THE EFECT OF ORAL **A**TORVASTATION ON **M**ICROVASCULAR **E**NDOTHELIAL FUNCTION AND **R**AYNAUD PHENOMENA IN EARLY DIFFUSE SYSTEMIC SCLEROSIS **(TAMER)**

Atorvastatin on endothelial function and Raynaud in diffuse scleroderma

Test drug:	Atorvastatin
Study purpose:	Safety and efficacy
Clinical study phase:	II
Sponsor:	University of Pittsburgh

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Synopsis

Title	**T**he Effect of **A**torvastatin on **M**icrovascular **E**ndothelial Function and **R**aynaud in Early Diffuse Scleroderma.
Short title	TAMER
Clinical study phase	II
Study objective(s)	The primary objective of this study is to assess the effect of atorvastatin therapy on change in microvascular endothelial function
Test drug(s)	Atorvastatin
Name of active ingredient	Atorvastatin
Dose(s)	40 mg once daily
Route of administration	Oral
Duration of treatment	16 weeks
Reference drug(s)	Placebo
Name of active ingredient	Not applicable
Dose(s)	Matching placebo tablets to atorvastatin 40 mg once daily
Route of administration	Oral
Duration of treatment	16 weeks
Background treatment	Not applicable
Indication	Early diffuse systemic sclerosis with Raynaud phenomenon
Diagnosis and main criteria for inclusion	1. Men or women aged 18 years and older 2. Early diffuse SSc defined as: < 3 years from the first symptom attributable to scleroderma Meeting the 2013 the ACR/EULAR classification criteria 3. Raynaud phenomenon 4. No use of lipid lowering medication within 60 days of trial entry. 5. women of childbearing potential must have a negative serum pregnancy test at the screening visit.
Study design	Randomized (1:1), double-blind, placebo-controlled, parallel-group, single-center study

Methodology	This study is designed to investigate the efficacy and safety of atorvastatin 40 mg once daily in patients with early diffuse SSc on microvascular endothelial function and clinical Raynaud symptom.
Type of control	Placebo
Number of subjects	30 randomized subjects
Primary variable	Change in microvascular endothelial function as measured by EndoPAT
Plan for statistical analysis	An intention to treat analysis will be performed including all who receive one dose of drug. Initial analysis will describe the baseline population, sociodemographic and clinical characteristics, and compare by treatment group. Means of continuous measures will be conducted using a t-test or Wilcoxon test and discrete measures compared with a chi-square test. *The goal of all trial analyses is to provide effect size estimates for design of a later phase 3 clinical trial for statin therapy in early diffuse SSc.* The means of EndoPAT for the two groups will be calculated and a 95% confidence interval of the difference of the means will be generated. A t-test will be used to compare the mean levels between the two groups.

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List of abbreviations

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase (also known as SGPT, *qv*)
AST	aspartate aminotransferase (also known as SGOT, qv)
ARB	Angiotensin receptor blocker
AUC	area under the plasma concentration versus time curve
BMI	body mass index
CI	confidence interval
CPK	creatine phosphokinase
CRP	C-reactive protein
DU	digital ulcers
EPC	Endothelial progenitor cell
EULAR	European League Against Rheumatism
FMD	Flow-mediated dilation
g	gram
GFR	glomerular filtration rate
HR	heart rate
HRQoL	health-related quality of life
ICAM	intracellular adhesion molecule
IDS	Investigational Drug Service
IRB	institutional review board
ITT	intent to treat
kg	kilogram
L	liter
LSCI	Laser speckle contrast imaging
MD	medical doctor
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
mRSS	modified Rodnan skin score
NO	nitric oxide
PDE	phosphodiesterase
PDE5	phosphodiesterase 5
RHI	reactive hyperemia index
RP	Raynaud's phenomenon
s	second
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SHAQ	Scleroderma Health Assessment Questionnaire
SSc	systemic sclerosis
SUSAR	suspected unexpected serious adverse reaction

US	United States
VAS	visual analog scale
VCAM	vascular cell adhesion molecule
VEGF	vascular endothelial growth factor

1. Introduction

1.1 Background

1.1.1 Scleroderma (systemic sclerosis)

Systemic sclerosis (SSc) is an uncommon disease, however has the highest case specific mortality of any of the rheumatic disease. The features of this disease include chronic, fibrosing, autoimmune responses characterized by small vessel vasculopathy, autoantibody production, and fibroblast dysfunction leading to increased deposition of extracellular matrix.[1]

Systemic sclerosis is further divided into two subtypes defined by the extent of skin involvement: limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis[2]. According to LeRoy and colleagues, classification to limited or diffuse disease is based on the extent of skin tightening[3]. In limited disease skin tightening is confined to the fingers, hands, and forearms distal to the elbows, with or without tightening of skin of the feet and of the legs distal to the knees. Proximal extremities and the trunk are not involved. In dcSSc, the skin of the proximal extremities and trunk is also involved. Both diffuse and limited SSc are associated with internal organ involvement; however, patients with diffuse SSc are at greater risk for clinically significant major organ dysfunction.

SSc is an orphan disease with an estimated US prevalence of 276 patients /10^6 [4].

Vascular burden in SSc: Raynaud's phenomenon (RP) is an almost universal manifestation of SSc, with 95% of all patients being affected. The burden of SSc-associated vascular complications is high, with up to 65% of patients experiencing DU, 10% gangrene or amputation, 15% renal crisis, 15%pulmonary hypertension and 17% peripheral vascular disease[5 6]. The progression of microvascular and macrovascular abnormalities in SSc and their associated complications are not well described. Thus, we are unable to predict which patients will develop severe vascular complications. Moreover, there are no FDA-approved therapies for SSc-associated Raynaud phenomenon and DU. Identifying a therapy that diminishes or prevents the progression of SSc vasculopathy and complications would significantly improve outcomes, and increase our understanding of the underlying mechanistic abnormalities[7].

