WaveCRESST
Wave Crossover ECP Study for Simplified Therapy

Unique Protocol Identification Number:	RA-C01
National Clinical Trial (NCT) Identified Number:	NCT06571370
Sponsor:	Pression, LLC 190 W. Lincoln Hwy Coatesville, PA 19320
Funded By:	Sponsor
Version Number:	2.0
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Table of Contents

SPONSOR APPROVAL PAGE

Version	Summary of Revision Change and Rationale	Sponsor Authorized Signature
1	N/A – Initial Version	[Signature on File] Adam Salamon, CEO
2	Inclusion and Exclusion Criteria: • Subjects that are unable to lie on their backs for long periods of time may experience discomfort. (Inclusion added) • The goal of this study is to enroll subjects with mild to moderate disease; therefore the age minimum has been reduced to 35, as long as they do meet all other eligibility requirements. (Inclusion expanded) • In Version 1, many subjects on anticoagulant use were excluded. Newer novel oral anticoagulants target different proteins as opposed to warfarin, and act for a shorter period of time reducing the risk of bleeds. Therefore, the exclusion was clarified to only exclude those on warfarin, or those with a PT-INR >2.5 or those who have and need routine INR or PTT testing. (Exclusion clarification) Analysis Methods: • The analysis methods for the predicate and investigational devices have been adjusted to employ the same steps to process and analyze the respective collected PPG data • In Version 1, human-in-the-loop analysis was employed for the predicate device which required subjective placement of points. Incorporation of the same analysis steps as the investigational device removes any potential human bias in the analysis and instead employs a consistent, fixed algorithmic analysis	Adam Salamon, CEO

INVESTIGATOR STATMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH E6(R2)), United States (US) Code of Federal Regulations (CFR) applicable to medical device clinical studies (21 CFR Part 50, 21 CFR Part 56, the abbreviated IDE requirements of 21 CFR Part 812), and ISO 14155:2020, *Clinical investigation of medical devices for human subjects – Good clinical practice*.

I agree, as an Investigator conducting this study, to the following:

- The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.
- To assume responsibility for the proper conduct of the study at this site.
- Not to implement any deviations from or changes to this protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to the participants or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with, Good Clinical Practice and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational device and that they are qualified to perform their study-related duties and functions, as described in this protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the Qualified Investigator's ownership interest in the Sponsor or the study device and more generally about his/her financial ties with the Sponsor. The Sponsor will obtain and disclose any relevant information in this regard solely for the purpose of complying with regulatory requirements. Hence,
    - I Agree to supply the Sponsor with all information regarding ownership interest and financial ties with the Sponsor (including those of my spouse and dependent children);
    - Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study; and
    - Agree that the Sponsor may disclose this information about such ownership interests and financial ties to regulatory authorities.

Printed Name of Investigator:	
Site Name/Number:	
Site Address:	
Signature:	

1 PROTOCOL SUMMARY

1.1 SYNOPSIS (BRIEF)

Title:	Wave Crossover ECP Study for Simplified Therapy
Short Title:	WaveCRESST
Sponsor:	Pression, LLC
Investigational Device Type:	External Counter-Pulsation (ECP)
Investigational Device Name:	Pression Wave PRO External Counter-pulsation System
Control Predicate Device:	Applied Cardiac Systems (ACS) NCP-2 External Counter-Pulsation System
Intended Use/Indication(s) for Use:	The Pression Wave PRO External Counter-Pulsation System is indicated for the treatment of chronic stable angina (CSA) that is refractory to optimal anti-anginal medical therapy and without options for revascularization. In addition, it is intended for use in healthy patients to provide improvement in vasodilation, increased VO2, and increased blood flow. It is intended for use under the oversight of a healthcare professional.
Device Description (Brief):	The Pression Wave PRO External Counter-Pulsation System applies compression to the calves, timed to ventricular diastole, with the aim of increasing blood flow towards the coronary arteries when the heart is relaxed, thereby increasing cardiac perfusion.

