SSO_2 THERAPY: IC-HOT STUDY

A MULTI-CENTER EVALUATION OF THE DELIVERY OF INTRACORONARY HYPEROXEMIC SUPERSATURATED OXYGEN THERAPY FOR 60 MINUTES IN ANTERIOR ACUTE MYOCARDIAL INFARCTION PATIENTS WITH SUCCESSFUL REPERFUSION (VIA PCI) ≤ SIX HOURS AFTER SYMPTOM ONSET

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A MULTI-CENTER EVALUATION OF THE DELIVERY OF INTRACORONARY HYPEROXEMIC SUPERSATURATED OXYGEN THERAPY FOR 60 MINUTES IN ANTERIOR ACUTE MYOCARDIAL INFARCTION PATIENTS WITH SUCCESSFUL REPERFUSION (VIA PCI) ≤ SIX HOURS AFTER SYMPTOM ONSET

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational devices and conduct of the study according to 21 CFR parts 50, 54, 56 and 812, to GCP as described in ICH guideline E6 and to hospital IRB/ethics committee requirements.

Clinical Site _____

Investigator Signature _____

Date _____

Investigator (PRINT) _____

IC-HOT PROTOCOL SUMMARY

Study Description	A Multi-Center, Consecutively Enrolled Single-Arm Study to confirm the safety and effectiveness of the delivery of supersaturated oxygen (SSO_2) Therapy for 60 minutes selectively into the left main coronary artery (LMCA) with a commercially available qualified SSO_2 delivery catheter used with the TherOx® DownStream® System and Cartridge in the treatment of qualified patients presenting with anterior acute myocardial infarction in whom reperfusion with PCI is successful within six hours after symptom onset.
Investigational Product	The TherOx IC-HOT Clinical Study incorporates the use of three primary components. These include a hardware device called the TherOx DownStream System ("system"), a single-use disposable device called the TherOx DownStream Cartridge ("cartridge") and a commercially available, qualified SSO_2 delivery catheter ("delivery catheter"). The cartridge is loaded into and operated by the DownStream System; the cartridge has a tubing set that connects to an arterial sheath on the patient blood draw side and the SSO_2 delivery catheter on the supersaturated infusate patient return side. SSO_2 Therapy is delivered selectively into the LMCA via the SSO_2 delivery catheter, which is positioned at the ostium of the left coronary arterial tree proximal to the bifurcation.
Indications for Use	The TherOx DownStream System, DownStream Cartridge, and SSO_2 delivery catheter are indicated for: the preparation and delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms.
Objective	To collect confirmatory data supporting the safety and effectiveness of SSO_2 Therapy in the treatment of anterior acute myocardial infarction (AMI) patients who have undergone successful percutaneous coronary intervention (PCI) with stenting within six hours of experiencing AMI symptoms.
Study Design	This is a non-randomized, single-arm study. Subjects who present with anterior STEMI requiring stent placement in the proximal and/or mid LAD who meet all inclusion and exclusion criteria and provide informed consent will be treated with primary PCI with stenting, and if successful and uncomplicated then immediately with post-procedure

	delivery of SSO_2 Therapy for a duration of 60 minutes.
Patient Enrollment	One hundred (100) patients enrolled and treated with SSO_2 Therapy at up to fifteen (15) centers in the US.
Patient Population	Qualifying anterior STEMI patients (1 mm or greater of ST-segment elevation in 2 or more contiguous leads in V1-V4) successfully treated with PCI and stenting within 6 hours from time of symptom onset.
Study Blinding	This study is not blinded.
Inclusion Criteria	Patients must meet **ALL** of the following criteria: **GENERAL INCLUSION CRITERIA:** Candidates for this study must meet **ALL** of the following criteria: **Pre-PCI:** 1. The subject must be ≥18 and ≤80 years of age. 2. AMI must be anterior (ST-segment elevation ≥1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block). 3. Subject is experiencing clinical symptoms consistent with acute MI of ≤6 hour duration from time of symptom onset until admission to the emergency room. 4. The subject or legally authorized representative has been informed of the nature of the study, agrees to its provisions and has been provided and signed written informed consent, approved by the appropriate Institutional Review Board (IRB). 5. Subject and his/her physician agree to all required follow-up procedures and visits. **ANGIOGRAPHIC INCLUSION CRITERIA:** These are evaluated after the subject has provided signed Informed Consent but prior to enrollment: 6. Based on coronary anatomy, PCI is indicated for revascularization of the culprit lesion(s) with use of a commercially available coronary stent (bare metal or drug-eluting, at operator discretion) in the LAD. 7. The primary stented infarct-related lesion(s) must be in the proximal and/or mid-LAD coronary artery (other lesions in the

	LAD target vessel, including diagonal branches, may be treated if clinically indicated). 8. Baseline (pre-PCI) TIMI flow grade 0, 1, 2, or 3 flow in the LAD. 9. Successful angioplasty is completed ≤6 hrs from symptom onset, as documented by <50% diameter residual angiographic stenosis within all treated culprit lesions with TIMI 2 or 3 flow and no major complications such as perforation or shock. 10. Expected ability to place the SSO_2 delivery catheter in the coronary ostium of the left main coronary system to deliver SSO_2 Therapy with stable, coaxial alignment.
Exclusion Criteria	Patients will be excluded if **ANY** of the following conditions apply: **GENERAL EXCLUSION CRITERIA** **Pre-PCI:** 1. Prior CABG surgery. 2. Prior myocardial infarction, or known prior systolic dysfunction (known ejection fraction <40% by any prior measure or regional wall motion abnormalities; this criterion does not include left ventricular dysfunction induced by the acute MI). 3. Thrombolytic therapy administered for this STEMI. 4. An elective surgical procedure is planned that would necessitate interruption of anti-platelet agents during the first 30 days post-enrollment. 5. Subjects who previously underwent coronary stent implantation and in whom coronary angiography demonstrates stent thrombosis to be the cause of the anterior AMI. 6. Subjects who have previously undergone an angioplasty or stenting procedure in the left anterior descending coronary artery. 7. Subjects with ventricular pseudoaneurysm, VSD, or severe mitral valve regurgitation (with or without papillary muscle rupture). 8. Any contraindication to MRI imaging. This will include any of the following exclusions: a. Cardiac pacemaker or implantable defibrillator;

	b. Non-MRI compatible aneurysm clip; c. Neural Stimulator (i.e., TENS unit); d. Any implanted or magnetically activated device (insulin pump); e. Any type of non-MRI compatible ear implant; f. Metal shavings in the orbits; g. Any metallic foreign body, shrapnel, or bullet in a location which the physician feels would present a risk to the subject; h. Any history indicating contraindication to MRI, including claustrophobia or allergy to gadolinium; i. Inability to follow breath hold instructions or to maintain a breath hold for >15 seconds; and j. Known hypersensitivity or contraindication to gadolinium contrast. 9. Known impaired renal function (creatinine clearance <30 ml/min/1.73 m^2 by the MDRD formula) or on dialysis. 10. Known platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3 or a known Hgb <10 g/dL. 11. Subject has active bleeding or a history of bleeding diathesis or coagulopathy (including heparin induced thrombocytopenia), or refusal to receive blood transfusions if necessary. 12. History of intracerebral mass, aneurysm, arteriovenous malformation, or hemorrhagic stroke. 13. Stroke or transient ischemic attack within the past six (6) months, or any permanent neurological defect. 14. Gastrointestinal or genitourinary bleeding within the last two (2) months, or any major surgery (including CABG) within six weeks of enrollment. 15. Subject has received any organ transplant or is on a waiting list for any organ transplant. 16. Subject has other medical illness (e.g., cancer, dementia) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause non-compliance with the protocol, confound the data interpretation, or is associated with limited life expectancy of less than one year. 17. Subject has a known hypersensitivity or contraindication to unfractionated heparin, abciximab, aspirin, bivalirudin, cangrelor, clopidogrel, ticlopidine, prasugrel, eptifibatide,

	tirofiban or ticagrelor that cannot be adequately premeditated. 18. Current use of warfarin, dabigatran, or factor Xa inhibitors, or known intent to administer these agents after the primary PCI. 19. Subjects presenting with or developing in the cath lab prior to completion of the primary PCI procedure any of the following conditions: cardiogenic shock (SBP <80 mmHg for >30 minutes), or requiring IV pressors or emergent placement of an intra-aortic balloon pump (IABP), Impella, or other hemodynamic support for hypotension treatment, or cardiopulmonary resuscitation for >10 minutes, or ventricular fibrillation or tachycardia requiring cardioversion or defibrillation. 20. Severe known cardiac valvular stenosis or insufficiency, pericardial disease, or non-ischemic cardiomyopathy. 21. Any significant medical or social condition which in the investigator's opinion may interfere with the subject's participation in the study or ability to comply with follow-up procedures, including MRI (e.g. alcoholism, dementia, lives far from the research center, etc.). 22. Current participation in other investigational device or drug trials. 23. Previous enrollment in this study. **ANGIOGRAPHIC EXCLUSION CRITERIA:** These are evaluated after the subject has provided signed Informed Consent but prior to enrollment: 24. Anticipated inability to achieve a stable coaxial position in the left main coronary artery with the SSO_2 delivery catheter. 25. Treatment during the index procedure of any lesion in either the left main, LCX (including the ramus), and/or RCA. 26. Post-index procedure planned intervention within 30 days (i.e., PCI of non-target lesions in any vessel, or CABG). Note: Planned revascularization (PCI or bypass) of a non-target lesion >30 days following the index procedure is allowed. 27. Anterior MI is due to thrombosis within or adjacent to a previously implanted stent. 28. Left ventriculography demonstrates severe mitral regurgitation, a ventricular septal defect, or a pseudoaneurysm. 29. Any left main coronary artery stenosis >20%.

	30. Any untreated LAD or diagonal branch lesion is present with diameter stenosis ≥ 50% in a vessel with reference vessel diameter > 2.0 mm (visually estimated), or for which PCI will be required before the MRI study. 31. Presence of a non-stented coronary dissection with NHLBI grade ≥B upon completion of the PCI procedure.
Treatment Strategy	Study clinical investigators and research staff will be trained according to the clinical protocol, device Instructions for Use, and study regulatory and reporting requirements. The procedural strategy is as follows: • Subjects presenting with anterior STEMI with symptom to presentation time of less than or equal to 6 hours will be screened for clinical eligibility. • If all clinical eligibility criteria are met, the subject or legal representative must sign an IRB-approved Subject Informed Consent Form. • After Informed Consent is signed, if not already administered, subject will receive a loading dose of aspirin 324 mg chewed or 250-500 mg IV, and at least one ADP antagonist, either clopidogrel 600 mg p.o. or prasugrel 60 mg p.o. or ticagrelor 180 mg p.o. per investigator discretion. These loading doses must be given even if the patient is on home dual anti-platelet therapy. • Subject will undergo coronary arteriography and left ventriculography (required before enrollment). • Subject is screened for angiographic eligibility criteria. Patients who are being considered as potential subjects for enrollment into study may be treated with standard anticoagulation prior to and during the procedure. Procedural anticoagulation must consist of either bivalirudin with or without the addition of cangrelor (in which case GP IIb/IIIa inhibition is not recommended unless required for refractory procedural thrombotic complications) or heparin with either cangrelor or a GP IIb/IIIa inhibitor. If bivalirudin is used, an infusion of 1.75 mg/kg/hr should be continued during the SSO_2 infusion and for 3-4 hours post procedure. Note: if a GP

	IIb/IIIa inhibitor is used, it should be continued during the SSO_2 infusion and for a total of at least 12 hours post procedure, as per local standard of care. The dose of the GP IIb/IIIa inhibitor and bivalirudin infusions should be down-adjusted for renal insufficiency as per FDA labeled instructions. Intravenous cangrelor may also be used according to label per investigator discretion, administered as a bolus plus infusion, with the infusion continued for 2-4 hours post-PCI. • The patient must receive a commercially available intracoronary stent with post-index procedure angiographic TIMI flow grade 2 or 3. • Post index procedure, if all clinical and angiographic entry criteria are met, the patient is formally enrolled into the study and may receive SSO_2 Therapy. The introduction of the infusion catheter is the point of intent-to-treat enrollment, whether SSO_2 Therapy is successfully administered or not. • The patient will remain in the cardiac catheterization laboratory for the entire SSO_2 Therapy procedure. Cine angiography w/o contrast will be performed at the beginning of and 30 minutes into the SSO_2 infusion procedure to document stable position of the delivery catheter. • Post SSO_2 Therapy control angiography will be obtained in each enrolled patient to document position of the delivery catheter, TIMI flow, and to assess for intravascular complications.
Patient Follow-Up	Baseline, procedural, post-procedure, in-hospital, and clinical follow-up at 30 days. Cardiac MRI will be performed at 4 days (acceptable range 3-5 days) and at 30 days (±7 days; range 23-37 days) to evaluate device effectiveness. Primary data collection including adverse event reporting is through 30 days; patient safety will be tracked and reported through one year.
Safety Endpoint	The primary endpoint of the study is the rate of Net Adverse Clinical Events (NACE), comprised of the composite incidence of death, reinfarction, clinically-driven target vessel revascularization, stent thrombosis (ARC definite or probable), new onset heart failure or readmission for heart failure, and TIMI major or minor bleeding.