The goal of the current pilot study is to evaluate the efficacy and safety of a 16-week treatment with atorvastatin vs. placebo in patients with early diffuse SSc and Raynaud phenomenon.

1.1.2 Atorvastatin

1.1.3 Mechanism of Action

Atorvastatin is a HMG coenzyme-inhibitor, which was FDA approved in 1996. Atorvastatin is a hydrophobic statin with the ability to enter endothelial cells and has a long history of safety in multiple diseases, including prior use in SSc patients. Atorvastatin has been shown in other rheumatic diseases (rheumatoid arthritis, lupus, Behçet disease) to improve endothelial function and disease activity[8-10] and is available in a generic form.

1.2 Rationale of the study

Raynaud phenomenon affects 95% or more of patients with SSc. Unfortunately, there are no drugs approved in US for the treatment of Raynaud phenomenon. Raynaud is felt to represent the earliest signs of microvascular endothelial dysfunction in SSc.

Statins have beneficial pleiotropic effects on the vasculature and may modify all three aspects of the SSc disease process. Statins are known to improve endothelial function by increasing nitric oxide (NO) production (vasculopathy), down-regulating vascular adhesion molecules that subsequently inhibit lymphocyte migration from the vasculature (immune system activation)[1], and inhibiting overproduction of matrix components (fibrosis)[3 11 12]. Given these mechanisms, statins have the potential to improve vascular dysfunction and abnormalities in SSc.

Five small studies have examined the effect of statins on Raynaud and DU with mixed results [10 13-16] in predominantly later disease SSc, when the vasculopathy may not have been amenable to intervention, and have assessed macrovascular endpoints such as brachial flow-mediated dilation (FMD) for a microvascular disease. Of the five studies, two small placebo controlled randomized trials of atorvastatin. The lower dose study (atorvastatin 20 mg daily for 8 weeks) was negative but used patients with late disease (up to 47 years). The higher dose study (40 mg daily) was positive, but also using late disease patients and found an increase in brachial FMD as a positive outcome. No studies have evaluated the effect of statins on microvascular endothelial function in SSc, although this is the primary vasculature affected in Raynaud phenomenon and early SSc**.** In our preliminary work in early SSc patients, arteriole-level microvascular changes appear attenuated by statin use (40% with abnormal EndoPAT in statin users versus 100% in non-statin users, p= 0.03). Based on this, we propose that early statin intervention will improve microvascular endothelial function and thus reduce Raynaud activity.

Benefit-risk assessment

There are currently no disease-specific pharmacotherapies approved for Raynaud phenomenon. Considering the mechanism of action and pleiotropic effects of atrovastatin we believe the potential benefits of atrovastatin include:

- Improvement of microvascular endothelial function
- Decrease severity of Raynaud's attacks.

- Improvement of microcirculatory flow as evaluated by laser speckle contrast imaging
- Improvement of macrovascular endothelial function as evaluated by brachial flow-mediated dilation.
- Taking into account the seriousness of the disease as well as the medical need for an effective and safe therapy, on balance the expected benefit to subjects with this condition outweighs potential risks.

2. Study objectives

The primary objective of this study is to assess the effect of atorvastatin therapy on change in microvascular endothelial function as measured by EndoPAT technology.

The secondary objectives of this study are to assess the efficacy and safety of treatment with atorvastatin 40 mg once daily as follows:

Secondary objectives

- Change in Raynaud symptoms
- Change in microcirculatory flow assessed by laser speckle contrast imaging
- Change in macrovascular function assessed by brachial FMD
- SHAQ and PROMIS
- To assess serum biomarkers
- To assess EPCs.
- To assess nitrite analysis

3. Investigators and other study personnel

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External data evaluation bodies

An independent safety monitor will provide safety oversight.

4. Study design

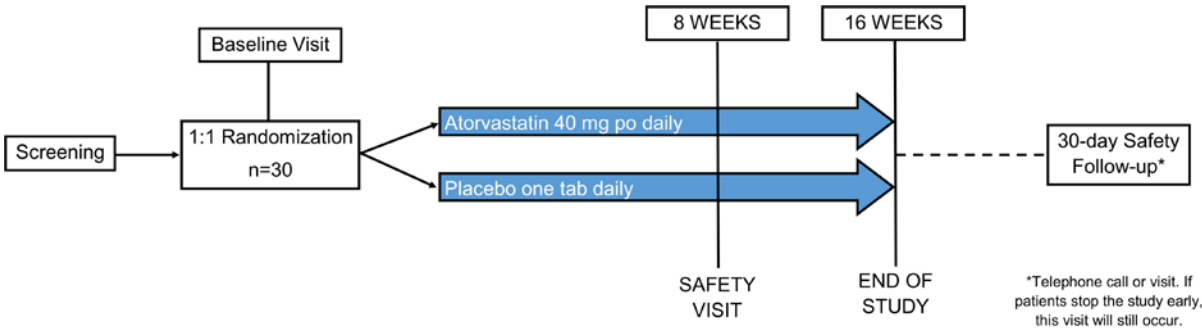
4.1 Design overview

In this single-center, (1:1), double-blind, placebo-controlled, parallel-group study, a total of 30 subjects are planned to be randomized (approximately 15 subjects to the atorvastatin group and 15 to the placebo group).