Clinical Background (Brief):	• Ten human volunteer studies were conducted with the predecessor technology to the Wave PRO System that support the safety and effectiveness of the Wave device. A combined total of 150 healthy volunteers ranging from 18-85 years of age were studied. In all previous studies, the primary effectiveness endpoints were related to increasing athletic performance.
	  • There were no reported adverse events in any of the studies.
	  • Furthermore, the studies identified that patients found the pressure applied to the calves of up to 100 mmHg comfortable. Recent research on the Wave PRO System found that individuals easily tolerated pressure up to 300 mmHg.
	
	• The most recent volunteer pilot study for the Wave PRO System itself involved seven age-appropriate participants in a head-to-head comparison with the ACS NCP-2 (predicate ECP device). The Wave PRO device produced the intended hemodynamic effects with no adverse events.

Purpose of Study:	The purpose of this study is to demonstrate substantial equivalence between Pression's Wave PRO System and a commercially available predicate ECP device to support a U.S. 510(k) Premarket Notification for the Wave PRO System.

Study Objectives:	The study objective is to demonstrate substantial equivalence (non-inferiority) of the hemodynamic effect between the Wave PRO System and the predicate ECP device (ACS NCP-2) as measured by the diastolic augmentation (DA) ratio and systolic unloading.
Study Design:	Participants will receive compressions from both ECP systems, one system at a time, in random order. Diastolic augmentation ratio will be evaluated for each participant on each test ECP system. Participants will be aged 35+, with a history of mild to moderate coronary artery disease, serve as their own control, and meet the Inclusion Criteria and none of the Exclusion Criteria. Total participant time is approximately 2.5 – 3 hours. Data to be collected includes pulse photoplethysmography (PPG) and vital sign information. Demographic data and a device-related questionnaire will be collected. Data Analysis will include calculating the average DA ratio for each ECP system from the pulse waveforms collected, for each participant. Systolic unloading level will be recorded for Wave PRO.
Number of Participants:	The required sample size is 44 participants with paired DA ratio data. Allowing up to 12% attrition, approximately 50 participants will be randomized to the ECP device order.
Number and Location of Investigational Sites:	One study site in the United States.
Expected Study Duration:	Recruitment: 6 Weeks Participant Follow-up: Phone call 1 day after the ECP session Total Study Duration: 10 Weeks
Randomization:	The order in which the participant will receive the two ECP sessions will be randomized.
Safety Endpoint 1:	Occurrence of device-related Serious Adverse Events (SAEs).
Safety Endpoint 2:	Rate of device-related Adverse Events (AEs). Follow up questionnaire to address bruising, abrasion, soreness.
Primary Performance and/or Effectiveness Endpoint:	The average DA ratio for each ECP session, calculated from the eighth minute of compressions for each participant.
Secondary Performance and/or Effectiveness Endpoint(s):	• The level of systolic unloading for the Wave PRO based on the systolic peaks during compressions compared to baseline of the PPG data, captured using the independent data acquisition system. • Number of participants that complete 10 mins of each of the ECP devices (Wave PRO and predicate ECP device) • Participant comfort level with the Wave PRO and predicate ECP device, assessed at the conclusion of each ECP session