Additional Study Endpoints	Effectiveness is a secondary endpoint for this study. Effectiveness data from dual time point cardiac MRI scans at day 4 and day 30 will be collected and reported, using 30-day median infarct size (% left ventricle (LV) necrosis) as the primary effectiveness outcome measure. Infarct size data in this study will be compared to a matched control population from the INFUSE-AMI clinical trial, and to the AMIHOT II study. In addition, myocardial structural and functional data, including microvascular obstruction at 4 days, and global and regional LV volumes and function at both time periods will be evaluated. Data will only be analyzed in subjects completing the cardiac MRI study in which the imaging data is received and analyzable by the core laboratory.
Additional Safety Data	In addition to 30-day NACE, the following information will be reported and summarized: • Additional bleeding events through 30 days, categorized by the BARC criteria • All other 30-day adverse events • Individual NACE component event rates through 1 year
Event Assessment	An independent Clinical Events Committee (CEC) will review and adjudicate all significant study adverse events, including any potential NACE events or cardiac-related events. Adjudication will be performed in accordance with a prospective CEC Charter including clinical event definitions.
Safety Oversight	An independent Data Safety Monitoring Board (DSMB) will review and assess overall study safety both during and at the conclusion of the study.
Economic Data	In addition to safety and effectiveness data, hospital charge data as reported on the UB -04 claim form will be collected. The economic data will be used to support applications to the Center for Medicare and Medicaid Services and other health plans for additional reimbursement for procedures using the TherOx DownStream System.
Study Sponsor	TherOx, Inc. 17500 Cartwright Road, Suite 100 Irvine, CA 92614 USA TEL: (949) 757-1999 FAX: (949) 757-1989

DATA COLLECTION PROCEDURES AND TIMEFRAMES

Table 1. Data Collection Procedures

PROCEDURE / TEST	Pre-PCI - Stent	PCI / Stent Procedure	Post- PCI / Stent	Baseline SSO_2	30 min SSO_2	60 min SSO_2	60 (±30) min post-SSO_2	12 (±2) hrs	24 (±2) hrs	Cardiac MRI (4 ± 1 days)	30 (±7) days	6 and 12 mos (±30 days)
Subject Medical / Clinical History / Physical Exam	√											
Subject Informed Consent	√											
General Inclusion / Exclusion Criteria	√											
Angiographic Inclusion / Exclusion Criteria			√									
Cardiac Enzymes: CK, CK-MB, and Troponin	√							√	√	√[1]		
Arterial blood gas				√								
WBC, hemoglobin, creatinine, platelet count	√[8]								√[2]			
Cardiac MRI										√[3]	√[4]	
HR, BP	√	√	√	√	√	√						
ECG	√						√[5]			√	√	
Anticoagulation (per protocol)	√											
Antiplatelet loading dose	√											
Cardiac cath lab procedures and information		√										
Cine angiogram w/o contrast of angiographic delivery catheter				√	√	√						
Coronary angiogram with TIMI flow grade assessment	√	√[6]	√			√						
ACT (per protocol)		√		√	√[9]	√						
SSO_2 Therapy Procedure			√	√	√	√						
Per Protocol Medications	√	√	√	√	√	√		√			√	√
Dual Antiplatelet Medication	√	√	√					√[7]			√[7]	√
Concomitant Cardiac Medications	√	√	√	√	√	√		√			√	√
Adverse Events				√	√	√	√	√	√	√	√	√

[1]Required only if cardiac events.
[2] Measured the day after the index procedure and then daily until the nadir value for Hgb, Hct, platelet count and the peak value for serum creatinine is reached or the patient is discharged. Baseline and nadir information will be collected.
[3]All subjects to have in hospital cardiac MRI.
[4]A protocol deviation will be recorded if the MRI is performed between 38 and 90 days but those images will be evaluated by the core laboratory and the results will be analyzed.
[5] ECG to be performed 60±30 minutes after the last angiogram after the SSO_2 procedure.
[6] Left ventriculography required prior to enrollment.
[7] Post procedure DAPT is according to current recommended standards as published by the AHA/ACC/ESC, which recommends a minimum of twelve (12) months DAPT for subjects receiving a stent.
[8] Must have screening HCT, HGB, platelet count and creatinine measurement per inclusion/exclusion criteria; however, lab results do not need to be available prior to enrollment.
[9] The mid-procedure 30-min ACT sample is required if patients receive heparin for procedural anticoagulation.

1 INTRODUCTION

The IC-HOT clinical study presented in this Investigational Plan is designed as a confirmatory study enrolling 100 patients with qualifying anterior acute myocardial infarction (AMI) treated with successful percutaneous coronary intervention (PCI) with stenting within 6 hours of symptom onset. This study population is similar to a previously examined IDE study population enrolled as a sub-group of the AMIHOT I clinical trial, and the entire AMIHOT II and Optimized SSO_2 pilot study populations[1]. A brief synopsis of the previous IDE study experiences is provided below.

2 BACKROUND INFORMATION

TherOx has conducted four FDA-approved IDE clinical studies for treatment of AMI patients. The first study was a pilot effort conducted on twenty-nine patients; study results included promising trend data towards improved left ventricular ejection fraction and wall motion score in SSO_2 Therapy treated subjects[2], and served as a foundation for the AMIHOT I multi-center randomized trial. No safety concerns were noted during this early pilot study. The AMIHOT I study[3] was a randomized trial that examined outcomes in AMI subjects treated with SSO_2 Therapy following PCI with stenting as compared to a Control group receiving PCI with stenting alone for patients experiencing inferior or anterior AMI treated within 24 hours. Study results showed improvement in infarct size reduction, reduced ischemic burden, and left ventricular contractility for a subgroup of patients with anterior wall infarctions treated within six hours of symptom onset. This promising AMIHOT I patient cohort was the target population for the pivotal AMIHOT II study.

During the AMIHOT I study, two hundred eighty-nine (289) patients were enrolled and followed from January 16, 2002 through April 3, 2004, including 20 run-in subjects and 269 randomized patients. Three independent biomarkers (infarct size reduction, regional wall motion score improvement at three months, and reduction in ST segment elevation) were designated as co-primary endpoints to evaluate the effectiveness of SSO_2 Therapy. The study was designed to demonstrate superiority of the SSO_2 Therapy group as compared to Controls for each of these endpoints, and to demonstrate non-inferiority of the SSO_2

[1] An I/E change was made prior to the Optimized SSO2 pilot study to include pre-PCI TIMI flow 3 patients, who were excluded by protocol in AMIHOT II but were still found to comprise 7.4% of SSO_2 Therapy subjects (core lab measurement).

[2] Dixon SR, Bartorelli AL, Marcovitz PA, *et al*. Initial Experience with Hyperoxemic Reperfusion after Primary Angioplasty for Acute Myocardial Infarction. J Am Coll Cardiol 2002:39(3);387-92.

[3] O'Neill WW, Martin JL, Dixon SR, *et al*. Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT). J Am Coll Cardiol 2007:50(5);397-405.

Therapy group as compared to Control with respect to 30-day MACE. The study population was comprised of qualifying AMI patients treated with either PCI alone or with SSO_2 Therapy as an adjunct to successful PCI within 24 hours of symptom onset.

Results for the SSO_2 Therapy group compared to the Control group for the three co-primary effectiveness endpoints demonstrated a nominal improvement in the test group; this nominal improvement did not achieve clinical and statistical significance in the entire population. However, an analysis of SSO_2 Therapy patients who were revascularized within 6 hours of AMI symptom onset and who had anterior wall infarction showed a marked improvement in all three co-primary endpoints as compared to Controls.

Infarct size results were expressed as a percentage of the left ventricle. This endpoint was established on the basis of numerous peer-reviewed publications of this biomarker that demonstrate a 5% median infarct size reduction is clinically meaningful. The all-patient < 24-hour group showed a 2% absolute reduction in median infarct size, from 13% in Control subjects to 11% in the SSO_2 Therapy group (Wilcoxon rank-sum test; one-sided p-value = 0.3). The infarct size reduction for anterior STEMI subjects treated within 6 hours of symptom onset showed that SSO_2 Therapy subjects exhibited a 14% absolute reduction in median infarct size from 23% in the Control group to 9% in the SSO_2 Therapy group (Wilcoxon rank-sum test; one-sided p-value = 0.04).

Effectiveness results for the other two co-primary endpoints (regional wall motion score index improvement, ST area reduction) in the AMIHOT I trial were consistent with the infarct size data. The results for regional wall motion score index improvement (decrease) at 3 months (90 days), as compared to baseline, demonstrated a nominal improvement in all patients in the SSO_2 group as compared to Controls (-0.62 vs. –0.57, respectively, ANCOVA one-sided p-value = 0.24); the results were statistically significant when only the anterior $\leq$6 hr population was examined (-0.75 vs. –0.54 for SSO_2 and Controls, ANCOVA one-sided p-value =0.03). As seen in the infarct size measurements, the observed improvement in SSO_2 Therapy subjects versus Controls was greatest in the $\leq$6 hr anterior patient population.

ST-segment area reduction was believed to represent the continuing ischemic burden on the heart in the post-acute phase for AMI patients. Results for this biomarker obtained at 3 hours post-PCI were consistent with both infarct size and wall motion data; results were comparable for all patients studied (median ST area = 0 μV-min for both groups, Wilcoxon rank-sum test one-sided p-value = 0.5) and significantly better in the anterior $\leq$6 hr patient

group (median areas = 0 vs. 311 μV-min for SSO_2 and Controls, Wilcoxon rank-sum test one-sided p-value = 0.01).

Key safety data revealed no statistically significant differences in the composite primary endpoint of one-month (30 days) Major Adverse Cardiac Event (MACE) rates between the SSO_2 Therapy and Control groups. MACE includes the combined incidence of death, reinfarction, target vessel revascularization, and stroke. In total, 9/134 (6.7%) subjects in the SSO_2 Therapy group and 7/135 (5.2%) subjects in the Control group experienced 30-day MACE (p=ns).

Following the experience of the AMIHOT I study, which suggested that anterior AMI patients treated with PCI and stenting within 6 hours could benefit from SSO_2 Therapy, the AMIHOT II study[4] was designed as a prospective randomized evaluation of this focused study population. The AMIHOT II study objective was to determine whether intracoronary perfusion of hyperoxemic blood in the SSO_2 Therapy group immediately after successful PCI/stenting within 6 hours of symptom onset for the treatment of anterior acute myocardial infarction reduces the area of infarction (% left ventricle) as measured by Tc-99m Sestamibi SPECT imaging at 14 days post-PCI, with no worse than a 6% (absolute) increase in the incidence of Major Adverse Cardiac Events (MACE), comprising the combined incidence of death, re-infarction, target vessel revascularization, and stroke at the latter of either 30 days post-PCI or hospital discharge, when compared to a Control group receiving PCI/stenting alone.

A total of 317 patients were enrolled in the AMIHOT II trial, including 13 run-in (training) patients and 301 randomized patients (222 SSO_2, 79 Control). The study enrollment was conducted from September 13, 2005, the date of the first patient enrollment, to June 28, 2007, the date of completion for the last 30-day patient follow up.

The AMIHOT II study results demonstrated effectiveness of SSO_2 Therapy in reducing median infarct size from 26.5% of the left ventricle in the Control group to 20.0% in the SSO_2 Therapy group in the AMIHOT II study, an absolute median reduction of 6.5%. This infarct size reduction was evaluated using a pre-specified formal Bayesian hierarchical model that considered AMIHOT I data as well. The Bayesian posterior probability of superiority was 96.9% using the pre-specified model, achieving the study endpoint.

[4] Stone GW, Martin JL, de Boer MJ, *et al*. Effect of Supersaturated Oxygen Delivery on Infarct Size after Percutaneous Coronary Intervention in Acute Myocardial Infarction. Circ Cardiovasc Intervent 2009:2;366-75.

The primary safety endpoint for the AMIHOT II trial required a determination of non-inferiority in the 30-day MACE rate, comparing the SSO_2 Therapy group with the Control group, using a one-sided safety delta of 6.0%. Endpoint evaluation was performed using a Bayesian hierarchical model that factored in the 30-day MACE data from both the AMIHOT I and II studies. Study results demonstrated that the primary safety endpoint was achieved successfully, with observed 30-day MACE rates of 3.8% in the Control group and 5.4% in the SSO_2 group in the AMIHOT II trial. The posterior probability of an increase of less than 6% in 30-day MACE rate was 99.5%, successfully achieving the study endpoint. The 30-day rates of mortality were 0% in the Control arm vs. 1.8% in the SSO_2 arm (P=0.58). Stent thrombosis occurred in 2.5% of patients in the Control arm vs. in 4.1% of patients treated with SSO_2 (P=0.73).

In summary, the AMIHOT II study demonstrated that SSO_2 Therapy administered adjunctively following PCI with stenting significantly reduces infarct size with no statistically significant difference in 30-day Major Adverse Cardiac Events (MACE). Following the results of an FDA Advisory Committee hearing regarding SSO_2 Therapy on March 18, 2009, FDA requested additional safety data regarding SSO_2 Therapy in the target patient population. TherOx management made the decision to refocus its clinical study plans on Optimized SSO_2 Therapy. Specifically, the previous studies were conducted by administering SSO_2 Therapy through an infusion catheter placed within the infarct-related artery and adjacent to the recently implanted stent site for 90 minutes. The AMIHOT Executive Committee and TherOx management team decided that the risk of procedural complications would be minimized if SSO_2 delivery could be achieved without the requirement for the in-dwelling infusion catheter.

The key advantage with Optimized SSO_2 Therapy administration is the delivery point change for the infusion, from the sub-selective coronary artery to a proximal position in the left main coronary artery (LMCA). **Figure 1** shows a side-by-side schematic comparison of the two approaches.

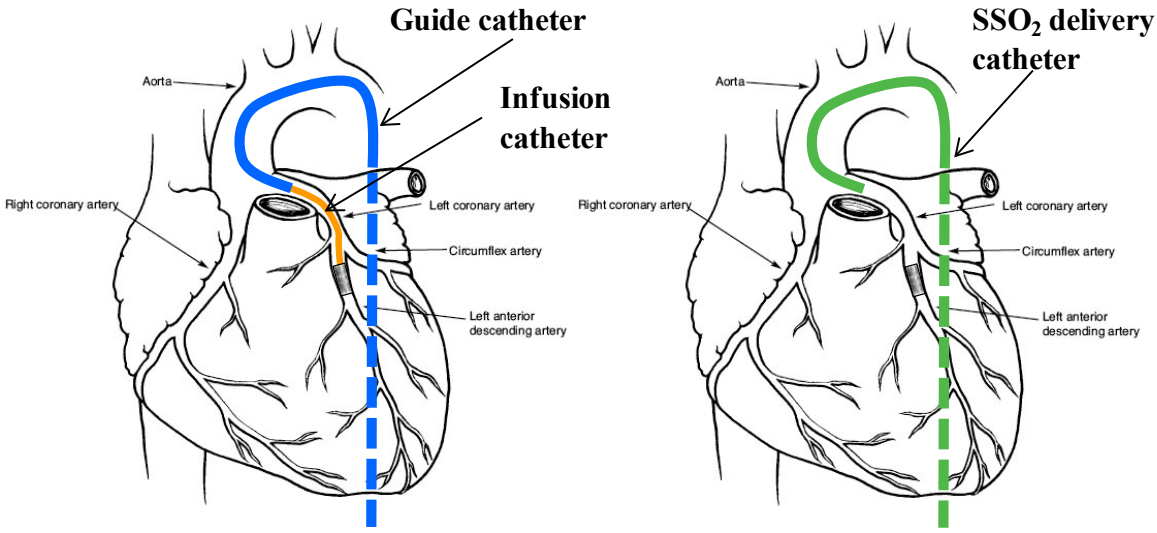

Figure 1. Comparison of SSO_2 Therapeutic Delivery Approaches

The Optimized SSO_2 Therapy approach offers advantages in both real and perceived safety and effectiveness, as well as operator preference. By moving the infusion point proximally, patient safety is improved due to elimination of mechanical manipulation near the PCI injury zone. The infusion may be performed through a qualified SSO_2 delivery catheter (i.e., a 5F angiographic catheter qualified through testing for this procedure) in the LMCA, eliminating the need for the extra infusion catheter. The use of a guidewire through the target vessel and placement of the infusion catheter near the freshly placed stent is therefore unnecessary using this approach. In addition, the infusion is performed in a higher flow main artery, reducing concerns about restricting flow in part of the sub-selective target vessel. Advantages in effectiveness may be observed because flow of superoxygenated blood will be directed to the entire left coronary system (including collateral vessels) instead of just the target vessel. Infarct data from the AMIHOT studies show that anterior AMI patients may benefit from the collateral supply of SSO_2 to treat the entire ischemic zone and thus further reduce the extent of infarction.