The study design consists of a single 16 week study treatment phase

- **Screening phase:** up to 4 weeks
- **Main Study Treatment phase:** 16 weeks of double-blind treatment
- **Termination Visit and Safety follow-up visit:** A termination visit and a safety follow-up visit will take place for all patients who discontinue study drug or withdraw from the study.

Figure 4-1: Study Design



4.1.1 Screening phase (up to 4 weeks)

After signing the informed consent document, subjects will undergo a screening to include baseline labs (creatinine and LFTs) and review of the inclusion/exclusion criteria. Screening

and baseline can occur on the same day if clinical labs (creatinine and LFTs) have been drawn as part of routine care within 28 days of the baseline.

4.1.2 Study Treatment phase (Week 0 to Week 16)

At the baseline (week 0) visit, subjects who have met all of the inclusion and none of the exclusion criteria will be randomized using a 1:1 randomization scheme that will be regulated centrally through the UPMC IDS. Each patient enrolling in the study will be assigned an ID. At week 0 patients will undergo assessment of Raynaud activity/severity and noninvasive vascular imaging.

Patients will have a visit at week 8 to assess safety, tolerability and adverse effects of the study drug. Raynaud activity/severity and DU will be assessed.

Patients will have a final end of study visit at week 16 to assess safety, tolerability and adverse effects of the study drug. They will also undergo assessment of Raynaud activity/severity and noninvasive vascular imaging.

Dose Interruptions

If treatment is interrupted for any reason the following rules should be applied:

- ≤ 14 consecutive days without treatment it is at the discretion of the investigator if the study medication can be restarted
- >14 consecutive days without treatment: withdraw the subject from study medication.

4.1.3 Termination Visit and Safety Follow-up Visit

A termination visit and a safety follow-up visit (30 days after last dose of study medication) should be performed for only those patients who withdraw or discontinue study drug before the completion of the trial at 16 weeks.

In all other patients a follow-up phone call at 30 days will be used to assess and follow-up on adverse events.

A detailed schedule of evaluations is presented in Sections 7.1.1 and 7.1.2.

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

Subjects must meet the following criteria to be eligible for enrollment in the study:

1. Written informed consent
2. Men or women age 18 -70 years
3. Systemic sclerosis, as defined by ACR/EULAR 2013 criteria[17] with disease duration of less than 3 years from the first symptom attributable to SSc.

4. Raynaud phenomenon.
5. No use of lipid-lower medication within 60 days.
6. Ability to comply with the clinical visits schedule and the study-related procedures

5.1.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from enrollment in the study:

- Medical and surgical history
  - History of known cardiovascular disease or myocardial infarction
  - History of stroke
  - Diabetes mellitus
- Hepatic-related criteria
  - Hepatic insufficiency classified as Child-Pugh C
  - Elevated liver enzymes > two times normal at screening
- Renal-related criteria
  - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 (MDRD formula), creatinine > 2.0 mg/dL or history of scleroderma renal crisis at the screening visit
- Known allergy or adverse reaction to atorvastatin or another statin drug
- Laboratory examinations
  - Subjects with elevated CPK (greater than two times normal) at screening.
- Prior and concomitant therapy
  - Concomitant use of calcium channel blockers or angiotensin receptor blockers are allowed, provided the participant has been on a stable dose for four weeks or longer at the time of randomization.
  - Concomitant therapy with prostacyclin analogs.
  - nitrates or NO donors (such as amyl nitrate) in any form, including topical; phosphodiesterase (PDE) 5 (PDE5) inhibitors (such as sildenafil, tadalafil, vardenafil); and nonspecific PDE5 inhibitors (theophylline, dipyridamole)
  - concomitant use of strong inhibitors of CYP 3A4 to include: clarithromycin, protease inhibitors, itraconazole, cyclosporine, gemfibrozil or other fibrates, niacin, rifampin, digoxin.
- Other
  - Pregnant women or breast feeding women

- Women of childbearing potential not willing to use adequate contraception (as defined in the aforementioned inclusion criteria, Section 5.1.1) and not willing to agree to pregnancy testing at weeks 8 and 16.
- Smoking or tobacco use within four weeks of screening.
- Any other condition or therapy that would make the subject unsuitable for this study and will not allow participation for the full planned study period

Note: One re-assessment of laboratory parameters is allowed during the screening phase to re-assess the eligibility of subjects.

5.1.3 Justification of selection criteria

The selection criteria were carefully selected to exclude subjects from the study who may potentially be exposed to specific risks after administering the study drug as well as subjects with conditions that may have an impact on the aims of this study.

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects *must* be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative

  At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If serum transaminases are greater than 3 times the upper limit of normal
- If serum CPK elevations are greater than 5 times the upper limit of normal.
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- Occurrence of AEs or intercurrent diseases which the investigator judges unacceptable for continuation of participation in the study
- Occurrence of adverse drug reactions, which in the investigator’s opinion have a negative impact on the subject’s individual risk-benefit ratio.
- Non-compliance with the conditions for the trial or instructions by the investigator
- Although not preferred, subjects may interrupt their intake of study medication for reasonable circumstances/reasons at any time (eg, hospitalization in a remote hospital without study medication access, safety reasons, and side effects). If an interruption lasts longer than 14 consecutive days, the subject must be withdrawn. In case treatment requires interruption for> 3 days and ≤ 14 days, it is at the discretion of the investigator if the study medication can be restarted.
- In case of pregnancy or breast feeding.
- In case the subject does not tolerate the drug.

5.2.2 Replacement

There will be no replacement of randomized subjects who withdraw from the study.