	• Time to set up a participant (i.e., sleeved up and sensors attached) and ready to start treatment • Participant preference for one of the two ECP systems (assuming 35 hours for a full course of ECP)
Key Inclusion Criteria:	○ Age 35 years or greater ○ History of mild to moderate coronary artery disease (CAD) ○ Able to ambulate without assistance ○ Able to lay down (approximately 5 degree angle) for the duration of the protocol required procedures ○ Able and willing to give informed consent ○ Able and willing to participate in the clinical study and complete all questionnaires provided
Key Exclusion Criteria:	○ Unstable angina within prior 3 months ○ Canadian Cardiovascular Society (CCS) Class III or IV Angina ○ Moderate to severe peripheral arterial disease (PAD) ○ Myocardial infarction in the past 3 months ○ Coronary artery bypass grafting (CABG) in the past 3 months ○ Any major surgery within the past 3 months ○ Decompensated heart failure ○ Cardiac catheterization or arterial femoral puncture in the past 2 weeks ○ Presence of mechanical circulatory support (MCS) device ○ Pacemaker or other implantable pulse generating device ○ Valve disease, including aortic insufficiency ○ Abdominal or thoracic aortic dissection or aortic/cerebral aneurysms requiring clinical intervention ○ Severe pulmonary disease ○ Bleeding diathesis ○ Patients undergoing warfarin anti-coagulation therapy, or with PT-INR > 2.5, or who have routine INR or prothrombin time tests ○ Active thrombophlebitis ○ Uncontrolled hypertension (greater than 180/110 mmHg) ○ Baseline heart rate >120 BPM or <40 BPM ○ Arrhythmia and/or abnormal heart rhythm ○ Major hand injuries or amputation that would interfere with finger PPG ○ Unhealed wounds/fractures below the waist or lower limb amputation, major lower body musculoskeletal injuries ○ Lower body vascular stents (arterial/venous) ○ Currently undergoing ECP treatment ○ Pregnancy ○ Currently participating in any other clinical study of an investigational device or drug where treatment has not yet been completed ○ Any medical condition that, in the opinion of the principal investigator (PI), would present undue risk to the participant

Key Data to be Collected:	**Baseline Data:** • Demographics: age, sex, race, ethnicity • Relevant medical history and vital statistics **Hemodynamic Measurements During ECP:** • PPG: Flow and heart rate • EKG (aka. ECG): Heart rhythm **Follow-up and Safety:** • Participant Survey • Safety/AE Assessment
Statistical Analysis:	Assuming a true difference in DA Ratio of 0 with standard deviation of 0.30 for Wave PRO – predicate ECP, a sample size of 44 participants is adequately powered with at least 90% power with a 1-sided alpha of 0.025 to test non-inferiority of Wave PRO vs predicate with a margin of –0.15. Factoring in 12% attrition, approximately 50 participants will be randomized. Primary effectiveness: An analysis of variance (ANOVA) model for crossover design will be performed and the pairwise difference between two treatments DA ratios (Wave PRO – predicate ECP) in the treatment least square mean and its 95% CI will be constructed. If the lower bound of this 95% confidence interval is greater than -0.15, then the null hypothesis will be rejected, concluding that Wave PRO is not inferior to the predicate ECP. A *p*-value will be constructed using the LS means parameter estimates and standard error to test the hypothesis. Descriptive statistics will be used to summarize all other secondary endpoints.

1.2 SCHEDULE OF ACTIVITIES (SOA)

Study Assessment/Procedure Time Frame, Days (Window)	**Pre-Screen (-14 to 0)**	**Baseline Procedure (0)**	**Follow-Up (+1 to +3)**
Phone Screen/Eligibility Determination[1]	X	X	
Participant Orientation Material	X	X	
Informed Consent		X	
Eligibility Review		X	
Data Collection (Medical History, Medications, Etc.)	X	X	
Presenting Vitals and Limited Physical Exam		X	
Pression Wave PRO Procedure[2] and associated Data Collection		X	
ACS NCP-2 Procedure[2] and associated Data Collection		X	
Participant Questionnaire		X	X
Safety Assessment		X	X
Phone Call			X
Study Exit			X

[1] Phone screen to assess potential eligibility may be performed with IRB approved phone script; Eligibility to be confirmed at the time of Baseline Procedure Visit.

[2] To be performed in random order.

2 INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to demonstrate substantial equivalence between Pression's Wave PRO External Counter-pulsation (ECP) System and a commercially available predicate ECP device to support a U.S. 510(k) Premarket Notification for the Wave PRO System.

Existing ECP systems are based on technology originating from the 1980s. As a result, current ECP systems are large, heavy, loud, and require constant input from a dedicated clinical operator. Pression's Wave PRO system is significantly lighter, easily moved and incorporates automation features that support accurate treatment delivery in terms of pneumatic inflation and deflation, without the need for a dedicated operator.