TherOx conducted an IDE pilot study in 20 patients enrolled at 3 US sites to confirm the viability of the modified infusion. The target population was the same as previous IDE studies – qualifying anterior AMI patients treated with PCI within six hours of symptom onset. Primary data collection was performed through 30 days, including adverse event

reporting and cardiac MRI (cMRI) imaging. Results showed a low complication rate – one patient (5%; 1/20) experienced a 30-day MACE event (stent thrombosis and reinfarction). This event was attributed to an underdeployed stent placement during the index PCI procedure and non-use of aspirin. Post SSO_2 infusion angiography showed no thrombus in this patient. No patient deaths were observed and all patients were followed through 30 days. MRI results were obtained in 90% (18/20) of patients had at 30 days (2 were not obtainable due to patient claustrophobia). The median [interquartile range] infarct size at 30 days was 9.6% [2.1%, 14.5%], representing a potential reduction as compared to infarct size measured in AMIHOT II at 14 days (20% [6%, 37%]). The IC-HOT clinical trial is designed to confirm these safety and efficacy results in a larger 100-patient IDE study in the target patient population.

2.1 Description of Device

SuperSaturated Oxygen Therapy ("SSO_2 Therapy") is an adjunctive cardiac catheterization laboratory initiated procedure with superoxygenated blood delivered via a qualified delivery catheter to the left main coronary artery (LMCA) in a patient with acute myocardial infarction (AMI) after successful percutaneous intervention (PCI) with stenting has been performed. The equipment necessary for SSO_2 Therapy is comprised of three components: the DownStream® System ("system"), the DownStream® Cartridge ("cartridge"), and the SSO_2 delivery catheter ("delivery catheter"). The system and cartridge function together to create a highly oxygen-enriched saline solution called SuperSaturated Oxygen solution ("SSO_2 solution"). A small amount of autologous blood is mixed with the SSO_2 solution producing oxygen-enriched hyperoxemic blood which is then delivered to the LMCA via the SSO_2 delivery catheter at a flow rate of 100 ml/min. The duration of SSO_2 Therapy is 60 minutes as detailed in this protocol.

2.1.1 DownStream System

The system is the electromechanical device (console) that controls the cartridge and monitors performance and safety during administration of SSO_2 Therapy. The system has safety features that continuously monitor system parameters such as the blood flow rate and pressure, and detect potentially unsafe conditions such as the presence of air-in-line. A display screen guides the health care professional through setup and clinical operation. The system is non-sterile and has no direct contact with the patient or the blood flow path. The system is intended to be mains-operated (AC-powered) and stationary during use but is equipped with battery backup power. The system is designed for operation in a cardiac

catheterization laboratory and must be operated and monitored by trained personnel when providing SSO_2 Therapy. The DownStream System is shown in **Figure 1a** and **Figure 1b** (closeup).

Figure 1a. TherOx® DownStream® System

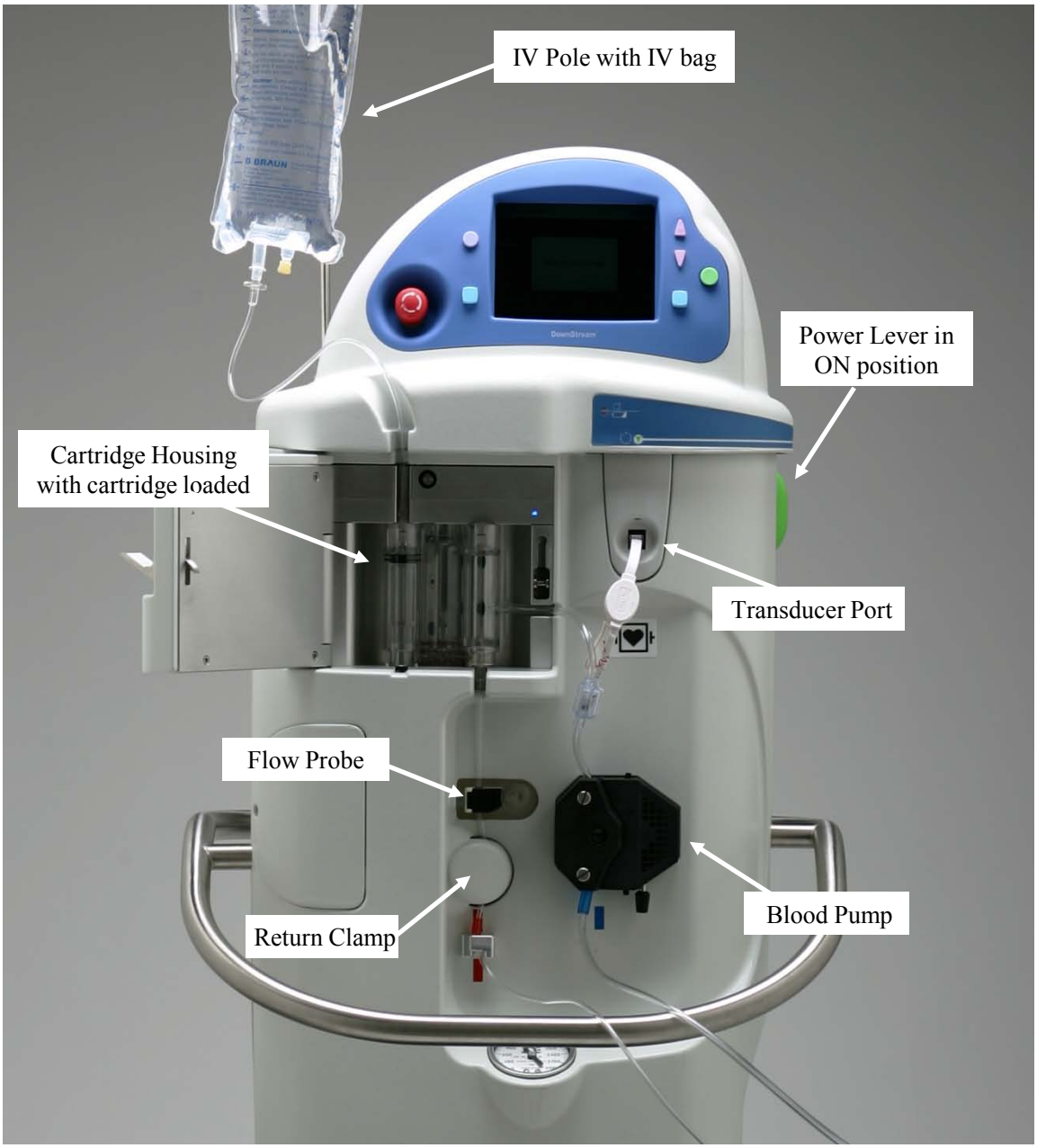

Figure 1b. Close-up of DownStream® System Components

The major subsystems of the DownStream System are the Cartridge Control Subsystem ("CCS"), Display Subsystem ("Display"), Power Supply Subsystem ("Power Supply"), and Oxygen Supply Subsystem ("Oxygen Supply").

The CCS monitors and controls the operation of the cartridge during operation. The CCS has a cartridge housing that contains the cartridge. An oxygen valve controls the flow of oxygen to the cartridge from the E-bottle source that is securely mounted onto the system. A piston actuator operates the piston (syringe) inside the cartridge to withdraw saline from the IV bag and pump it into the cartridge to make superoxygenated saline. A peristaltic blood pump operates on the cartridge draw tubing to withdraw arterial blood from the patient and pump it through the cartridge, returning hyperoxemic blood back to the patient. A modular jack on the front panel of the CCS connects to the cartridge transducer assembly. The transducer communicates with the system and is written to after use to prevent re-use. An ultrasonic probe (for bubble/air in line detection and flow monitoring) and return clamp on the front panel of the CCS operate on the Cartridge Return tubing. A Prime switch and Emergency Stop switch located on the Display are also part of the CCS.

The Display Subsystem located at the top of the system is the user interface. A keypad provides user control of system operation. An LCD display provides visual feedback, and a speaker provides audible feedback for the user. Users are cardiologists and nurses administering the treatment in the cardiac catheterization laboratory (CCL). The user has seven keys (buttons) on the Display Subsystem that control system operation. An LCD display provides visual feedback, and a speaker provides audible feedback for the user.

The Power Supply Subsystem is an electronic assembly that provides DC power to the CCS and Display Subsystems. The Power Supply receives power from the AC Mains or an internal battery. Component features of the Power Supply include: appliance inlet receptacle with fuses, medical grade 15 VDC power supply, battery charger, DC-to-DC power supplies, and a battery. The battery provides at least one half hour of system operation when fully charged. When connected to AC Mains, the system automatically charges the battery.

The Oxygen Supply Subsystem is a mechanical assembly that provides regulated oxygen to the CCS. The Oxygen Supply uses pressurized oxygen from a medical grade E-bottle, which it regulates to 750 ± 50 psig. Component features of the Oxygen Supply include: E-bottle (yoke-type) connection, oxygen regulator with 900 psi relief valve, bottle pressure

gauge, and oxygen filter. The Oxygen Supply can support over 50 treatments on one E-bottle.

2.1.2 DownStream Cartridge

The cartridge is a single-use disposable device that is loaded into the system by a trained healthcare professional. The cartridge has a three-chambered body that creates SSO_2 solution from inputs of hospital-supplied oxygen and physiologic saline and mixes the SSO_2 solution with arterial blood within the cartridge blood path. The cartridge has a tube set that draws the patient's arterial blood through the draw line, and returns oxygen-enriched hyperoxemic blood through the return line to the SSO_2 delivery catheter. The cartridge draw line connects to the sidearm of an arterial sheath. Sheath placement may be coaxial (single arterial access site) or contralateral (two arterial access sites) at the physician's discretion. A physician makes two line connections during the initiation of SSO_2 Therapy: the cartridge draw line is attached to the arterial sheath before priming the blood flow path, and the return line is attached to the SSO_2 delivery catheter after the blood flow path is successfully primed. The priming volume of the cartridge is approximately 60 ml. The cartridge is shown in **Figure 2**.

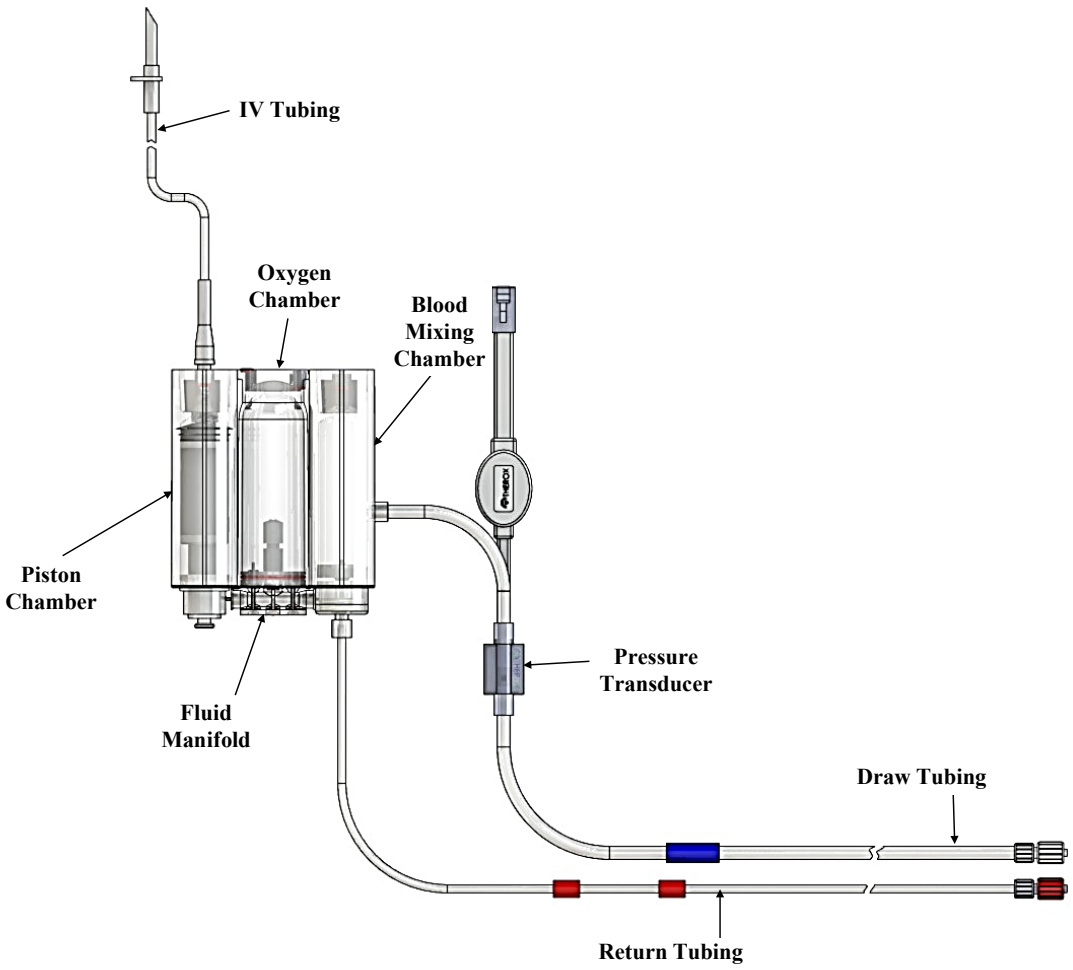

Figure 2. TherOx® DownStream® Cartridge

A fluid manifold in the Oxygen Chamber provides the fluid path between the three chambers. The IV tubing set connects the Piston Chamber to a 1-liter bag of sterile saline provided by the hospital. The draw tubing set connects the blood mixing chamber to an arterial draw sheath (blood from the patient), and the return tubing set connects the blood mixing chamber to the delivery catheter (hyperoxemic blood to the patient). **Figure 3** depicts the fluid flow paths through the cartridge and the fluid flow control features.