5.3 Subject identification

After a subject signs the informed consent form, a subject identification number will be created. This will be a unique code composed of study name and subject number

First 5 letters = TAMER (to identify this as this trial)

Last 4 digits = Unique subject number

6. Treatment

6.1 Treatments to be administered

Test Drug:	Atorvastatin
Dosage:	40 mg
Route of administration:	oral
Time and frequency of administration:	once daily

6.2 Identity of study treatment

Atorvastatin

Atorvastatin will be supplied at 40 mg as film-coated, immediate-release tablets. All study drug and placebo tablets will be provided through the UPMC Investigational Drug Service, who will also be handling patient randomization.

A complete record of batch numbers and expiry dates of all study treatment, as well as the labels, will be maintained in the study file.

Matching placebo

Matching placebo tablets will appear identical to active atorvastatin tablets but will not contain active study drug.

6.3 Treatment assignment

This is a randomized, double-blind, placebo-controlled, parallel-group, single-center study. Subjects who complete all screening procedures and meet all the eligibility criteria are to be randomized in a 1:1 ratio by the UPMC IDS.

6.4 Dosage and administration

6.4.1 Selection of doses in the study

Atorvastatin has been safe and well tolerated in previous clinical studies in the general population, cardiovascular disease populations and systemic sclerosis patients at doses of 40 mg once daily. 40 mg once daily atorvastatin has been shown to improve brachial FMD in patients with cardiovascular disease as well as SSc[13].

6.5 Blinding

The study will be conducted in double-blind fashion. Active atorvastatin and placebo tablet formulations will be identical in appearance (size, shape, color) and smell. The packaging and labeling will be designed to maintain blinded conditions for the investigator and the study team. The study data will remain blinded until database lock.

Emergency unblinding by the investigator

In case of emergency, the investigator is permitted to unblind individual cases. However, this will be restricted to cases of emergency where the unblinding result is of importance for the acute treatment strategy. The occurrence of an SAE should not routinely precipitate the immediate unblinding of the label. Date, time, and reason for unblinding will be captured. Unblinding will be coordinated through the Investigational Drug Service

6.6 Drug logistics and accountability

A drug dispensing log will be completed for each subject. Subjects will receive all study medication dispensed at the baseline visit. At weeks 8 and 16, subjects will be instructed to bring all study drug packaging, including unused study drug and empty packaging, to the investigative site at each study visit. Tablets will be counted for a compliance check and drug accountability. At week 16, unused study drug will be returned to the IDS for destruction.

If a dose of study drug is missed, the subject should take a dose immediately if on the same day. Otherwise, they can resume normal once daily dosing the following day. The dose should not be doubled to make up for a missed dose within the same day.

6.7 Post-study therapy

In case subjects discontinue study drug treatment during this study, further therapy is at the discretion of the investigator.

6.8 Prior and concomitant therapy

A summary of the prohibited prior and concomitant therapy, outlined in the exclusion criteria (Section 5.1.2), is provided in Table 6-1.

Table 6-1 Prohibited prior and concomitant therapy

Therapy	Timeframe
Concomitant use of calcium channel blockers and ARBS are allowed	Stable doses for four weeks prior to randomization
Nitrates or NO donors (such as amyl nitrate) in any form, including topical; phosphodiesterase (PDE) 5 (PDE5) inhibitors (such as sildenafil, tadalafil, vardenafil); and nonspecific PDE inhibitors (theophylline, dipyridamole) are prohibited	Concomitant therapy with study drug
Prostacyclin analogs are not allowed.	Concomitant therapy with study drug
Use of strong inhibitors of CYP 3A4 to include: clarithromycin, itraconazole, cyclosporine, gemfibrozil or other fibrates, niacin, rifampin, digoxin and colchicine.	Concomitant therapy with study drug

7. Procedures and variables

7.1 Schedule of procedures

Please refer 7.1.1 to for a schedule of evaluations.

7.1.1 Tabulated overview

Schedule of events

Assessment Window (days)	**Screening**	**Baseline**	**Week 8** +/- 7	**Week 16** +/- 7
Window				
Informed Consent	X			
Complete Medical History	X			
Physical Exam		X		X
Randomization		X		
Concomitant Medications	X	X	X	X
Adverse Events		X	X	X
Urine pregnancy test	X	X	X	X
Liver function tests, Creatinine w/ GFR	X	X	X	X
CPK		X	X	X
Fasting lipid panel, C-reactive protein, C3, C4		X		X
Vascular studies: EndoPAT(ischemia and post-NTG) Laser Speckle Contrast Imaging (ischemia and post-NTG) Brachial FMD (ischemia and post-NTG)		 X X X		 X X X
Questionnaires: RCS, Raynauds and Digital Ulcer VAS	X	X	X	X
Questionnaires: PROMIS and SHAQ	X	X	X	X
Digital Ulcer Count	X	X		X
Biomarker (serum, plasma) and cEPC assessment		X		X
Nitrite Analysis		X		X

* VCAM, ICAM, E-selectin, p-selectin, endothelin-1 (ET-1), VEGF, VEGF), angiopoietin -1 and -2, interleukin-2, interleukin-13

7.1.2 Timing of assessments

Screening and baseline visits can occur on the same day.

7.1.2.1 Visit 0 – Screening

Screening evaluations will occur after the subject has provided written informed consent. The following evaluations will be performed and information obtained up to 28 days before randomization and the start of study drug treatment:

- Patient information and obtaining of written informed consent
- Eligibility: Assessment of inclusion and exclusion criteria (see Section 5.1)
- Demographic data, including age, gender and ethnicity.
- Complete medical history
- Liver function tests and creatinine with GFR. Labs obtained as part of routine clinical care up to 28 days prior to screening will be accepted.

