases, including iPAH. Thus, positive findings may have far-reaching implications beyond SSc. If the findings are negative, patients will be spared the potential risk, inconvenience and cost of anticoagulation. As 30% of patients with SSc-PAH are being anticoagulated at present in clinical practice,[19] this presents a unique situation where a negative study may be as important in terms of changing practice, as a positive study. Regardless of outcome, our study has the potential to re-define the standard of care in a disease entity where there is much uncertainty.

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AUTHORS' CONTRIBUTIONS

AC participated in design of the study and coordinated drafting of the manuscript. WS, DP, HN, EG, SP, TW, DC, PY, JS, MR, PW, VT, ND, JW, WC, MS and RB made substantial contributions to conception and design of the study. MN conceived of the study, coordinated its design and drafted the manuscript. All authors read and were involved in critically reviewing and revising important intellectual content of the manuscript. All authors approved the final manuscript prior to submission.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

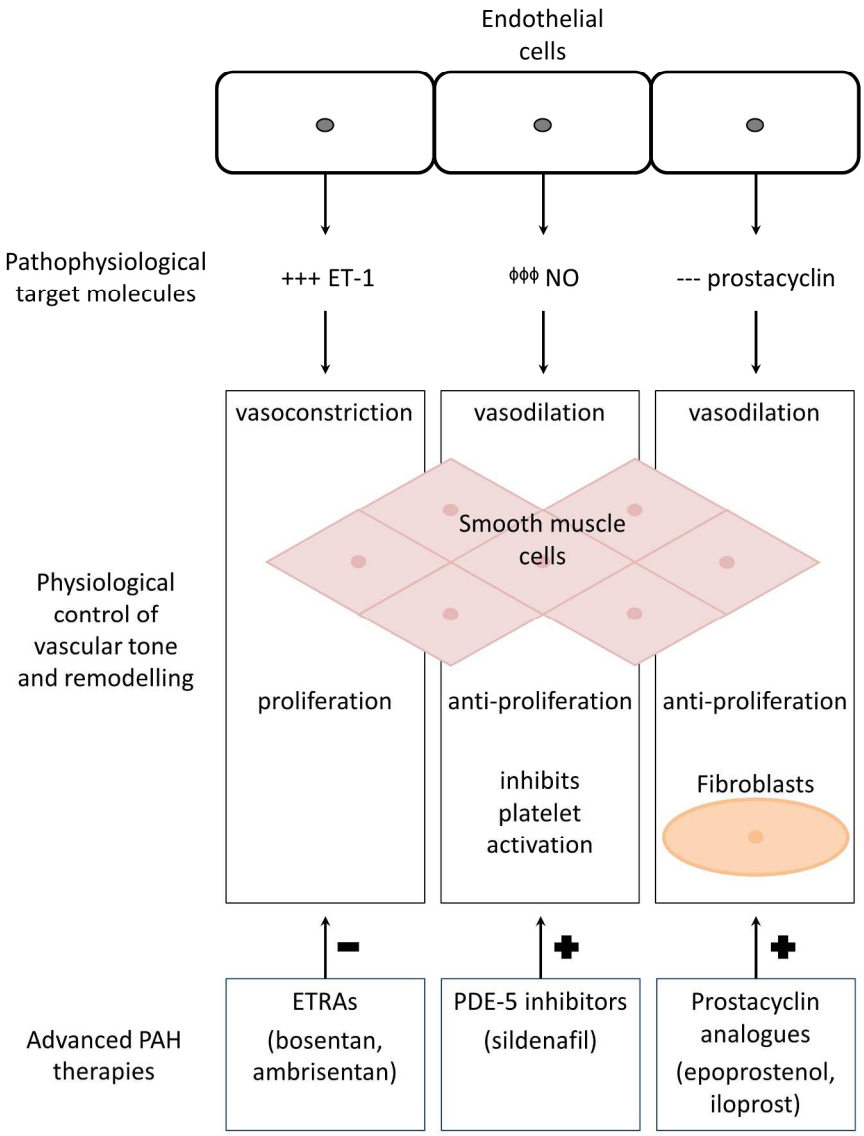
FIGURE LEGENDS

Figure 1: The pathophysiological targets of advanced pulmonary arterial hypertension therapies. Pulmonary artery endothelial cell dysfunction impacts on vascular smooth muscle cell tone and remodelling in the following ways, targeted by the three main classes of advanced PAH therapy to prevent (–) or promote (+) the physiological mechanisms described in the centre of the diagram: (+++) Over-expression of endothelin-1 (ET-1) has a potent vasoconstrictor effect. Thus ET-1 receptor antagonists (ETRAs) such as bosentan and ambrisentan, block vasoconstriction of pulmonary artery smooth muscle cells. (ϕϕϕ) Impaired production of nitric oxide (NO) is remedied by phosphodiesterase type-5 (PDE-5) inhibitors such as sildenafil, that enhance NO-mediated vasodilation. (---) Prostacyclin is a vasodilator with anti-proliferative effects that is deficient in the setting of PAH. Prostacyclin analogues such as epoprostenol, treprostinil and iloprost, therefore promote vasodilation in pulmonary smooth muscle cells and prevent vascular remodelling which may involve numerous cells, including platelets and fibroblasts.