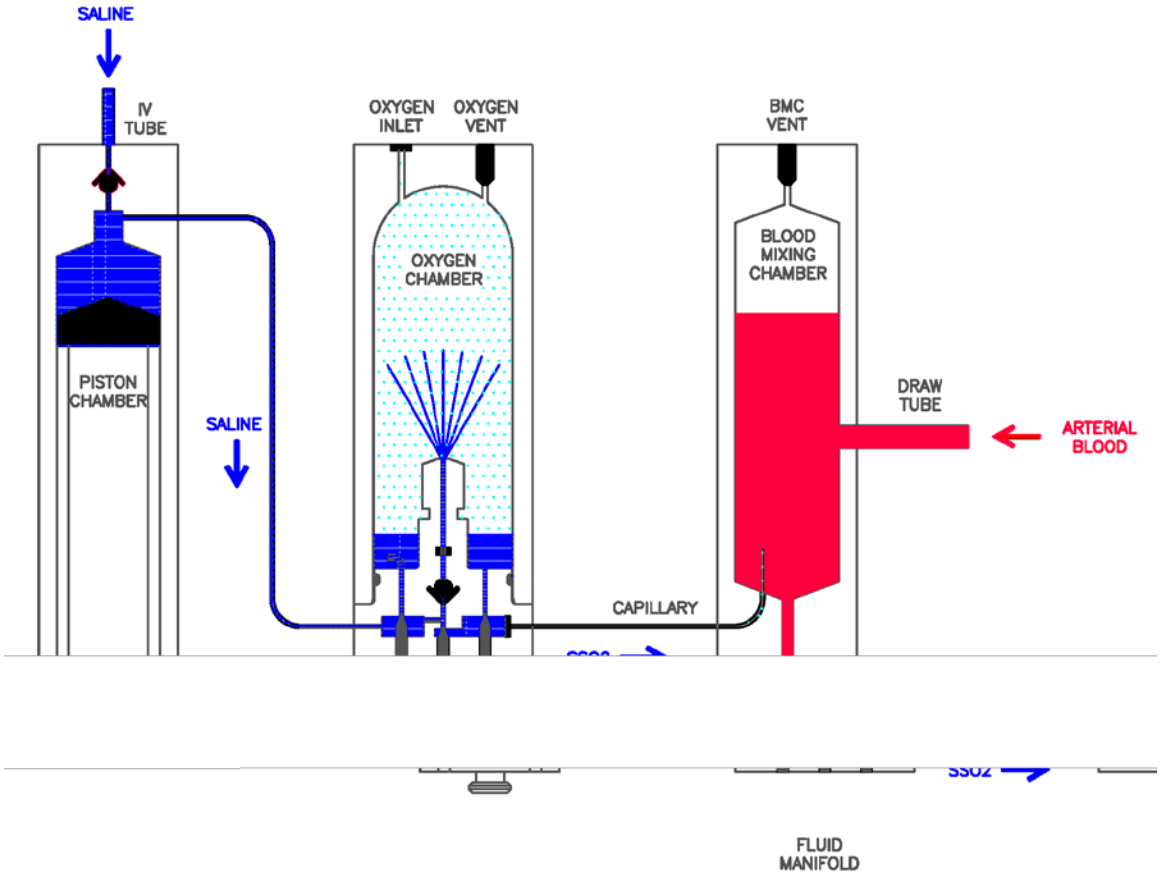

Figure 3. DownStream® Cartridge Fluid Flow Path

The DownStream Cartridge utilizes medical grade polyvinyl chloride ("PVC") tubing for blood withdrawal and return to the patient. The cartridge housing is constructed primarily of injection-molded medical grade polycarbonate, a common plastic material used in medical devices. The tubing and Blood Mixing Chamber ("BMC") comprise the blood-wetted fluid path of the cartridge.

The production and flow of SSO_2 solution are continuous within the DownStream Cartridge; control of these processes is maintained through the use of the Fluid Manifold shown in **Figure 3**. The Fluid Manifold connects and controls the flow of saline and SSO_2 solution between the three chambers of the cartridge with three needle valves and one check valve. The Piston Chamber delivers saline to the Fluid Manifold through a small tube. The

saline can be delivered to the Oxygen Chamber through the atomizer to create SSO_2 solution, through a dilution port to adjust concentration, or directly to the BMC to flush the capillary tube. The SSO_2 solution's dissolved oxygen concentration is controlled by the DownStream System.

The DownStream Cartridge is equipped with a pressure transducer that monitors the blood mixing chamber pressure in the device during operation; the transducer connects to the DownStream System. An IV spike and flexible tube are attached to the Piston Chamber, enabling easy connection to an IV bag during the procedure. The draw and return tubing are equipped with luer connections. The DownStream Cartridge is a single-use Ethylene Oxide ("EO")-sterilized device.

The draw tubing is connected to the patient with a luer fitting that is attached to the femoral access sheath. The return tube is attached to the SSO_2 delivery catheter that has been placed in the ostium of the left main coronary artery.

2.1.3 SSO_2 Delivery Catheter

The SSO_2 delivery catheter is a 5F (O.D.) over-the-wire catheter that is equipped with a standard luer fitting at the proximal end for attachment to the return line of the cartridge. The SSO_2 delivery catheter has a total length of 100 cm and is placed over a guidewire to reach the coronary vasculature. During administration of SSO_2 Therapy, the SSO_2 delivery catheter is placed in the ostium of the LMCA and connected to the cartridge by the trained physician.

Only a catheter that is qualified by TherOx may be used as the SSO_2 delivery catheter. The qualified SSO_2 delivery catheter is the 5F Boston Scientific Impulse® angiographic catheter. Superoxygenated blood may not be infused with a non-qualified catheter because of the risk of bubble nucleation and the introduction of air emboli to the patient, therefore the use of a non-qualified delivery catheter is contraindicated. TherOx has qualified the 5F Boston Scientific Impulse® for compatibility with superoxygenated blood and this catheter must be used in this study.

2.1.4 Patient Connections

The DownStream Cartridge draw tubing connects to a femoral arterial sheath that may be used for angioplasty and stenting procedures. Sheath placement may be coaxial (using one femoral arterial access site) or contralateral (using both the right and left femoral arteries for

access sites), at the physician's discretion. A single sheath is recommended as prior studies have shown that single femoral artery access, even with a larger sheath, results in less bleeding and fewer vascular complications that bilateral femoral access. In the preferred coaxial configuration, a single introducer sheath can be used. The DownStream Cartridge draw tubing luer fitting connects to the sheath sidearm. The SSO_2 delivery catheter (the 5F Boston Scientific Impulse® angiographic catheter) is placed to the ostium of the left main coronary artery using standard cath lab techniques. When extracorporeal blood flow is initiated, the delivery catheter and DownStream Cartridge return tubing are wet-connected to ensure that no gaseous emboli are introduced to the patient during priming. The cartridge return tubing luer fitting connects to the luer hub of the delivery catheter. For the contralateral approach, a 5F introducer sheath is used in a second femoral access site for blood withdrawal. This alternative approach may be used by physicians who prefer to use two smaller sheaths for arterial access instead of a single sheath.

Figure 4 provides a schematic of the patient connections during SSO_2 Therapy administration.

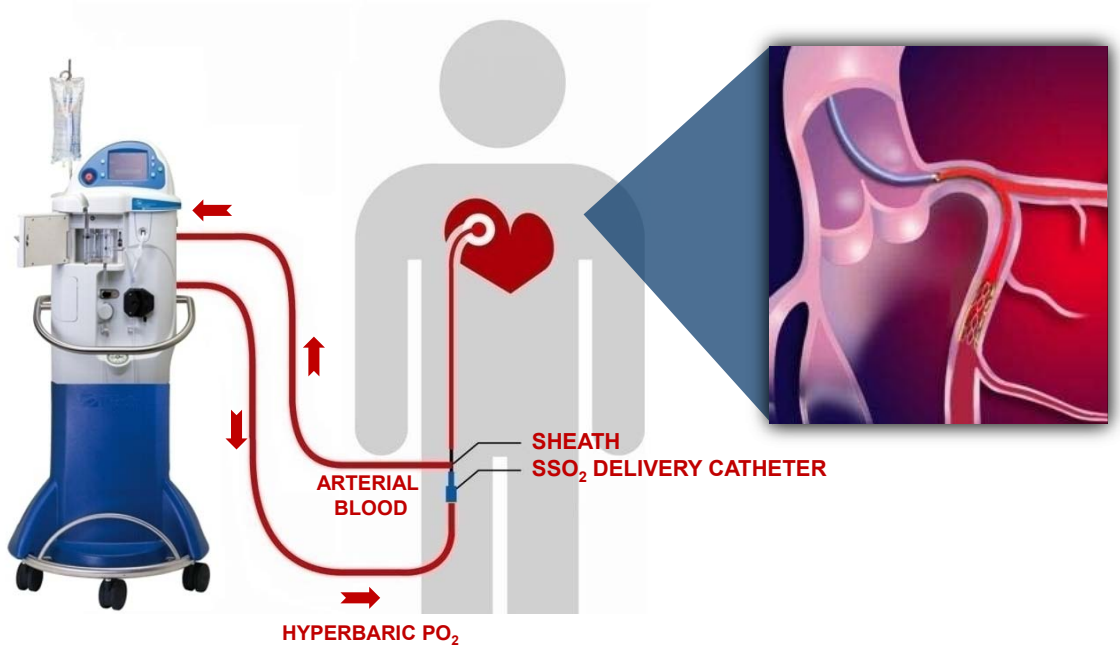

Figure 4. Patient Connections

3 STUDY OBJECTIVE

To collect confirmatory data supporting the safety and effectiveness of SSO_2 Therapy in the treatment of anterior acute myocardial infarction (AMI) patients who have undergone successful percutaneous coronary intervention (PCI) with stenting within six hours of experiencing AMI symptoms.

4 STUDY DESIGN

This is a non-randomized, single-arm study. Subjects who present with anterior STEMI requiring stent placement in the proximal and/or mid LAD who meet all inclusion and exclusion criteria and provide informed consent will be treated with primary PCI with stenting, and if successful and uncomplicated then immediately with post-procedure delivery of SSO_2 Therapy for a duration of 60 minutes.

4.1 Patient Enrollment

100 qualifying patients with anterior acute myocardial infarction will be enrolled into this study and treated with SSO_2 Therapy only after successful and uncomplicated revascularization of the LAD infarct artery.

4.2 Patient Follow-Up

Subjects will be followed clinically at baseline, procedural, in hospital, at 30-days (±7 days; i.e., between 23 and 37 days), at 6-months (±30 days) and at 12-months (±30 days) following the index procedure. The clinical investigator or designee will conduct the 30-day follow-up assessment as an office visit, and the 6-month and 12-month follow-up assessments via telephone call. Patient adverse events will be tracked, monitored, and adjudicated through 12 months post-procedure. For the purpose of reporting study results, a clinical summary report will be issued after 30-day data are finalized and a supplementary report will be issued upon completion of 12-month assessments.

4.3 Cardiac Magnetic Resonance Imaging (MRI)

Patients will be evaluated with two cardiac MRI scans. The first scan will be conducted between day 3 and day 5 post-procedure (day 4 ± 1). The second scan will be conducted in conjunction with the mandatory 30-day clinical follow-up visit, on day 30 (±7) post-procedure (between days 23-37). Every effort will be made to obtain the required MRI

scans, and scans obtained outside the protocol window will be reported. The necessary procedural details for conducting the cardiac MRI scans are provided in **Appendix E**.

Cardiac MRI images will be evaluated by the MRI Core Laboratory and the following information will be reported: microvascular obstruction (MVO) at day 3-5, infarct size at both imaging time points, and left ventricular volume at both imaging time points. Other standard MRI measures will also be reported at each time point.

4.4 Early Study Termination

No statistical rule for early termination is defined. However, TherOx, Inc. may discontinue the study at any stage with written notice to the investigators. Possible reasons for early termination may include identification of safety risks that pose an unreasonable risk to the patient. The independent Data Safety Monitoring Board will have responsibility for study oversight, including the timely review of critical safety events, and may make recommendations for study modification, suspension, or termination.

The study Executive Committee makes a final decision for early study termination. If the trial is terminated early, TherOx will provide a written statement describing why premature termination will occur, and notify the participating clinical investigators, investigational site IRBs, and FDA. All applicable clinical study documents will be subject to the same retention policy as detailed in **Section 10.10.1** Required Data.

4.5 Measures Taken To Avoid / Minimize Bias

In order to minimize bias in assessing both effectiveness and safety data, the independent cardiac MRI Core Laboratory will evaluate patient scans independent of clinical outcome data, and an independent Clinical Events Committee (CEC) will be utilized for adverse event coding and relationships after review of original source documentation, blinded to the MRI results. An independent Data and Safety Monitoring Board (DSMB) will conduct reviews of overall study conduct and safety both during the enrollment period and at the conclusion of the study.

5 SSO_2 THERAPY PROCEDURAL AND SAFETY DATA

5.1 SSO_2 Therapy Procedural Data

Procedural information will be collected and reported for every patient treated with SSO_2 Therapy in this trial. The data collected and reported will include:

- SSO_2 Therapy device and infusion specifics
- Confirmation of stable delivery catheter position
- Intra-procedural hemodynamics
- Procedural complications, therapy interruptions or device shutdowns

5.2 Safety Data

All major adverse events will be evaluated and reviewed by an independent Clinical Events Committee ("CEC"). The following safety and procedural information will be reported and summarized:

- AEs and SAEs
- Adverse event relationships
- Intraprocedural complications
- Clinical, technical and procedural success

5.3 Number of Sites

Up to fifteen (15) centers located in the U.S.

5.4 Sample Size

One hundred (100) patients, non-randomized. All patients will receive a 60-minute SSO_2 Therapy infusion.

6 PATIENT SELECTION AND WITHDRAWAL

6.1 Patient Population

Patients must meet all of the study criteria outlined below in **Section 6.4.1** and **6.4.2** (reference Inclusion/Exclusion Criteria Case Report Form (CRF), **Appendix A**). No exclusion criteria outlined in **Section 6.4.2** may apply in order to be enrolled.