7.1.2.2 Visit 1 – Baseline (Day 0, Week 0)

The following assessments will be performed at the Baseline visit (Day 0 of study drug treatment):

- Reconfirmation of eligibility (assessment of inclusion/exclusion criteria; Section 5.1), if performed at separate visits
- Cardiovascular history and assessment or risk factors
- Physical Exam
- Assessment of Raynaud and digital ulcer activity and severity (questionnaire)
- Digital ulcer assessment
- Questionnaires
    - SHAQ
    - PROMISE-29
- Vital signs (blood pressure, heart rate, height, weight).
- Vascular Imaging (to be performed simultaneously)
    - EndoPAT
    - Laser speckle contrast imaging
    - Brachial FMD
- Pregnancy test (urine) for all women of childbearing potential (see Section 7.5.2)
- Blood samples for safety (LFTs, creatinine with GFR, CPK)
- Blood sample for biomarkers
- Blood sample for nitrite analysis

- Recording and assessment of AEs (see Section 7.5.1)
- Concomitant therapy
- Randomization to atorvastatin or placebo (see Section 6)
- Dispense study drug

7.1.2.3 Visit 2: 8 weeks

- Assessment of Raynaud and digital ulcer activity and severity (questionnaire)
- Digital ulcer assessment
- Questionnaires
    - SHAQ
    - PROMISE-29
- Recording and assessment of AEs (see Section 7.5)
- Blood samples for safety (LFTs, CPK)
- Pregnancy test (urine) for all women of childbearing potential (Visit 3 and Visit 5) (see Section 7.5.2)
- Concomitant therapy

7.1.2.4 Visit 3: 16 weeks (end of study)

During the maintenance period of the double-blind treatment period, the following assessments will be performed according to the Schedule of evaluations (Section 7.1.1):

- Physical Exam
- Assessment of Raynaud and digital ulcer activity and severity (questionnaire)
- Digital ulcer assessment
- Questionnaires
    - SHAQ
    - PROMISE-29
- Vital signs (blood pressure, heart rate, height, weight).
- Vascular Imaging (to be performed simultaneously)
    - EndoPAT
    - Laser speckle contrast imaging
    - Brachial FMD
- Pregnancy test (urine) for all women of childbearing potential (see Section 7.5.2)
- Blood samples for safety (LFTs, creatinine with GFR, CPK)
- Blood sample for biomarkers

- Blood sample for nitrite analysis

7.1.2.5 Premature discontinuation of study drug treatment

In the event of premature discontinuation of study drug treatment, subjects must undergo the same procedures as outlined for the Week 16 end of study visit if they have completed 8 weeks or more of therapy. If subjects discontinue prior to 8 weeks of therapy, then they will undergo the same procedures as outlined for Week 8. All subjects who discontinue study drug treatment early will have an additional 30 day safety follow-up visit.

7.2 Population characteristics

7.2.1 Demographic

The following demographic data will be recorded:

- Date of birth (month and year) (age)
- Sex
- Ethnicity

7.2.2 Medical history

Medical history findings (ie, previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Pertaining to the study indication and inclusion/exclusion criteria
- Detailed cardiovascular history and risk factors (including family history of cardiovascular events)
- Medical history related to concomitant therapy

7.3 Efficacy

Primary efficacy outcome measure:

- Change in microvascular endothelial function as measured by EndoPAT technology.

Secondary efficacy measures:

- Change in Raynaud and digital ulcer symptom and severity
- Change in microcirculatory flow assessed by laser speckle contrast imaging
- Change in macrovascular function assessed by brachial FMD
- Health related quality of life (SHAQ and PROMIS)
- To assess vascular biomarkers in the sera (VEGF, tPA, sE-Selectin, BFGF, VCAM-1, ICAM)
- To assess EPCs.
- To assess nitrite analysis

7.4 Pharmacokinetics / pharmacodynamics

Pharmacokinetic will not be performed in this study.

7.5 Safety

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (ie,any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In the following differentiation between medical history and AEs, the term "condition" may include abnormal eg, physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent will be recorded as medical history (eg, seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, will be recorded as medical history (eg, allergic pollinosis).
- Conditionsthat started or deteriorated after signing of informed consent will be documented as AEs.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (ie, elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (eg, social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

Mild is defined as asymptomatic or mild symptoms; intervention not indicated.

Moderate is defined as moderate symptoms present; only minimal intervention indicated.

Severe is defined as severe or medically significant symptoms requiring hospitalization or urgent intervention.

7.5.1.2.3 Causal Relationship/Definitions of Attribution

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

An assessment of "not related" is defined as an adverse event being clearly not related or unlikely to be related. Adverse events can also be attributed as "possible/probable" defined as reasonably possible or likely to be related, or "definite" defined as the adverse event is clearly related.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

7.5.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Not applicable
- Unknown

7.5.1.2.5 Outcome

The outcome of the AE is to be documented as follows:

- Recovered, without treatment
- Recovered, with treatment
- Still present, no treatment
- Still present, being treated
- Residual effect(s) present, no treatment
- Residual effect(s) present, being treated
- Subject died

7.5.1.3 Assessments and documentation of adverse events

The investigator has the obligation to report AEs. All non-serious events will be assessed and recorded during this trial from the baseline visit and until the end of study visit at week 16, whether believed to be related or unrelated to the treatment. The record will include clinical symptoms or final diagnosis when available, date of appearance, duration, severity, relationship to treatment and outcome. A record will also be kept of the action taken and the follow-up until resolution of the AE. For patients who stop study drug or withdraw before the end of the trial (16 week visit), AE will be re-assessed at 30 days after stopping the drug at a follow-up study visit. For all others, adverse events will be followed for 30 days, with patients contacted by phone call.