In accordance with prior FDA feedback, the study objective is to demonstrate substantial equivalence (non-inferiority) of the hemodynamic effect between the Wave PRO System and the predicate ECP device as measured by the diastolic augmentation (DA) ratio and secondary endpoints, including levels of systolic unloading.

2.2 BACKGROUND

External counter-pulsation (ECP) is a non-invasive circulatory enhancement treatment currently cleared for Chronic Stable Angina (CSA). Per FDA's 2013 re-classification of ECP devices, ECP is classified as "Class II (special controls) when the device is intended for the treatment of chronic stable angina that is refractory to optimal antianginal medical therapy and without options for revascularization." ECP enhances circulation by applying compressions to the lower limbs timed to the cardiac cycle.

Current ECP systems are large, loud, expensive, are only accessible in clinics, and must be operated by dedicated staff. Compressions in commercially available ECP systems are applied to the entire leg and buttocks and are timed to the patient's EKG. Treatment effectiveness is measured using a pulse photoplethysmography (PPG) finger sensor. A typical treatment course is a 1-hour session in a dedicated clinical facility five times per week for seven weeks (35 total sessions).

The Wave PRO ECP system consists of calf-worn sleeves which contain five pneumatically-inflated bladders that peristaltically compress the calf muscles distally to proximally towards the heart. This compression generates retrograde arterial flow back to the heart, thus augmenting coronary flow during ventricular diastole. Unlike existing systems, Pression's technology uses PPG for both detection and to measure treatment effectiveness, enabling direct hemodynamic feedback of the treatment.

Prior in-house testing data collected using the Wave PRO system demonstrated that Pression's underlying compression technology and algorithm worked in synchrony with the cardiac cycle to

enhance early-diastolic velocities, measured by ultrasonography at the abdominal aorta. This translates to improved perfusion of the coronary arteries during ventricular diastole. Prior studies related to athletic performance and recovery (combined total of 150 healthy participants) using the predecessor technology to the Wave PRO demonstrated that compressions increased retrograde arterial flow, mean arterial pressure and cardiac output, arterial blood flow to the heart and brain, and vascular conductance with no reported adverse events in any of the studies.

In accordance with ECP literature and available instructions for use, this study will measure the Diastolic Augmentation (DA) ratio, also referred to as Diastolic/Systolic (D/S) ratio and Effectiveness Ratio (ER), which noninvasively characterizes the hemodynamic effect and thus the clinical effectiveness of ECP treatment. DA ratio is a unitless measure which is “calculated as the ratio of the peak diastolic amplitude divided by the peak systolic amplitude” [1]. In a typical, non-augmented, cardiac cycle, the diastolic peak is seen as a small increase in the arterial waveform just after the aortic valve closes (dicrotic notch). With augmentation, the peak diastolic amplitude is distinctly elevated and may reach a significant proportion of the peak systolic amplitude or in some cases exceed it. “In general, [ECP] therapists attempt to obtain the maximum DA [ratio] obtainable by finger [PPG]” [2].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Pression completed a hazard analysis/risk assessment through design failure modes and effects analysis (DFMEA), classifying risk based on severity of harm and anticipated occurrence with the Wave PRO ECP system, in accordance with ISO 14971. As Pression has mitigated almost all risks of the Wave PRO device, only the residual clinical risks are discussed here.

The risk analysis identifies that the participant may experience minor abrasions, bruising and/or calf muscle soreness/tenderness from the pressure application during compression. Both abrasions and bruising can be minimized by using an interfacing layer, such as a tight-fitting knee-high sock or sleeve, between the participant’s skin and the compression sleeve of the Wave PRO. Calf muscle soreness/tenderness as a result of normal compressions during system operation is expected to resolve without medical intervention.

Known side effects for existing ECP systems on the market, including the predicate ACS NCP-2 device, include skin abrasion, bruising, muscle ache, blistering, and paresthesia (prickling sensation), all of which are also potential side effects of the Wave PRO ECP system. Side effects of ECP treatment are generally well tolerated and can be minimized with additional padding at the interface of the compression cuffs and the participant. Other side effects can be resolved with the application of topical creams.