6.2 Patient Screening

All patients admitted to the emergency room or cardiac catheterization laboratory with symptoms ≤6 hours after symptom onset and ECG findings suggestive of acute anterior AMI (ST-segment elevation of ≥1 mm in 2 or more contiguous leads in V1-V4, or new left bundle-branch block), and who are considered potential candidates for percutaneous

revascularization with stenting, are potentially eligible for this protocol. All patients who meet clinical inclusion criteria should be documented (entered) on the site's study screening log. Thus, patients without ST-segment elevation and those with non-anterior MI or new left bundle branch block do not need to be recorded in the screening log. Reasons for screening failure will be noted in the final study report. If the potential study candidate has one or more clinical exclusion criteria present, or subsequently fails to meet angiographic selection criteria, the reason for screening failure must be entered on the screening log. A member of the research team should screen all eligible patients to determine eligibility and document any applicable reasons for non-enrollment on the screening log.

A signed Informed Consent must be obtained before cardiac catheterization begins, and before any study-related tests or procedures are undertaken.

6.3 Informed Consent

A member of the research team will approach the patient (or legal representative) to obtain written Informed Consent. The Informed Consent will be carefully explained to the patient. The patient (or legal representative) must sign the consent form approved by the Sponsor, FDA, and the study site's Institutional Review Board ("IRB"). The sample Informed Consent Form is attached as **Appendix B**. Signed Informed Consent Forms will be maintained at each investigational site.

6.4 Eligibility Criteria

6.4.1 Inclusion Criteria

Candidates for this study must meet **ALL** of the following criteria:

General Inclusion Criteria

Pre-PCI:

1. The subject must be ≥18 and ≤80 years of age.
2. AMI must be anterior (ST-segment elevation ≥1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block).
3. Subject is experiencing clinical symptoms consistent with acute MI of ≤6 hour duration from time of symptom onset until admission to the emergency room.

4. The subject or legally authorized representative has been informed of the nature of the study, agrees to its provisions and has been provided and signed written informed consent, approved by the appropriate Institutional Review Board (IRB).
5. Subject and his/her physician agree to all required follow-up procedures and visits.

ANGIOGRAPHIC INCLUSION CRITERIA: These are evaluated after the subject has provided signed Informed Consent but prior to enrollment:

6. Based on coronary anatomy, PCI is indicated for revascularization of the culprit lesion(s) with use of a commercially available coronary stent (bare metal or drug-eluting, at operator discretion) in the LAD.
7. The primary stented infarct-related lesion(s) must be in the proximal and/or mid-LAD coronary artery (other lesions in the LAD target vessel, including diagonal branches, may be treated if clinically indicated).
8. Baseline (pre-PCI) TIMI flow grade 0, 1, 2, or 3 flow in the LAD.
9. Successful angioplasty is completed ≤6 hrs from system onset, as documented by <50% diameter residual angiographic stenosis within all treated culprit lesions with TIMI 2 or 3 flow and no major complications such as perforation or shock.
10. Expected ability to place the SSO_2 delivery catheter in the coronary ostium of the left main coronary system to deliver SSO_2 Therapy with stable, coaxial alignment.

6.4.2 Exclusion Criteria

Subjects will be excluded if **ANY** of the following conditions apply:

General Exclusion Criteria

Pre-PCI:

1. Prior CABG surgery.
2. Prior myocardial infarction, or known prior systolic dysfunction (known ejection fraction <40% by any prior measure or regional wall motion abnormalities; this criterion does not include left ventricular dysfunction induced by the acute MI).
3. Thrombolytic therapy administered for this STEMI.
4. An elective surgical procedure is planned that would necessitate interruption of anti-platelet agents during the first 30 days post-enrollment.

5. Subjects who previously underwent coronary stent implantation and in whom coronary angiography demonstrates stent thrombosis to be the cause of the anterior AMI.
6. Subjects who have previously undergone an angioplasty or stenting procedure in the left anterior descending coronary artery.
7. Subjects with ventricular pseudoaneurysm, VSD, or severe mitral valve regurgitation (with or without papillary muscle rupture).
8. Any contraindication to MRI imaging. This will include any of the following exclusions:

    a. Cardiac pacemaker or implantable defibrillator;
    b. Non-MRI compatible aneurysm clip;
    c. Neural Stimulator (i.e., TENS unit);
    d. Any implanted or magnetically activated device (insulin pump);
    e. Any type of non-MRI compatible ear implant;
    f. Metal shavings in the orbits;
    g. Any metallic foreign body, shrapnel, or bullet in a location which the physician feels would present a risk to the subject;
    h. Any history indicating contraindication to MRI, including claustrophobia or allergy to gadolinium;
    i. Inability to follow breath hold instructions or to maintain a breath hold for >15 seconds; and
    j. Known hypersensitivity or contraindication to gadolinium contrast.

9. Known impaired renal function (creatinine clearance <30 ml/min/1.73 m^2 by the MDRD formula) or on dialysis.
10. Known platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3 or a known Hgb <10 g/dL.
11. Subject has active bleeding or a history of bleeding diathesis or coagulopathy (including heparin induced thrombocytopenia), or refusal to receive blood transfusions if necessary.
12. History of intracerebral mass, aneurysm, arteriovenous malformation, or hemorrhagic stroke.
13. Stroke or transient ischemic attack within the past six (6) months, or any permanent neurological defect.

14. Gastrointestinal or genitourinary bleeding within the last two (2) months, or any major surgery (including CABG) within six weeks of enrollment.
15. Subject has received any organ transplant or is on a waiting list for any organ transplant.
16. Subject has other medical illness (e.g., cancer, dementia) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause non-compliance with the protocol, confound the data interpretation, or is associated with limited life expectancy of less than one year.
17. Subject has a known hypersensitivity or contraindication to unfractionated heparin, abciximab, aspirin, bivalirudin, cangrelor, clopidogrel, ticlopidine, prasugrel, eptifibatide, tirofiban or ticagrelor that cannot be adequately premeditated.
18. Current use of warfarin, dabigatran, or factor Xa inhibitors, or known intent to administer these agents after the primary PCI.
19. Subjects presenting with or developing in the cath lab prior to completion of the primary PCI procedure any of the following conditions: cardiogenic shock (SBP <80 mmHg for >30 minutes), or requiring IV pressors or emergent placement of an intra-aortic balloon pump (IABP), Impella, or other hemodynamic support for hypotension treatment, or cardiopulmonary resuscitation for >10 minutes, or ventricular fibrillation or tachycardia requiring cardioversion or defibrillation.
20. Severe known cardiac valvular stenosis or insufficiency, pericardial disease, or non-ischemic cardiomyopathy.
21. Any significant medical or social condition which in the investigator's opinion may interfere with the subject's participation in the study or ability to comply with follow-up procedures, including MRI (e.g. alcoholism, dementia, lives far from the research center, etc.).
22. Current participation in other investigational device or drug trials.
23. Previous enrollment in this study.

ANGIOGRAPHIC EXCLUSION CRITERIA: These are evaluated after the subject has provided signed Informed Consent but prior to enrollment:

24. Anticipated inability to achieve a stable coaxial position in the left main coronary artery with the SSO_2 delivery catheter.
25. Treatment during the index procedure of any lesion in either the left main, LCX (including the ramus), and/or RCA.

26. Post-index procedure planned intervention within 30 days (i.e., PCI of non-target lesions in any vessel, or CABG). Note: Planned revascularization (PCI or bypass) of a non-target lesion >30 days following the index procedure is allowed.
27. Anterior MI is due to thrombosis within or adjacent to a previously implanted stent.
28. Left ventriculography demonstrates severe mitral regurgitation, a ventricular septal defect, or a pseudoaneurysm.
29. Any left main coronary artery stenosis >20%.
30. Any untreated LAD or diagonal branch lesion is present with diameter stenosis ≥ 50% in a vessel with reference vessel diameter > 2.0 mm (visually estimated), or for which PCI will be required before the MRI study.
31. Presence of a non-stented coronary dissection with NHLBI grade ≥B upon completion of the PCI procedure.

Subjects who meet the selection criteria will be enrolled into this multi-center clinical trial after successful screening and providing Informed Consent.

Please note: An Enrollment Notification Form should be completed and sent via facsimile to the study CRO after the procedure has been completed.

6.5 Patient Discontinuation

Once enrolled, each patient should remain in the study until the required follow-up period is complete. However, the patient has the right to withdraw from the study at any time. The following events will result in terminating the patient's follow-up:

- Patient death
- Patient voluntary withdrawal
- Patient withdrawn by investigator as clinically indicated
- Patient lost to follow-up (unofficial withdrawal)
- Study is terminated according to **Section 4.4** Early Study Termination

Appropriate case report forms must be completed for both study-terminated patients and patients who complete the entire follow-up. TherOx, Inc. must be notified of the reason of patient discontinuation. The site will provide this information on the appropriate case report form. Investigators must also report this information to their IRBs as defined by their institutions' procedures.

6.5.1 Lost To Follow-Up

Patients who do not complete the scheduled 30-day follow-up clinical visit or who cannot be contacted for their 6 and 12-month telephone surveys and have not officially withdrawn from the study are considered lost to follow-up; this term does not apply to missed visits. Site personnel should make considerable effort to locate and communicate with the patient using all available methods (e.g., telephone, email and postcards). The following contact procedure is recommended at the 30-day follow-up time point:

- A minimum of 2 telephone calls on different days after discharge and over the 30-day follow-up window. This should be recorded including date, time, and site personnel initials for staff attempting to contact the patient.
- If these attempts are unsuccessful, a certified letter should be sent to the patient.
- If the patient misses two (2) consecutive scheduled contact time points and the above mentioned attempts at communicating with the patient are unsuccessful, the patient will be considered lost to follow-up.

7 STUDY PROCEDURES

7.1 Patient Evaluation Procedures

For those patients who agree to participate in the study by signing the approved Informed Consent, the following baseline examinations and tests will be performed:

- Medical History and physical examination
- 12 Lead ECG
- Administration of protocol required procedure medications
- Cardiac Biomarkers (CK, CKMB and troponin)
- Clinical Chemistry and Hematology
- Coronary Angiography

7.2 Procedure Medications

All enrolled patients receive the following protocol required medications:

Patients must receive one of the following oral ADP antagonist regimens:

- Clopidogrel 600 mg in the ER, followed by 75 mg to 150 mg per day.
- Prasugrel 60 mg in the ER followed by 5 mg to 10 mg per day.

- Ticagrelor 180 mg in the ER followed by 90 mg b.i.d.
- Ticagrelor or prasugrel is preferred to clopidogrel in patients without bleeding contraindications, according to FDA labeled instructions for use. Prasugrel (but not ticagrelor) is contraindicated in patients with prior stroke or TIA. Ticagrelor is recommended rather than prasugrel in patients <60 kg or >75 years of age.
- These loading doses must be given even if the patient is on home dual anti-platelet therapy.

Patients must also receive:

- Aspirin – 324 mg chewable aspirin given in ER prior to catheterization (regardless of earlier administration of aspirin). Alternatively, 250-500 mg IV may be administered[5]. Thereafter, 81 mg of oral aspirin per day is administered.
- Intravenous bivalirudin or unfractionated heparin (as in **Section 7.3.1** below), initiated either before or in the catheterization laboratory, but in all cases before the first balloon inflation. At operator discretion, the patient may have received unfractionated heparin prior to cardiac catheterization, and then be switched to bivalirudin in the cath lab prior to PCI as described in **Section 7.3.1** below.
- Low-flow nasal oxygen (3-5 l/min) or oxygen mask (5-10 l/min) to maintain systemic arterial pO_2 > 80 mmHg.

Use of cangrelor or glycoprotein IIb/IIIa receptor inhibitors is required prior to PCI in patients treated with only unfractionated heparin. For patients receiving bivalirudin as their procedural anticoagulant, routine use of cangrelor is allowed but use of glycoprotein IIb/IIIa receptor inhibitors is not recommended, but may be administered during the procedure if refractory thrombotic complications occur. If a GP IIb/IIIa inhibitor is used, abciximab (bolus + a 12 hour infusion) is recommended, although eptifibatide (double bolus + a 12-18 hour infusion) or tirofiban according to label is an acceptable alternative. Dosing of either should be performed per the package insert, adjusted for renal insufficiency. The IIb/IIIa inhibitor may be initiated prior to catheterization (e.g., in the emergency room), or in the cardiac catheterization laboratory prior to first balloon inflation.

The use of procedure medications will be documented on the appropriate Case Report Forms.

[5] IV aspirin is applicable to EU sites only.

7.3 Cardiac Catheterization Laboratory (CCL) Procedure

7.3.1 Patient Anticoagulation

Patient anticoagulation throughout the SSO_2 Therapy procedure is aligned with current practice in STEMI patients treated with primary PCI as outlined below. Bivalirudin is recommended for this study, but patient anticoagulation must consist of one of the following regimens:

1) Bivalirudin and cangrelor, with provisional (bail-out) use of GP IIb/IIIa inhibitors allowed
2) Bivalirudin, with provisional (bail-out) use of GP IIb/IIIa inhibitors allowed
3) Heparin and cangrelor, with provisional (bail-out) use of GP IIb/IIIa inhibitors allowed
4) Heparin and routine use of GP IIb/IIIa inhibitors

If bivalirudin is selected as the procedural anticoagulant, it should be administered as a bolus of 0.75 mg/kg IV prior to PCI, followed by an infusion of 1.75 mg/kg/h initiated as soon as possible. The infusion is continued at this rate through the end of SSO_2 Therapy administration and for 3-4 hours post-procedure. The infusion dose should be adjusted for renal insufficiency as per the FDA labeled Instructions for Use.

Exception: If the patient received intravenous heparin prior to cardiac catheterization (bolus or infusion), the heparin should be discontinued, and the bivalirudin should be started 30 minutes after the last dose of heparin or prior to PCI whichever occurs first. An ACT or aPTT does not need to be checked before starting the bivalirudin. In all cases the bivalirudin should be initiated before the first PCI balloon inflation or aspiration.

The use of bivalirudin is preferred but unfractionated heparin along with the routine pre-PCI use of a GP IIb/IIIa inhibitor *or* bivalirudin with the provisional (bailout) post-PCI use of a GP IIb/IIIa inhibitor may be used as the procedural anticoagulant in the IC-HOT clinical study.

If unfractionated heparin is selected, local dosing regimens may be used, although it is recommended that an initial bolus of 60 IU/kg is administered, followed by titration to the ACT of 200-250 seconds. Heparinized patients must also receive a GP IIb/IIIa inhibitor or cangrelor.

For all subjects, ACT is measured as a baseline reading prior to starting SSO_2 Therapy and after the 60-min infusion is completed. For patients receiving heparin, a 30-min ACT is also required and bolus administration of heparin to maintain ACT levels may be necessary.