7.5.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 7.5.1.1.

Investigator's notification to the Safety Monitor

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 48 hours of the investigator's awareness) be reported to KAI, NIAMS and the internal Safety Officer. An SAE form must also be completed within 48 hours of the investigator awareness and forwarded. Each SAE must be followed up until resolution or stabilization by submission of updated reports.

Notification of the IRB

Notification of the University of Pittsburgh IRB about all relevant events (eg, SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed according to IRB regulations.

7.5.1.5 Adverse events

7.5.1.6 Expected adverse events, and events of special safety interest

Common expected adverse events include: myalgias/arthralgias (> 10%), diarrhea (5-14%), nasopharyngitis (4-13%), and dyspepsia (3-6%).

There are four significant adverse events associated with the use of atorvastatin which include 1) increase in fasting blood glucose in patients with diabetes mellitus; 2) hepatotoxicity; 3) rhabdomyolysis; and 4) the very rare event of immune-mediated necrotizing myopathy. Diabetes mellitus is an exclusion criteria for this study.

In regards to hepatotoxicity, elevated serum transaminases have been reported in as high as 2-3% of patients taking a higher dose of atorvastatin (80 mg once daily), although postmarketing reports of hepatic failure are rare. These will be monitored at baseline, week 8 and week 16. We will discontinue if hepatic enzymes are > three times the upper limit of normal.

Many patients receiving HMG-CoA reductase inhibitors experience myalgias, and this is an expected adverse event. Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy. This risk is dose-related and is increased with concurrent use of CYP3A4 inhibitors (eg, clarithromycin, protease inhibitors), fibric acid derivatives (eg, gemfibrozil), or niacin (doses ≥1 g/day) (see Drug Interactions), which will be monitored. Serum CPKs will be checked at baseline, week 8 and week 16. We will advise patients not to perform unusual or heavy bouts of exercise in the 24 hours before visits. We will discontinue in any patient in which CPK levels are markedly elevated (> 5 times ULN) or if myopathy is suspected/diagnosed. Patients will be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine. If they develop any of these symptoms, they will return for an interval visit with repeat CPK and exam at that time.

Patients receiving HMB-CoA reductase inhibitors have also been rarely reported to develop an immune-mediated necrotizing myopathy (IMNM. IMNM presents as proximal muscle weakness with elevated CPK levels, which persists despite discontinuation of HMG-CoA reductase inhibitor therapy. Serum CPKs will be checked at baseline, week 8 and week 16. We will discontinue in any patient in which CPK levels are markedly elevated (>5 times ULN) or if myopathy is suspected/diagnosed.

Declaration of an event as serious should only occur when 1 or more of the serious criteria (as defined in Section 7.5.1.1) are applicable.

7.5.1.7 Expected adverse events

Expected adverse events are those listed as common (incidence > 2%) in patients treated with atorvastatin per the package insert. These include nasopharyngitis, arthralgia, diarrhea, extremity discomfort and urinary tract infection.

7.5.1.8 Unxpected adverse events

An adverse reaction is considered “unexpected” if it is not listed in the package insert for atorvastatin (please see Appendix I of the MOOP)

7.5.1.9 Pregnancies

A report of a confirmed pregnancy by serum testing will be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up to completion.

OTHER PROCEDURES AND VARIABLES

7.5.2 Pregnancy testing

Pregnancy testing is to be performed at the Baseline visit, Week 8 visit and Week 16 visit. In the event of pregnancy, a referral to a gynecologist for confirmation of pregnancy will be promptly organized. Further consequences with regard to ongoing participation in the study must be discussed with the patient.

Women of childbearing potential and non-vasectomized male participants must agree to use adequate contraception when sexually active. 'Adequate contraception' is defined as any combination of at least 2 effective methods of birth control, of which at least one is a physical barrier (e.g. condoms with hormonal contraception or implants or combined oral contraceptives, certain intrauterine devices). The exception will be women who have undergone tubal ligation and men who have undergone a vasectomy.

7.5.3 Vascular Assessments

Prior to beginning vascular testing, all patients will rest for 15 minutes in a quiet, dark and temperature-controlled room (set at 77 degrees Fahrenheit or warmer). Measurement of EndoPAT™, LSCI and brachial FMD will be performed simultaneously. Measurements will be obtained before and after vascular occlusion for all studies to assess endothelial dependent vasodilation. LSCI and brachial FMD will then be performed before and after administration of 0.4 mg of sublingual NTG to assess endothelial-independent vasodilation.

During the acclimation period a pneumatic cuff will be placed on the subject's right arm. Once the acclimation period has ended, a baseline pulse and flow measurements will then be obtained for 5 minutes for all modalities. Following this vaso-occlusion will be induced by inflating the pneumatic cuff to a pressure of 280 mmHg or 60 mmHg higher than systolic blood pressure (whichever was the highest), for 5 minutes. After 5 minutes the cuff will be rapidly deflated and measurements will be obtained for an additional 5 minutes. Subjects will then receive a single 0.4 mg sublingual spray of NTG. We will then obtain measurements as detailed in the individual vascular studies below over a period of 10 minutes.