Figure 2: The pathogenic triad of systemic sclerosis related pulmonary arterial hypertension. Vasoconstriction, vascular remodelling and thrombosis constitute the pathogenic 'triad' of pulmonary arterial hypertension in systemic sclerosis (SSc-PAH). The endothelin receptor antagonists (ETRAs), phosphodiesterase type-5 (PDE-5) inhibitors and prostacyclin promote vasodilation and prevent vascular remodelling, while anticoagulants may have a beneficial effect in SSc-PAH by preventing thrombosis.

Figure 3: Study design and assessment timeline. During the initial stages of Screening, scleroderma-related pulmonary arterial hypertension (SSc-PAH) patients will be identified via review of medical records at the multidisciplinary study sites. Formal screening assessments to confirm eligibility for the study will occur after the patient has provided informed consent. Patients who meet all inclusion

criteria and none of the exclusion criteria will be randomized in a 1:1 ratio, stratified by study site, to receive double-blinded treatment with either 2.5mg apixaban or placebo, twice daily for 36 months. Over the course of study treatment, participants will visit study sites at the following times post-randomization: 1, 3, 6, 12, 18, 24, 30 and 36 months (* = end of study visit, performed on the day of permanent cessation of study drug, sooner than 36 months in exceptional circumstances). Telephone follow-up will occur monthly in the first 12 months, then third-monthly thereafter, between scheduled visits until 30 days after the end of study visit (ϕ = 37 months post-randomisation at the latest), to ensure no adverse events have occurred and to capture all health care utilisation, including changes to concomitant medication.



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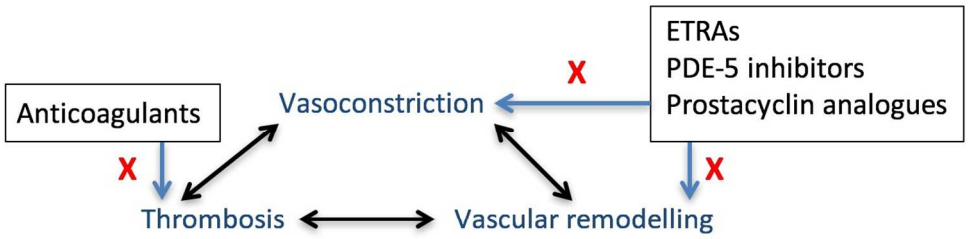

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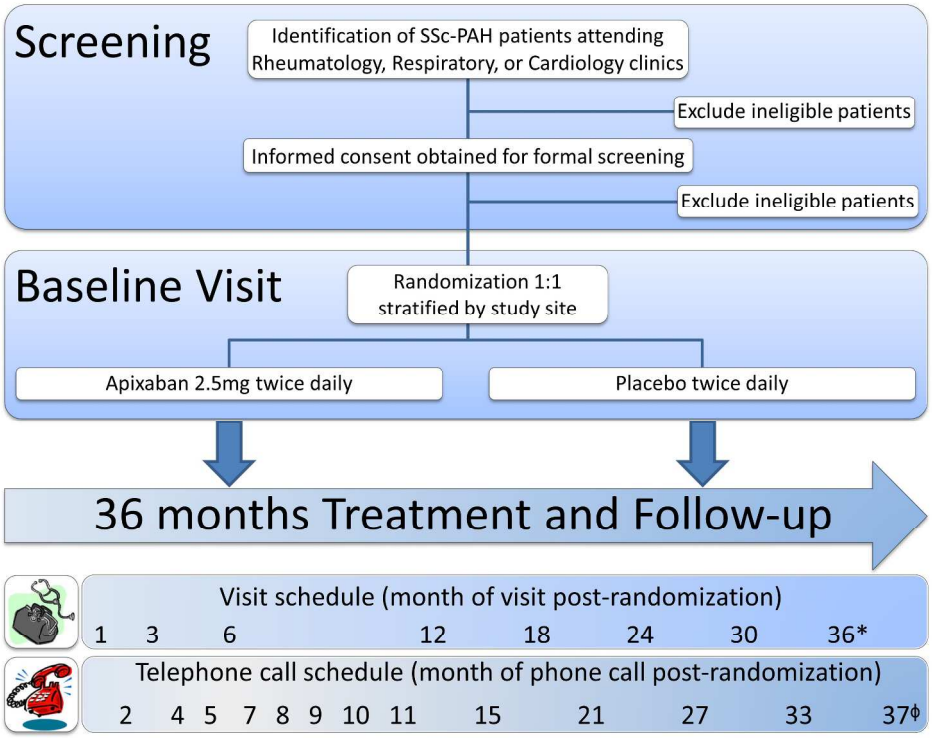

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____NA_____
Protocol version	3	Date and version identifier	_____NA_____
Funding	4	Sources and types of financial, material, and other support	_____31_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1, 2 and 31__
	5b	Name and contact information for the trial sponsor	_____2_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____31_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_8, 11, 13, 16, 21_

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-7, 22-23 and Figures 1 & 2
	6b	Explanation for choice of comparators	5-6, 12-13 & 22-23
Objectives	7	Specific objectives or hypotheses	_____7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3, 7 & Figure 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-10, Table 1 & 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____12-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____12-13____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___12 & 16_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_9-10, 12-13___
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____16-18_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____Figure 3___

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____18_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8 & 18____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____11_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___13-16_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_13, 16-18___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__11-13_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___18-20_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____18-20_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___18-20_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___21_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___17, 21_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____21_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___20_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____21_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	31
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

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