Intravenous cangrelor may also be used according to label per investigator discretion, administered as a bolus plus infusion, with the infusion continued for 2-4 hours post-PCI. For patients receiving bivalirudin, cangrelor may be administered in the same IV.

7.3.2 Coronary Angiography

It is recommended that the prospective patient be transferred to the catheterization laboratory as quickly as possible. Once in the catheterization laboratory, the patient should be prepared for the interventional procedure according to standard hospital procedures. Left ventriculography is required and must be obtained prior to study enrollment.

When performing coronary angiography, all of the distal target vessel with capillary and collateral flow should be filmed to allow for assessment of pre-procedure and post-procedure TIMI flow and blush score. Left ventriculography should be performed in the right anterior oblique view (pre- or post-PCI, but before study enrollment) with at least two consecutive sinus beats available for analysis. Pre- and post-PCI angiographic data will be sent to the Angiographic Core Laboratory for analysis as per the instructions provided in **Appendix E**. Study investigators should follow procedural guidelines for angiographic imaging provided in **Appendix E**.

Patients must be excluded if an additional staged procedure is planned within 30 days.

7.3.3 PCI / Stenting Procedure

Following a successful diagnostic catheterization and identification of the target lesion(s) in the proximal and/or mid LAD as suitable for PCI with stenting, if heparin plus a GP IIb/IIIa inhibitor was used as the procedural anticoagulant, additional heparin boluses may need to be administered to maintain the ACT between 200 and 250 seconds. If bivalirudin alone was used as the procedural anticoagulant, the ACT should be verified to be >250 seconds.

Only commercially available bare metal or metallic drug-eluting stents are to be used in this study. Bioresorbable vascular scaffolds, if available during the enrollment period, are not permitted. Following successful PCI/stenting and left ventriculography, if all angiographic

eligibility criteria are met and none of the baseline laboratory or angiographic exclusion criteria apply, the patient may be enrolled.

7.4 SSO_2 Therapy

7.4.1 Arterial Sheath Selection

The coaxial (single arterial stick) approach is strongly recommended for SSO_2 Therapy as prior studies have shown that single femoral artery access, even with a larger sheath, results in less bleeding and fewer vascular complications than bilateral femoral access. When only one arterial site (coaxial access) is used with the DownStream System, an 8F sheath may be used, or a qualified 7F sheath[6]. Contralateral access with a second sheath may be used as an alternative if desired, in which case a smaller 5F introducer sheath in the contralateral femoral artery may be used. Ipsilateral insertion of a second sheath into the same femoral artery is strictly prohibited.

The TherOx SSO_2 delivery catheter requires a qualified 7F or 8F arterial sheath for coaxial setup because of the need for an adequate blood flow path for blood withdrawal between the catheter and sheath. If contralateral access is preferred, a minimum 5F sheath is required to withdraw blood from the second arterial access site.

If a 5-6F radial sheath was used for PCI, a second 5F sheath should be placed in a femoral artery for blood withdrawal.

7.4.2 SSO_2 Therapy Infusion

Note: Refer to the DownStream System Operators Manual (**Appendix C**) for proper setup and operation of the DownStream System.

1. For coaxial (one arterial access site) setup with the SSO_2 delivery catheter: introducer sheath with sidearm must be in place.
2. For dual access site setup, the investigator has the option of inserting a smaller sheath (minimum 5F) in a femoral artery for blood withdrawal (note: ipsilateral dual sheath insertion into the same femoral artery is prohibited).
3. The SSO_2 delivery catheter (i.e., 5F Boston Scientific Impulse® angiographic catheter) is placed in the ostium of the left main coronary artery (LMCA). Select the

[6] The Merit Medical 7F Short Sheath Introducer supports blood withdrawal for SSO_2 Therapy.

appropriate curve shape of the catheter so it seats in the left main as securely and coaxially as possible. After placement, inspect the SSO_2 delivery catheter under fluoroscopic visualization and with a small injection of contrast to ensure that it is seated correctly in the LMCA, and does not restrict blood flow (contrast "blowback" is present, and no pressure damping is seen). Record this injection on cineangiographic film for review in the core laboratory.

4. Ensure that fluoroscopic contrast and infusate agents delivered through the SSO_2 delivery catheter have been flushed with saline prior to priming circuit; these viscous solutions may result in a flow stoppage after connection to the cartridge return line is made.
5. SSO_2 Therapy must be performed in the cardiac catheterization laboratory for the duration of the infusion.
6. The DownStream System and DownStream Cartridge are set up per the Instructions For Use (**Appendix D**). The draw tubing of the DownStream Cartridge is connected to the sidearm of the draw sheath prior to circuit priming.
7. To prime the circuit, the system operator must depress and hold the PRIME button on the DownStream System display keypad. Blood flow is initiated and when the cartridge is fully primed (blood flow is present from the return line), the return tubing of the cartridge is connected to the proximal end of the SSO_2 delivery catheter.
8. The target blood flow rate of the DownStream Cartridge is 100 ml/min and is controlled by the DownStream System.
9. Prior to initiation of SSO_2 Therapy, baseline systemic arterial pO_2 and blood pressure are recorded (reference SSO_2 Therapy Procedure CRF, **Appendix A**). The patient's systemic arterial pO_2 must be greater than or equal to 80 mmHg to proceed with SSO_2 Therapy.
10. When the DownStream System indicates readiness, infusion of SSO_2 solution may now be initiated. The time of initiation of SSO_2 infusion must be noted on the SSO_2 Therapy Procedure CRF.
11. SSO_2 Therapy infusion runs for 60 minutes for each enrolled patient. During this time the patient parameters such as blood pressure and heart rate/rhythm will be obtained at 15-minute intervals and recorded on the SSO_2 Therapy Procedure CRF.

12. At 30 minutes after the infusion has been initiated, the cath lab operator must confirm the position of the SSO_2 delivery catheter with a fluoroscopic (no contrast required) image. Record this position on a brief cineangiographic run for review in the angiographic core laboratory. If the delivery catheter has moved from its initial infusion position or is not moving in concert with the cardiac silhouette with each heartbeat, SSO_2 Therapy must be stopped in order to re-seat the delivery catheter and finish the infusion with a new cartridge.

13. After patients complete the 60-minute SSO_2 Therapy infusion, the user must press "End Procedure". The time of cessation of SSO_2 infusion must be noted on the SSO_2 Therapy Procedure CRF.

14. The delivery catheter is withdrawn from the patient per standard practice. The DownStream Cartridge tubing is disconnected from the sidearm of the arterial sheath and the delivery catheter. The cartridge and the blood contained therein should be discarded per hospital practice (do not return this blood to the patient). The cartridge transducer is retained for shipment to the sponsor.

15. After the SSO_2 Therapy procedure is complete and all components removed the cath lab operator must take a final angiogram according to the procedural guidelines for angiographic imaging provided in **Appendix E**.

7.4.2.1 Device Performance

DownStream System and DownStream Cartridge device usage information, including date and time of SSO_2 Therapy infusion, the number of DownStream Cartridges used, DownStream Cartridge tracking information, and total SSO_2 Therapy infusion time, is recorded on the SSO_2 Therapy Procedure CRF. System and cartridge usage information is also retained in electronic files stored on the DownStream System and will be retrieved by the Sponsor or their authorized representative.

Concerns related to device performance should be reported immediately to the TherOx, Inc. Technical Support function at 1-888-2-THEROX or 1-949-757-1999. This service is available 24-hours a day, 7-days a week.

7.5 Other Procedural Considerations

If an IABP, Impella, or other hemodynamic support device is indicated at any point after initiation of SSO_2 Therapy, prior to the completion of the 60-minute SSO_2 infusion, the SSO_2 procedure must be discontinued. These devices may not be operated simultaneously in this protocol.

7.6 Post Cardiac Catheterization Laboratory (CCL)

7.6.1 In-Hospital Procedures

Following treatment, patients will be sent to the CCU, Step-Down Unit, or Coronary Care Floor at the discretion of the Investigator.

7.6.2 Post-procedure ECG

A 12-lead post-procedure ECG must be obtained at 60 minutes (±30 minutes) after the last angiogram, which is taken after the final SSO_2 discontinuation.

7.6.3 Cardiac Enzymes, Clinical Chemistry, and Hematology

Cardiac enzymes (CK, CK-MB, and Troponin) are drawn at baseline, and at 12 and 24 hours (±2 hours) post-PCI. Clinical chemistry and hematology are obtained at baseline and at 24 hours (±2 hours) post-PCI.

7.6.4 Medications

All medications administered to study subjects must be recorded.

7.6.5 Cardiac MRI Scan

A Cardiac Magnetic Resonance Imaging scan must be performed on day 4 (±1) post-procedure (see **Appendix E** for detailed instructions). If the patient is unable to undergo cardiac MRI during this time window for any reason, a protocol deviation must be noted along with the reason for the inability to perform the scan.

7.6.6 Arterial Sheath Removal and Ambulation

Arterial sheath removal and ambulation are to be conducted per standard hospital care.

7.7 Hospital Discharge

Timing of hospital discharge is at the discretion of the investigator for each individual patient. An appointment for the 30-day follow-up visit should be made for a time agreeable to the patient prior to discharge. This evaluation must be performed at 30 (±7; range 23-37 days) days after index PCI and include the follow-up cardiac MRI scan (see **Appendix E**).

7.7.1 Post Discharge Medications

Post discharge medications must be recorded on the Medications CRF.

7.8 30-Day Clinical Visit Follow-up

A clinical follow-up visit is required at 30 days (±7 days; range 23-37 days) post-procedure and must be completed no later than day 37 post-procedure. If the patient is hospitalized longer than 37 days the follow-up should be completed at discharge. Refer to **Table 1** for details on the assessments to be performed and the information to be collected.

7.9 6-Month and 12-Month Telephone Follow-up

A telephone follow-up call is required at 6 months (±30 days) and 12 months (±30 days) post-procedure. Refer to **Table 1** for details on the assessments to be performed and the information to be collected.

7.10 Medical Economics Data Collection

In conjunction with this clinical trial, an economic study of hospital charges for all patients enrolled in the study will be conducted. The economic study is based on the information contained in UB-04 claim forms that are generated by the hospital billing department after patient discharge to request reimbursement from health insurance plans. The Informed Consent form authorizes us to obtain a copy of this claims information. At the study's conclusion, UB-04 data will be reported in the aggregate form; that is, no individual patient's results will be disclosed when reporting the economic study findings.

The goal of the economic study is to allow the study sponsor, TherOx, to apply to the Center for Medicare and Medicaid Services (CMS) for additional reimbursement for this technology so that once approved by the FDA, there will be adequate payment for this technology.

8 RISKS AND ADVERSE EVENTS

8.1 Risk Analysis

The risk management approach used by TherOx is based upon ISO 14971. The risk analysis for SSO_2 Therapy was developed by a multidisciplinary team within TherOx to assess the potential hazards and causes of hazards that need to be considered in product design, testing, training, and labeling. The risk analysis applies to the design and use of the DownStream System, DownStream Cartridge, and SSO_2 delivery catheter.

The risk analysis focuses on the incremental risk associated with SSO_2 Therapy, as compared to performing PCI alone for acute myocardial infarction ("AMI") patients. SSO_2 Therapy is initiated in the cardiac catheterization laboratory ("CCL") with the AMI patient following revascularization. One healthcare professional (operator) installs the DownStream Cartridge and operates the DownStream System during treatment. A second health care professional (physician) places the delivery catheter and is present when treatment is set-up and initiated. The users are trained to perform a sequence of steps, which are defined in the DownStream System Operators Manual (**Appendix C**). Hazards are identified and evaluated based upon these conditions of use and foreseeable misuse in this setting.

Risk Mitigation

Safety measures have been implemented to mitigate the risk of potential hazards. These safety measures include methods to detect unsafe conditions and a DownStream System Safety Response to isolate the patient from the extracorporeal circuit. When an unsafe condition is detected, the patient is isolated from the DownStream System and the treatment is stopped.

Safety Response

If the DownStream System detects an unsafe condition, the Safety Response isolates the patient from the system and stops treatment. The SSO_2 flow stops, the blood pump stops, and the draw and return tubes are clamped, and the oxygen pressure is vented. The system provides visual and audible notification. After a Safety Response, the cartridge must be replaced to continue treatment. System valves are designed for fail-safe conditions, so the patient is isolated in the event of a power loss.

In order to mitigate the occurrence of Safety Responses during treatment, the system performs tests (software checks) when certain processes are initiated. When the system preps (saline primes) the cartridge, several checks verify functions of the SSO_2 solution production and delivery process. During blood priming of the EC circuit, several checks verify functions of the Safety Response are ready. The system also provides the ability to recover from momentary restrictions in the tube set that would otherwise cause a shutdown. In addition, the Operators Manual (see **Appendix C**) and Instructions for Use (see **Appendix D**) clearly states that this procedure shall be supervised during therapy, allowing timely recovery from detected occlusions. The system in transportable and has battery back-up, but is intended to deliver SSO_2 Therapy when stationary and connected to AC Mains.

The specific mitigations for two important hazards, air emboli and blood loss/hemorrhage, are described below.

Mitigation of Air Emboli

After the blood path is primed, an ultrasonic bubble detector continuously monitors the return side of the blood path for gas emboli. The bubble detector also monitors signal strength, ensuring the return tube is properly loaded in the bubble detector probe. If the cumulative bubble volume reaches 10-microliters during the 60-minute treatment, or the signal strength is out of range, the bubble detector triggers the Safety Response.

Several other design features mitigate the possibility of gas in the blood path. The DownStream Cartridge blood mixing chamber is designed to be a gas trap for bubbles introduced in the draw tubing. Also, the DownStream System has a low-level sensor that verifies safe blood level in the blood mixing chamber. The BMC low-level sensor can trigger the Safety Response.

Mitigation of Blood Loss/Hemorrhage

The blood priming volume of the extracorporeal circuit is approximately 60 ml. A cause of the potential hazard of blood loss is leakage from the extracorporeal circuit. A pressure transducer monitors for either insufficient or excessive pressure that could potentially result in a leak. In addition, a blood mixing chamber high-level sensor will detect if the blood level is too high, which could indicate a blood leak at that location. Either the BMC high level sensor or return pressure transducer can trigger the Safety Response, mitigating the risk of blood loss. In addition, the IFU clearly states that this procedure shall be supervised.

The risk of hemorrhage is present in most interventional procedures, considering that these patients are given anticoagulants. The risk may be slightly greater for SSO_2 Therapy due to the increased time of catheterization and anticoagulation. The IFU identifies potential adverse events, including hemorrhage.