7.5.4 EndoPAT

Measurement of microvascular endothelial function will be performed using Peripheral Arterial Tonometry (PAT) device (EndoPAT 2000, version 3.3.2, Hamar Medical, Caesavea, Israel). EndoPAT is a well-validated instrument[18]. After the vascular assessment acclimation period, probes will be placed on the tips of both index fingers. PAT signal measurement will be performed with the digital probe inflation pressure set at 10mmHg below the diastolic pressure or 70 mmHg (whichever is lowest) (17). Baseline pulse amplitude will be recorded bilaterally on tips of the index fingers for 5 minutes. Following vaso-occlusion on the right the cuff will be deflated and the PAT signal measurement was recorded for an additional 5 minutes. Mean PAT amplitudes will be measured 90 seconds after the occlusion for a duration of 60 seconds. Finally, the ratio of the post-to-pre occlusion PAT amplitude of the tested arm, divided by the post-to-pre occlusion ratio of the control arm, will be calculated as the Reactive Hyperemia Index (RHI).

7.5.5 Laser Speckle Contrast Imaging

For assessment of LSCI we will use the PerCam PSI system (Perimed AB, Jarfalla, Sweden), which produces a near infrared (780 nm) laser light. The backscattered light forms a random interference (speckle) pattern. Movement, as produced by circulating red blood cells, causes the speckle pattern intensity to change, thus allowing for quantification of flow. The PeriCam PSI system will be used with the camera placed 20 cm above the SSc patient's hand, which will be immobilized by a fluid support. A region of interest on the 2nd proximal metacarpophalangeal joint will be identified prior to beginning assessments. Baseline LSCI measurements will be obtained continuously beginning five minutes prior to vaso-occlusion until 5 minutes after NTG administration.

7.5.6 Brachial FMD

Brachial artery FMD will be performed using the GE Vivid 7 Dimension ultrasound (GE Vingmed Ultrasound A/S, Horten, Norway). Brachial artery diameter will be measured and calculated at baseline, 1, 2 and 3 minutes after reactive hyperemia induced by 5-minute pneumatic cuff occlusion, and then at 3, 5 and 10 minutes after NTG administration by means of averaging 3 measurements. FMD will be calculated as the percent change (%FMD) in brachial diameter from the resting state (100*[hyperemic diameter at selected time−resting diameter]/resting diameter) for reactive hyperemia. Similarly, vasodilator response to NTG will be expressed as percentage change (NTG%) in diameter between baseline and after NTG administration.

7.5.7 Exploratory Biomarkers

Samples for exploratory vascular biomarkers will be drawn at the baseline visit and week 16 (end of study). Serum biomarkers will include vascular soluble adhesion molecules (VCAM, ICAM, E-selectin and p-selectin), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), angiopoietin -1 and -2, inflammatory cytokines (C-reactive protein (CRP), serum complement levels, interleukin-2, interleukin-13) and circulating endothelial progenitor cells (cEPC).

We will also assess levels of nitrite and nitrotyrosine at baseline and week 16.

Circulating EPCs will be assessed at baseline and week 16.

7.5.8 Raynaud's attacks assessment

Raynaud's attacks will be assessed using the following individual outcome measures: in Raynaud's condition score and patient assessment of Raynaud's phenomenon using the VAS[19]

The Raynaud's condition score is a daily patient-assessment of Raynaud's phenomenon activity using a 0-10 ordinal scale. It incorporates the cumulative frequency, duration, severity and impact of Raynaud's phenomenon attacks, reflecting the overall degree that Raynaud's has affected use of the patient's hands [19]. The Raynaud's condition score, along with details of the frequency and duration of Raynaud's attacks, will be incorporated into the daily diary that subjects will be asked to complete for 1 week (7 days) at the time points shown below.

The patient and physician assessment assesses the severity of Raynaud's phenomenon in the past week using a 0-100 VAS.

7.5.9 Digital ulcer assessment

Digital ulcers are defined as a full thickness skin lesion with loss of epithelium. Ulcers should be > 3mm in maximal diameter. Healing is defined by re-epithelialization with loss of pain and exudate. Pitting scars and hyperkeratotic lesions are always excluded. Also, eschar is not considered as DU.

Digital ulcer will be assessed by the following methods:

- Visual analog score for patient-reported severity of digital ulcers
- Ulcer count:
  - Total ulcer counts
  - Distal counts: distal (fingertip) – any ulcer including skin area distal to proximal interphalangeal (PIP) joint
- Non-ischemic ulcers over the PIP and MCP will also be evaluated for healing as secondary outcomes

7.5.10 Patient-Reported Outcomes (PROs) / Health-Related Quality of Life (HRQoL) questionnaires

Two patient-reported outcomes (PROs)—the SHAQand PROMIS-29—will be completed by all subjects in the study. In addition, a global for patient and physician should be considered.

Scleroderma Health Assessment Questionnaire (SHAQ)

The SHAQ consists of 8 domains from the Health Assessment Questionnaire disability index (HAQ-DI), a HRQoL instrument that measures self-reported function in 8 domains of activity in 20 weighted responses and a VAS of pain experienced in the past week. It additionally measures 5 domains specific to scleroderma using a continuous VAS: Raynaud's phenomenon, digital tip ulcers, lung symptoms, gastrointestinal symptoms, and a global patient assessment[7]. The VAS subscales of the SHAQ were shown to be significantly correlated with objective parameters,[7] and was responsive to change in a cohort and in a Raynaud's phenomenon trial in SSc.[7 20] The SHAQ requires approximately 5 minutes to complete.

Patient-Reported Outcomes Measurement Information System (PROMIS)-29

The PROMIS-29 is a validated instrument to measure the health status of SSc patients, demonstrating moderate to high correlation with other instruments validated in SSc, including the SF-36 physical component score and HAQ-DI.[21] It incorporates 7 core domains from the PROMIS questionnaire, which specifically relate to physical, mental, and social health aspects of chronic illness: pain, fatigue, depression, anxiety, sleep, and physical function, as well as one 11-point rating scale for pain intensity.[21] It contains 8 items with 29 weighted responses in total, and requires approximately 5 minutes to complete.