Rare side effects of ECP may include skin breakdown and increase in adverse cardiac events.

Any discomfort during an ECP session will be recorded for each participant, along with any adverse events during testing.

2.3.2 KNOWN POTENTIAL BENEFITS

Predicate ECP devices are indicated for the treatment of chronic stable angina (CSA) by creating diastolic augmentation during cardiac diastole. As noted in the literature, ECP treatment “create[s] a pressure wave that significantly increases peak diastolic pressure, benefiting circulation to the heart muscle and other organs, while also reducing systolic pressure and systemic vascular resistance to the general benefit of the vascular system” [3]. “[ECP] has marked effects on the magnitude of diastolic retrograde and systolic antegrade blood flow in the descending aorta” [1]. “[ECP] unequivocally and dramatically increases directly measured coronary flow velocity and pressure. This noninvasive counter pulsation technique generates a significant increase in diastolic pressure measured in the central aorta and the mid to distal coronary artery, representing diastolic augmentation” [4]. “Coronary blood flow velocity measured by both angiographic and intracoronary Doppler techniques is significantly increased during [ECP], whereas left ventricular afterload is reduced because of systolic unloading, thereby lowering left ventricular work” [4,5]. ECP treatments have been shown to reduce angina class by at least one Canadian Cardiovascular Society (CCS) score in 86% of patients, decrease nitroglycerin usage by over 80%, and increase exercise tolerance by 25% in patients with refractory angina, with benefits sustained for up to five years [6–8].

With compression of the calf muscles timed to the cardiac cycle, the Wave PRO ECP device imparts similar physiological and therapeutic benefits compared to commercially available ECP systems with anticipated greater patient comfort. Additional benefits include an ergonomically improved and lighter form factor and automation features controlling inflation and deflation timing, obviating the need for a dedicated technician to operate the system for all 35 treatment hours.

For the purposes of this study, participants are not expected to benefit from the two 10-min ECP sessions. However, data and knowledge acquired from this study are expected to positively impact future patients requiring ECP for anginal symptom relief.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The anticipated risks of the Wave PRO ECP system and this study protocol are minor and unlikely to cause serious harm to study participants. While study participants are not expected to gain any immediate health benefits, existing and future patients with CSA are expected to benefit from an ECP device that is more readily available and comfortable.

The Wave PRO ECP system does not meet any of the criteria defined by the FDA for a Significant Risk device, therefore the Sponsor considers this study to be Non-Significant Risk.

The Investigational Device Exemption (IDE) regulation (21 CFR 812) describes three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies. An investigational device is considered NSR if it does not meet the definition for an SR device.

21 CFR 812.3(m) defines a Significant Risk device as an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Since the Wave PRO system does not meet any of the criteria defined by the FDA for an SR device, the Sponsors consider this study to be NSR.

Risk controls have been implemented to minimize harm to the user and the recipient of the ECP treatment. Per Pression's DFMEA and resulting Risk Management Report, residual risks associated with the Wave PRO and the controls implemented to reduce those risks are presented in the Risk Benefit Analysis below:

Risk	**What are the Medical Benefits?**	**Risk-Benefit Analysis (Why do the medical benefits outweigh the residual risk?)**	**Is the Risk-Benefit Analysis Acceptable?**
DFMEA 2.10.011 – 2.10.015 Electrical shock from the Control Unit resulting in death due to water intrusion, line cord abrasion or damage, poor dielectric protections, leakage current, and poor ground continuity	The benefits of the Control Unit are that it powers the device and provides timed air pressure pulses to the sleeves to provide ECP therapy. Without the Control Unit, the sleeves and connecting tubing would not provide the air needed for efficient ECP therapy for the patient.	Product safety testing was conducted to reduce electrical shock risks as far as possible, thereby reducing the rate of occurrence of these risks as far as possible. The expected clinical benefits outweigh the residual risk of electrical shock.	Yes
DFMEA 2.10.021 The Control Unit emits electromagnetic interference (EMI) that causes other nearby devices from operating properly, resulting in death	The benefits of the Control Unit are that it powers the device and provides timed air pressure pulses to the sleeves to provide ECP therapy. Without the Control Unit, the sleeves and connecting tubing would not provide the air needed for efficient ECP therapy for the	Product safety testing was conducted to reduce EMI risks as far as possible, thereby reducing the rate of occurrence of these risks as far as possible. The expected clinical benefits outweigh the residual risk	Yes