Risk Analysis Summary

The DownStream System Instructions for Use identifies potential adverse events, which include hazards identified by risk analysis and the inherent condition of the patient population post-AMI. These adverse events are listed below in order of severity:

- Death
- Myocardial Rupture
- Acute Myocardial Infarction (AMI)
- Cardiogenic Shock
- Stroke/TIA
- Coronary Artery Occlusion
- Revascularization (CABG or PCI)
- Thrombosis
- Congestive Heart Failure
- Restenosis
- Tamponade
- Abrupt Vessel Closure/Spasm
- Hemorrhage
- Embolism (including air emboli and thromboemboli)
- Aneurysm
- Arteriovenous Fistula/Pseudoaneurysm
- Arrhythmias
- Vascular Damage (dissection, perforation, rupture, or other mechanical injury)
- Blood Loss/Damage
- Pericardial Effusion
- Renal Complications
- Pulmonary Edema
- Respiratory Complications
- Hematoma

- Hemolysis
- Infection
- Allergic Reactions
- Chest Pain/Angina
- Hypertension/Hypotension
- Neck/Back/Groin Pain
- Nausea/Vomiting
- Anxiety/Dizziness

These adverse events are associated with interventional cardiology procedures. SSO_2 Therapy introduces no new or incremental adverse events other than those known to exist within the standard of care (PCI with stenting).

Based upon the extended time of cath lab intervention required for SSO_2 Therapy, the accompanying requirement for anticoagulation throughout the procedure, and the extracorporeal circuit, SSO_2 Therapy may increase the following specific risks:

- Air emboli
- Vascular damage from the placement of an infusion catheter
- Bleeding requiring treatment, particularly at the catheterization site

8.2 Clinical Assessments

8.2.1 Clinical Follow-Up

Clinical follow-up with a cardiac MRI scan and an office visit will occur at 30 days (±7 days; range 23-37 days) or date of discharge, whichever is later. Additional telephone follow-up will occur at 6 months (±30 days) and 12 months (±30 days).

If available, the following data should be collected at the specified time points:

- Clinical events including event description, symptom onset, medical intervention, and resolution.
- AE related data including laboratory test results, ECG, and subsequent repeat coronary angiography results, at the time of the event.
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and SAE bleeding.

- Chronic concomitant medications (selected cardiac list).

8.2.2 Additional Event Driven Visits

Additional event driven visits may occur clinically as warranted. If available, the following data should be collected at these visits:

- Clinical event descriptions. Also, AE related data including laboratory test results, ECG, details and subsequent coronary angiography results.
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and major bleeding complications.
- Chronic concomitant medications (selected cardiac list).

If a patient completes a clinic visit independent of this protocol and outside of the protocol required follow-up time point, this information should be obtained from the patient's source documents. All efforts must be made to obtain follow-up information on study patients that have been treated for adverse events (AEs) in a non-study related health care facility.

8.3 Adverse Events

An adverse event is defined as follows for this study:

Adverse Event: Any undesirable clinical occurrence in a study patient, whether or not it is related to the investigational intervention, is considered an adverse event. Any condition that was recorded as pre-existing is not an AE unless there is a change in the nature, severity or degree of the condition.

During clinical follow-up, the investigator will determine adverse event (AE) occurrences. Collection of adverse events begins after informed consent has been provided and the SSO_2 Therapy procedure begins (defined as SSO_2 delivery catheter insertion into the patient). Adverse events will be reported for all subjects through 12 months post-procedure. The Adverse Event CRF is to be completed for each adverse event experienced by an individual subject. Serious adverse events are also reported on the Serious or Device Related Adverse Event CRF. Selected serious adverse events are further detailed on individual CRFs for greater specificity.

8.4 Unanticipated Adverse Events

All unanticipated adverse events MUST be reported to the study Contract Research Organization (CRO) within 24 hours of knowledge of the event. If an observed adverse event is not associated with any of the categories on the list found in **Section 8.1** Risk Analysis Summary, the event may be unanticipated and must be reported within 24 hours.

An Unanticipated Adverse Device Effect (UADE) is defined as follows for this study:

Unanticipated Adverse Device Effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol, investigator's brochure, labeling, or published literature, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.5 Serious Adverse Events (SAEs)

Serious Adverse Events must be reported to the CRO within 24 hours of occurrence of the event. A serious adverse event is defined as follows for this study:

Serious Adverse Event: An event that is fatal or leads to a serious deterioration in health that:

1. Results in death
2. Is life threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect
6. Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function
7. Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6 Clinical Events Committee (CEC)

During the course of the study, an independent Clinical Events Committee (CEC) will be responsible for the adjudication of clinical events.

The CEC shall consist of three members with the appropriate medical background in cardiology, including at least one interventional cardiologist, and will be appointed by the Sponsor. The CEC must consist of individuals who are impartial, independent of the investigator(s) and who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

Should a CEC member not be able to fulfill their commitment to the committee and the study for any reason, another member will be appointed to replace them according to the qualifications noted above.

The CEC is responsible for adjudicating protocol-defined adverse events. The committee determines whether the reported events meet the established definitions for the adverse events that will be tracked in this study. This process includes a thorough review of the source documents for the event and an independent adjudication of the event according to protocol definitions.

The CEC may or may not agree with conclusions drawn by the investigator from a specific investigational site; in this case, the CEC's conclusion will serve as the final decision for submission to regulatory authorities and for reporting and publication. Furthermore, should the committee members become aware of an event through the review of source documents from the research subjects, they will be able to adjudicate those events even if the site investigator has not reported them.

In the course of reviewing an event, the CEC will determine the following:

- Agreement or disagreement with event as reported by the study investigator
- Adverse event classification
- Relation of adverse event to investigational device
- Need for additional data

Events to be adjudicated for this study include:

- **Disease specific**:
  - Death (cardiac death, vascular death, non-cardiac death; if the cause of death is unknown it will be adjudicated as cardiac death)
  - Revascularization (PCI or CABG): clinically driven, non-clinically driven
  - Recurrent angina or reinfarction (Q-wave MI, Non-Q-wave MI, target vessel related, non-target vessel related)
  - Arrhythmias (2^{nd} and third degree heart block, atrial fibrillation, flutter or supraventricular tachyarrhythmias, non-sustained or sustained ventricular tachycardia or fibrillation)
  - Cerebrovascular accident (including stroke and TIA)
  - Stent thrombosis (ARC definite or probable)
  - New onset heart failure
  - Hospital readmissions (cardiac heart failure related, cardiac non-heart failure related, non-cardiac)
  - Embolism (including air emboli and thromboemboli)
  - All bleeding (TIMI scale and BARC scale) and blood produce transfusions
- **Procedure related:**
  - Vascular complications: access site hematoma, pseudoaneurysm, arteriovenous fistula peripheral ischemia or nerve injury
  - Bleeding complications, including Intracerebral Hemorrhage (ICH), and Hemolysis
  - Need for surgical intervention at the access site
  - Transfusion
  - Infection
- **Device specific:**
  - Dislodgement of the device requiring repositioning
  - Dissection of the LMCA or its branches
  - Thrombosis (including catheter thrombus)
  - Intra-procedural ischemia related to catheter position in LMCA
  - Any clinically-driven discontinuation of SSO_2 Therapy before 60 minutes

The CEC charter is included in **Appendix F** of the Investigational Plan.

8.7 Data Safety Monitoring Board (DSMB)

The DSMB is the primary data and safety advisory board for this study. The DSMB reviews study data, monitors for excessive occurrence of adverse events, and makes recommendations to the study Sponsor regarding safety issues and risks to research participants as well as the continuing validity and scientific merit of the study. The Chairman of the DSMB will notify the Sponsor by way of confidential memo regarding modification of the protocol, continuation/discontinuation of enrollment and/or temporary suspension of enrollment in the trial.

DSMB Responsibilities

The DSMB is an independent board formed to conduct reviews of safety data in accordance with the Protocol or other established procedures. The DSMB is comprised of three interventional cardiologists and one biostatistician. At periodic intervals during the course of the study, the DSMB shall:

- Evaluate all events with regard to interim results of the study for evidence of undue risk to research subjects or safety concerns. Establish criteria and assess possible early termination of the study because of the ascertainment of study objectives, or safety concerns.
- Evaluate study progress with projections of recruitment and timelines for study milestones. This also includes evaluation of any significant trends of performance that may influence the safety or conduct of the study.
- Advise the sponsor with regard to potential problem areas within the protocol regarding procedures, definitions, or endpoints, allowing timely notification of the FDA or other regulatory authority for protocol revisions.
- If applicable and accordance with this charter and the protocol, make recommendations regarding adapting the study design.

The IC-HOT DSMB charter is included in **Appendix G** of this Investigational Plan.

9 REPORTING OF TRIAL DATA

9.1 Overview

The intent of this study is to collect confirmatory safety and effectiveness data on the intracoronary perfusion of hyperoxemic blood into the left main coronary artery in patients with anterior acute myocardial infarction with successful PCI/stenting completed within 6 hours of symptom onset. 100 patients will be enrolled in this trial. Procedural success, cardiac MRI outcome measures, and patient safety outcomes will be analyzed at the conclusion of this trial. Patient data will be reported using categorical presentation and descriptive statistics where appropriate, for all treated patients. Study success will be based upon achieving an acceptable observed rate for Major Adverse Cardiac Events as defined in the Statistical Analysis Plan (**Appendix H**).

A Clinical Summary Report will be prepared at the conclusion of 30-day follow-up reporting and data validation activity for all procedural, effectiveness, and safety data. A supplemental report will be prepared after receiving follow-up survey and event data for patients 12 months post-procedure.

All enrolled subjects will be reported on for this study. All available data, regardless of whether data are derived within specified time windows, will be included in the analysis. Patients who do not complete the entire course of treatment with SSO_2 Therapy will be included.

9.2 Endpoints and Statistical Analysis Plan

Criteria for Study Success

Safety

The primary endpoint of the IC-HOT trial to achieve study success is the 30-day rate of Net Adverse Clinical Events (NACE), compared against an objective performance goal (OPG) based from the rate of an appropriate historical control population from the INFUSE-AMI trial. For safety, the composite NACE endpoint includes a hierarchical total of the following events:

- Death (all-cause)
- Reinfarction
- Target Vessel Revascularization (clinically driven)
- TIMI major or minor bleeding
- New onset severe heart failure or rehospitalization for heart failure

- Stent thrombosis (ARC definite or probable)

This composite endpoint includes safety categories that are of significance in contemporary AMI studies and includes the specific risks that were identified as areas of concern by FDA with regards to SSO_2 Therapy. It should be noted that an observed event of myocardial rupture would be included in the Death category. The IC-HOT study will use well-established clinical event definitions for the component NACE event categories as set forth in the Statistical Analysis Plan (**Appendix H**).

Safety Endpoint: Objective Performance Goal

As a benchmark with a similar anterior wall AMI population, the INFUSE-AMI study yielded a 10.7% 30 day NACE event rate for control subjects receiving no aspiration and no intracoronary abciximab (n =112 control subjects data analysis performed for TherOx by the INFUSE-AMI Principal Investigator Gregg Stone, MD, and the Biostatistics Department at the Cardiovascular Research Foundation). In INFUSE-AMI all of the components of the NACE endpoint were adjudicated using specific definitions, except TIMI bleeding. The same definitions will be used for the present study (except that TIMI bleeding will be adjudicated). The INFUSE-AMI study reflects current cath lab practice, and therefore the use of a composite endpoint benchmark from the control group's observed event rates is an appropriate comparator for the present prospective study.

The proposed threshold for success of the prospective trial is that the observed 30-day NACE rate in the SSO_2 group will be no greater than the 30-day MACE rate observed in the INFUSE-AMI control group, 10.7%.

Furthermore, the specific 30-day NACE event categories of death, stent thrombosis, myocardial rupture, and SAE bleeding will be examined in terms of individual events. The numbers provided in **Table 2** below represent the FDA-recommended 30-day event rate guidelines for these individual safety endpoints. FDA will conduct clinical review of event counts, severity, and patient circumstances. Events will be reviewed and evaluated in the context of individual patient circumstances, relationship to the investigational device, and overall patient status in an overall determination of device safety.

Table 2. FDA Guidelines for Acceptable Adverse Event Rates

30-Day MACE Event	IC-HOT Trial FDA Guideline
Death	≤3.0%
Stent Thrombosis (definite)	≤3.0%
Myocardial Rupture	≤1.0%
TIMI Major and Minor Bleeding	≤3.0%

Weighing the frequency, severity, and causal factors of the observed adverse events in this study, the safety profile of SSO_2 Therapy will be measured against the observed effectiveness results in an overall evaluation of the risk-benefit profile.

To further evaluate the safety profile of SSO_2 Therapy, the treatment cohort will be followed throughout the post-approval data collection period (12 months), however the primary endpoint will be at 30 days.

For the purpose of comparing the new, modified NACE endpoint for this confirmatory study with previous studies of SSO_2 Therapy, the data from the AMIHOT II study were re-examined using the new, modified NACE endpoint definitions. In total, 13.1% (29/222) of SSO_2 patients experienced 30-day NACE. Therefore, the IC-HOT clinical trial NACE endpoint OPG of 10.7% is more conservative than the AMIHOT II results.

In addition to 30-day NACE, the following data will also be reported and summarized:

- Additional bleeding events through 30 days, categorized by the BARC criteria
- All other 30-day adverse events
- Individual NACE component event rates through 1 year

Additional Study Endpoints

Effectiveness

Effectiveness is a secondary endpoint for this study. Effectiveness data from dual time point cardiac MRI scans at day 4 and day 30 will be collected and reported, using 30-day median infarct size (% left ventricle (LV) necrosis) as the primary effectiveness outcome

measure. 30-day cardiac MRI infarct size is often used for final infarct size measurement in clinical studies[7,8]. Final infarct size at days 4 and 30 will be analyzed and compared to the a matched set of patients from the INFUSE-AMI trial, a study of very similar entry criteria (STEMI with proximal or mid LAD treatment) in which infarct size was assessed by cardiac MRI at the same core laboratory at the same time frame (both 4 and 30 days). Matching (1:1) will be performed on the following parameters which are known affect infarct size: Time from symptom onset to first device; baseline and post PCI TIMI flow (core laboratory); proximal vs. only mid LAD treatment; and angiographic collateral flow (if possible). In addition, since intracoronary abciximab was associated with reduced infarct size in INFUSE-AMI, these patients will be excluded from the match if possible. Attempts will be made to match all 100 SSO_2 patients. However, as the 4-day MRI was pre-specified in INFUSE-AMI in only half the patients, this may not be possible for the early time point. In this case a 2:1 match will be performed.