Frequency of all PROs: Baseline (Visit 1, Day 0), Visit 5 (week 8), Visit 6 (week 10) and Visit 8 (week 16)

8. Statistical methods

8.1 General considerations

An intention to treat analysis will be performed including all who receive one dose of drug. Initial analysis will describe the baseline population, sociodemographic and clinical characteristics, and compare by treatment group. Means of continuous measures will be conducted using a t-test or Wilcoxon test and discrete measures compared with a chi-square test. The goal of all trial analyses is to provide effect size estimates for design of a later phase 3 clinical trial of statin therapy in early diffuse SSc, if deemed appropriate. If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of α=5%..

8.2 Statistical and analytical plans

8.2.1 Demographic and other baseline characteristics

Demographic variables and baseline characteristics will be summarized by treatment group.

8.2.2 Efficacy

The primary outcome of interest is the change in the EndoPAT measured RHI between baseline and week 16 between the atorvastatin and placebo group. A t-test will be used to compare the mean levels between the two groups. If differences in baseline characteristics across treatment groups are identified, multivariable linear regression models will be used to estimate the independent effect of treatment after controlling for the possible confounding variables.

The secondary outcomes of interest include the following:

1) Change in RCS
2) Change in Raynaud VAS
3) Change in reperfusion peak between the atorvastatin and placebo groups.
4) Change in reperfusion nadir between the atorvastatin and placebo groups.
5) Change in brachial FMD between baseline and week 16 between the atorvastatin and placebo group.

A t-test will be used to compare the mean change in RCS and Raynaud VAS between weeks 16 and baseline in the placebo and atorvastatin therapy groups. The means of reperfusion peak and nadir between groups will be calculated and a 95% confidence interval of the difference between means generated. A t-test will be used to compare the mean change in brachial FMD between baseline and week 16 between the two treatment groups.

For all of the above, assumptions of all tests (e.g., normality of residuals) will be evaluated. If violations are identified, transformations will be investigated. If adequate transformations cannot be identified, then nonparametric methods will be used.

8.2.3 Safety

Tables of adverse events and serious adverse events will be created. These will be maintained by the data manager or study statistician and reported twice yearly to the Safety Officer. The internal Safety Officer will be appointed by the Principal Investigator. These tables will include masked treatment group. This is detailed in the Safety Monitoring Plan.

8.3 Planned interim analyses

No formal interim analysis of the main study treatment phase is planned given that it is a small pilot study.

8.4 Determination of sample size

This is a pilot study. With a total sample of 30 participants (15 per treatment group), and to produce a 95% confidence interval of the difference in means between the two treatment groups, the width of the confidence interval would be +/- 0.374.

9. Data handing and quality assurance

9.1 Data recording

All data will be entered into the RDMS system. A source document checklist will be used at the site to identify the source data for all data points collected. .

9.2 Archiving

Documents shall be archived safely and securely in such a way that ensures that they are readily available if required, and in compliance with the University of Pittsburgh guidelines. According to the University of Pittsburgh IRB, all study-related documents will be stored for 7 years. The investigator site file is not to be destroyed without approval by NIAMS or the Safety Monitor.

9.3 Publication Policy

Following completion of the TAMER study, the investigators will publish the results of this research in scientific journals. The International Committee of Medical Journal Editors (ICMJE) member journals has adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. The TAMER study will be registered prior to commencement.

As this is a single-center study, there will be no publications committee. Authorship determination will be made in consultation with the co-investigators of the study (Drs. Dezfulian, Reis and Wisniewski).

Publication of the results of this trial will be governed by NIAMS publication policies. Any presentation, abstract, or manuscript will be made available for review by the NIAMS supporters prior to its submission. Dr. Domsic will maintain control of all TAMER-generated specimens and will decide on the scientific merit of any future sub-studies. They will adhere to the letter and the spirit of the prevailing NIH and NIAMS guidelines on the sharing of research resources produced from federally-funded research.

9.4 Confidentiality

This is a single-center study, with a relatively small number of subjects. All personnel involved in this study have undergone training and certification on the protection of human subjects, confidentiality, HIPAA compliance and research integrity. This training is conducted regularly by the University of Pittsburgh via an internet-based system of education in research.

The only individuals with access to identifiable information and treatment assignment will be the data manager and study statistician. Access to study data will be password protected. All linkage materials are stored separately and maintained in a secure area.

All blood samples will be collected in a de-identified manner using labels generated through the Rheumatic Disease Management System (RDMS) system, which is a Division-wide system for rheumatologic research. Linkage codes will be maintained by the data manager in the event of emergencies or future need, and these will be kept in a locked filing cabinet located in the Scleroderma Center research office.

10. Ethical and legal aspects

10.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. IRB approval has been obtained. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB approval. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment will then be submitted to the University of Pittsburgh IRB. Any deviations from the protocol will be explained and documented by the investigator. Protocol deviations will also be reported biannually to the Safety Monitor.

10.2 Subject information and consent

The investigator will discuss that written approval of the IRB has been obtained. Consent forms, describing in detail the therapies, procedures, and risks, will be given to the participant, and written documentation of informed consent is required prior to starting the study agent(s). Consent forms will be IRB-approved, and the participant will be asked to read and review the document. Upon reviewing the document, the study coordinator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants will have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. Only if the subject voluntarily agrees to sign the informed consent form and has done so, may s/he enter the study. Additionally, the PI will personally sign and date the form. The subject will receive a copy of the signed and dated form. The signed informed consent statement is to remain in the investigator site file. In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

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