As an additional effectiveness analysis, the final infarct size at 30 days from the present study will be compared to the final infarct size from the SSO_2 Therapy group of the AMIHOT II study. The AMIHOT II study utilized 14-day Tc-99m sestamibi SPECT imaging for final infarct size measurement, which was the gold standard at that time. SPECT has been replaced in favor of cardiac MRI due to several reasons, including the greater ease of use and convenient collection of myocardial functional and structural data from the scans. Both techniques measure final infarct size and are validated against histological measurements[9,10,11].

The effectiveness comparisons are not powered, and while statistical comparisons will be reported (as described below); they are for descriptive purposes only.

Study Population for Analysis

[7] Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 2012 May 2;307(17):1817-26.

[8] Carlsson M, Arheden H, Higgins CB, et al. Magnetic resoncance imaging as a potential gold standard for infarct quantification. *J Electrocardiol* 2008;41(6):614-20.

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[11] Hsu LY, Natanzon A, Kellman P, et al. Quantitative myocardial infarction on delayed enhancement MRI. Part I: Animal validation of an automated feature analysis and combined thresholding infarct sizing algorithm. J Magn Reson Imaging 2006;23(3):298-308.

Patients who meet the study's selection criteria and provide informed consent will be consecutively enrolled into this multi-center clinical trial. An all treated subjects population will be used as the primary analysis population for safety data. The all treated subjects population is defined as all patients enrolled into the trial. Study enrollment occurs when the study device is introduced into the patient (*i.e.*, the SSO_2 delivery catheter). The all treated subjects analyses will include patients who die, are lost to follow up, and patients with protocol deviations. All available data, regardless of whether data are derived within specified time windows, will be included in the analysis. For the all treated subjects analysis, patients who do not complete the entire course of treatment with SSO_2 Therapy will be included.

9.3 Medical Economics Data Analysis

UB-04 claim forms will be requested from the hospital billing department at least 30 days after patient discharge. At the study's conclusion, UB-04 data will be reported in the aggregate form; that is, no individual patient's results will be disclosed when reporting the economic study findings.

10 STUDY ADMINISTRATION

10.1 Roles of Sponsor and CRO

As the study sponsor, TherOx, Inc. has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration, Good Clinical Practice Guidelines, and TherOx standard operating procedures.

In this study, TherOx, Inc. will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants and the CRO. TherOx, Inc., through its CRO and the study's clinical monitors, will adhere to the necessary regulatory requirements for this investigational study.

10.2 Investigator Responsibilities

The investigator is responsible for ensuring the clinical study is conducted in accordance with the signed Investigator Agreement. Prior to study initiation, the investigator will forward the following essential documentation to TherOx, Inc. or their designee:

1. A signed and dated Investigator Agreement and Protocol Signature Page,
2. A signed and dated Hospital Trial Agreement,
3. Current medical license and Curriculum Vitae (CV) signed and dated within the 12 months prior to initiation for each investigator participating in the study,
4. A completed Financial Disclosure form for each investigator participating in the study per the requirements of 21 CFR part 54,
5. Laboratory certification or proficiency ratings and normal ranges for the determinations described by the protocol,
6. A copy of the laboratory director's license and CV signed and dated within the last 12 months prior to study initiation,
7. A copy of the formal written notification of approval of the protocol and consent form, to the investigator from the IRB,
8. A list of institutional review board/ethics committee members and their respective title, occupation, and institutional affiliations, or provide a general assurances number for the IRB,
9. A copy of the IRB approved Informed Consent form,
10. Disclosure of any potentially conflicting ongoing investigational study the investigator may be participating in,
11. If applicable, an explanation of the circumstances that led to the termination of any prior study involvement.

10.3 Direct Access to Source Data / Documents

The investigator, institution or designee will permit direct access to source data/documents in order for study-related monitoring, audits, IRB review, and regulatory inspections to be performed.

Consenting patients are agreeing to allow TherOx, Inc. or designee access and copying rights to pertinent information in their medical records relevant to study participation. As part of the informed consent, the investigator or designee will obtain permission for regulatory authorities to review any records identifying subjects in this study. TherOx, Inc. will not otherwise release any personal information.

10.4 Institutional Review Board (IRB)

The primary investigator at each site must submit the study protocol to the IRB and obtain the Committee's written approval before participating in this study. The investigator is also

responsible for fulfilling any conditions or approval imposed by the IRB, such as regular reporting, study timing, etc. The primary investigator will provide TherOx, Inc. with copies of these approvals and reports.

10.5 Consent Material

Part of the IRB approval must include approval of Informed Consent documents specific to the study. The investigator or other qualified personnel must administer this approved Informed Consent document to each prospective study patient, and obtain the patients signature on the document, prior to enrollment in the study. The study center, to meet specific site requirements, may modify the example Informed Consent; however, the Informed Consent must contain all of the elements of Informed Consent as outlined in CFR 21 Part 50.25. The primary investigator will provide the sponsor with a copy of the approved Informed Consent from his/her site.

10.6 Sponsor Responsibilities

No study site may receive shipment of all of the DownStream System components until TherOx or their designee receives the following documents:

- Signed Protocol Acceptance page
- Written IRB approval for conduct of the study
- Signed Investigators Agreement(s)
- Investigators', Co-Investigators' and Laboratory Directors current curriculum vitae (CV) and current license
- License (if applicable) and CV for study coordinators
- List of IRB members and IRB contact information
- Copy of all Laboratory Normal Values
- Financial disclosures for all participating physicians
- Confirmation by MRI Core Laboratory of site validation for this measure

10.6.1 Study Specific Duties

TherOx is the manufacturer of the DownStream System and the Sponsor of this study. TherOx has the overall responsibility for the study and will:

- Select qualified Principal Investigators, clinical investigators and study sites, as well as consultants (e.g., CRO), who will participate in the study.
- Communicate all regulatory standards per federal regulations for clinical study sites, core laboratories, and other participants, and perform regular site monitoring to assure compliance with them.
- Provide appropriate clinical training to investigators and study staff prior to site enrollment, and follow-up training as necessary.
- Ensure proper device usage, uniform data collection and protocol compliance, the Sponsor or their designee will present a formal training session to study site personnel which will review the instructions for use of the device, the Investigational Plan, techniques for identification of eligible patients, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study coordinators and regulatory requirements. Detailed telephone and/or fax or email feedback regarding completion of forms will be provided by the Sponsor or designee, and through regular site monitoring.
- Provide DownStream System and appropriate components to participating study sites, in quantities sufficient to support study activities, per agreement executed with the study sites.
- Coordinate and host conference calls between the contract research organization ("CRO"), the Core Laboratories or any clinical site, as necessary to resolve any problems concerning the protocol and/or data collection. Every effort will be made to assure compliance with the protocol.
- Provide financial support to each study site, the CRO, and the Core Laboratories per individual contracts.
- Perform or contract for site monitoring of clinical data at clinical study sites, Core Laboratories, and the CRO.
- Retain ownership of all clinical data generated in this study. TherOx will exercise no veto over publication of study results in the medical literature, but will retain the right to review any such submission, presentation, or publication for confidential information.

10.7 Regulatory Responsibilities

10.7.1 Maintaining Records

TherOx and/or its designee will maintain correspondence, data, adverse device events, and other records related to the clinical trial. TherOx will maintain records related to the shipment of devices and complaints. TherOx and/or its designee will maintain communication/correspondence files for each participating clinical site.

10.7.2 Submitting Reports

TherOx will submit required FDA reports for this investigational study.

10.7.3 Device Accountability

TherOx is responsible for ensuring that the investigational site maintains accurate, up to date inventory logs for all study devices supplied by TherOx, Inc. This includes the following: subject number, date study device used, quantity and date received, quantity used, quantity returned, and quantity disposed. All study devices received, used, and returned by the investigator will be inventoried and accounted for by TherOx throughout the study. All study devices must be stored in a restricted area with limited access.

10.7.4 Site Initiation

A pre-investigational meeting will be conducted with each potential study site in order to orient the prospective investigator and staff to the investigational devices, protocol, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for patient enrollment, patient selection, Informed Consent, required clinical data and record keeping. The prospective study site will be evaluated to ensure that it has an adequate patient population and support staff. A regulatory binder will be left with the site at the completion of site initiation.

Site initiation monitoring activities will include but not be limited to review of requirements for the following: protocol and data forms, ethics committee approvals, obtaining and documenting informed consent, device accountability and storage, medical records, adverse event reporting procedures, discussion of frequency of monitoring visits, reports and document retention and applicable FDA regulations governing investigational studies (21 CFR Parts 50, 54, 56, 812).

10.8 Monitor Responsibilities

TherOx personnel or its designees will perform study monitoring. The monitoring process begins with the site initiation activities and continues, in general, until the study close-out visit. While study monitoring normally involves a personal visit to the investigational site, some monitoring activities can be carried out by mail, email, or telephone. Each site will be visited regularly to ensure that the study is conducted in full compliance with all applicable regulations and study protocol.

10.8.1 Obligations / Qualifications of Study Monitors

Qualified study monitors will oversee the progress of the clinical investigation in accordance with 21 CFR Part 52.29. Monitoring procedures and monitor qualifications (i.e., curriculum vitae, training) will be retained by the CRO. A monitoring log will be maintained at each investigational site to document the monitor's presence and be signed and dated by both the monitor as well as a designated investigational site representative.

10.8.2 Periodic Monitoring Visit Activities

TherOx or their designee is responsible for assuring throughout the clinical investigation through periodic monitoring visits and personal contact that the investigator's obligations, as set forth in applicable regulations, are being fulfilled and that the facilities used in the clinical investigation continue to be acceptable.

Periodic monitoring visit activities will include but not be limited to the following: patient documentation, data form monitoring including comparison and compatibility with individual subject records for accuracy and completeness, protocol and informed consent compliance and monitoring, investigational device accountability, adverse event reporting and documentation, and site file maintenance check.

10.8.3 Study Close-Out Activities

When the study has been completed or terminated, the Monitor should assure that all site closeout activities have been addressed. These activities are documented in more detail in the clinical procedure for study close out.

10.8.4 Documentation of Monitoring Visits and Communications

The monitor will complete a written report for each site visit documenting the visit date, site personnel meeting, activities undertaken and a record of the findings, conclusions, and actions undertaken or recommended to correct deficiencies. Accordingly, monitoring activities and communications undertaken via email, telephone, electronic mail, and/or meetings should be documented in writing as well. All reports shall be maintained in the study files of the sponsor.

10.9 Contract Research Organization Responsibilities

The CRO for the IC-HOT clinical study is the Experien Group. The CRO will perform the below noted activities:

1. Site Initiation (jointly with TherOx)
2. Clinical Monitoring
3. Data base development
4. Data review
5. Data query and data clarification resolution
6. Adverse Event coding
7. CEC coordination
8. Database verification and validation
9. Database back-up, storage and transfer
10. Data analyses (performed in conjunction with the Cardiovascular Research Foundation)
11. Entry of UB-04 claims data into the database, including verification, validation, back-up, storage, and transfer.

10.10 Records and Reports

10.10.1 Required Data

All required clinical data for this study will be collected on standardized Case Report Forms (CRFs). A set of draft CRFs can be found in **Appendix A.** Source and other administrative records will be maintained for a minimum of two (2) years after the latter of either the completion of the investigational trial or the date the device receives FDA approval for the U.S. market release.

Investigational site records may not be discarded until the center receives notification by TherOx, Inc. In addition, TherOx, Inc. should be contacted if the investigator plans to leave the investigational site so that arrangements can be made for the transfer of records.

10.10.2 Data Submission

All data MUST be sent to the CRO, Experien Group, according to the following schedule:

Table 3. Data Submission Schedule

Form	Submission Time
Notification Form	Within 24 Hours of Procedure
Serious Adverse Event or Unanticipated Adverse Event CRFs	Within 24 Hours of Knowledge
Repeat Revascularization or Protocol Deviation CRFs	Within 14 Days
All other CRFs	Within 14 Days

Note: All Serious Adverse Events and Unanticipated Adverse Events must be reported to the CRO within 24 hours.

All clinical sites will be audited periodically by sponsor personnel or a designee for protocol adherence, accuracy of CRF completion and compliance to applicable regulations.

10.10.3 Investigator Reports

The investigator for each study center is responsible for the generation of the following reports according to the schedule of **Table 4**.

Table 4. Reports Required from Clinical Investigators

Type of Report	Prepared by Investigator For:	Time Constraints of Notification
Patient death during investigation	TherOx/CRO, IRB	Verbal within 24-hours followed by written report within 48-hours.
Unanticipated adverse event	TherOx/CRO, IRB	If serious or life threatening, within 24-hrs by facsimile, email or phone, followed by written copy and documentation of event within 5 working days.
Report of patient enrollment	TherOx/CRO	ASAP
Patient withdrawal	TherOx/CRO	Facsimile within 5 working days of withdrawal
Withdrawal of IRB approval	TherOx/CRO	Immediately by telephone followed by a copy of the notification within 5 working days.
Annual progress report	TherOx	Submitted annually.
Investigational Plan Deviations	TherOx/CRO	Within 5 working days
Informed Consent not obtained	TherOx/CRO, IRB	Within 5 working days
Final summary report	TherOx/CRO, IRB	Within 5 working days

10.11 Investigational Site Termination

TherOx reserves the right to terminate an Investigational Site for any of the following reasons:

1. Failure to secure Informed Consent from a patient or legal guardian representative prior to enrolling the patient into this study.
2. Repeated protocol violations.
3. Repeated failure to complete case report forms on a timely basis.
4. Repeated failure to collect and provide source documentation.
5. Failure to report adverse events on a timely basis.
6. Failure to maintain adequate records for product inventory.
7. Failure to maintain expected enrollment rates over a period of two months.

10.12 Study Committees

10.12.1 Executive Committee

The Executive Committee will review and approve the final trial design and protocol issued to the clinical sites. This committee is responsible for reviewing the final trial results and determining the methods of presentation and publication. The Executive Committee will also have discretion for stopping or otherwise modifying the trial based on recommendations from the IPA.

The Executive Committee for the IC-HOT clinical study includes:

Gregg W. Stone, MD	Professor of Medicine, Columbia University, Principal Investigator and Study Chair
Simon R Dixon, MD	Chair of Cardiovascular Medicine, Oakland University, William Beaumont School of Medicine
D. Chris Metzger, MD	Director of Cardiac and Peripheral Labs, Wellmont CVA Heart Institute
Kevin T. Larkin	President and CEO, TherOx, Inc.
Jeffrey L. Creech, PhD	Director, Regulatory and Research Programs, TherOx, Inc.