Risk	What are the Medical Benefits?	Risk-Benefit Analysis (Why do the medical benefits outweigh the residual risk?)	Is the Risk-Benefit Analysis Acceptable?
	patient.	of EMI.	

Per Pression's DFMEA and resulting Risk Management Report, the Benefit Risk Analysis is as follows:

What are the Overall Medical Benefits?	Risk-Benefit Analysis (Why do the overall medical benefits outweigh all risks?)	Is the Overall Risk-Benefit Analysis Acceptable?
The overall medical benefit of the Wave PRO device is to provide External Counter-Pulsation treatment to reduce angina symptoms in patients with chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization.	Use of the Wave PRO ECP device carries risk from procedural error, inherent use hazards, and device failure. Pression LLC has taken measures to ensure the device is designed, manufactured, and tested appropriately to mitigate and control these risks through systematic risk analysis, in-process controls and final inspection, labeling, instructions for use, and usability testing. As a result, the residual risk is reduced as far as possible. In conclusion, the benefits outweigh the risks in the use of the Wave PRO device.	Yes

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
	Performance/Effectiveness: DA Ratio of the Wave PRO system as compared to the predicate ECP device at the eighth minute of ECP compressions (out of 10 total compression minutes)	DA ratio was chosen as the primary endpoint of this study because it is a direct and objective measure of the hemodynamic effect of ECP. DA ratio is a unitless measure which is "calculated as the ratio of the peak diastolic amplitude divided by the peak systolic amplitude" [1]. ECP causes diastolic amplitude to increase relative to systolic amplitude. DA ratio noninvasively characterizes the hemodynamic effect of ECP and is correlated to clinical effectiveness of the treatment, as described in the literature cited in this protocol. DA ratio can be measured by use of a second independent PPG sensor for the Wave PRO and by the onboard PPG sensor on the predicate ECP device. Due to these characteristics, DA ratio is an appropriate endpoint for assessing substantial equivalence of Wave to the predicate device.
Secondary		
	Safety: ○ Occurrence of device-related Serious Adverse Events ○ Device-related Adverse Event rate	Occurrence of device-related SAEs and AEs are appropriate endpoints for evaluation of safety because they are direct measures of the effect of the Wave PRO device on study participants. It is reasonable to consider only device-related AEs/SAEs and not all AEs/SAEs when evaluating the investigational device, as non-device-related AEs/SAEs will be irrelevant.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Performance/Effectiveness: ○ The level of systolic unloading for the Wave PRO based on the systolic peaks during compressions compared to baseline of the PPG data, captured using the independent data acquisition system.	○ Systolic unloading is a corollary to DA ratio discussed above and is a suitable secondary endpoint for the same reasons – it is a direct and objective measure of the hemodynamic effect of ECP.
	○ Number of participants that complete 10 mins of each of the ECP devices (Wave PRO and predicate ECP device)	○ Proportion of participants that completed the 10-minute treatment sessions is an appropriate endpoint because it is a surrogate measure of the tolerability of the Wave PRO device compared to the predicate ECP device.
	○ Participant comfort level with the Wave PRO and predicate ECP device, assessed at the conclusion of each ECP session	○ Participant comfort levels is an appropriate endpoint because it is measured on a standard scale and reflects direct patient response to the two devices.
	○ Time to set up a participant (i.e., sleeved up and sensors attached) and ready to start treatment	○ Tracking participant setup time enables Pression to quantify ease of use compared to the predicate ECP technology. It is appropriate as it quantifies the amount of time that can be reduced from patient visits and can help maximize treatments that clinical entities can provide in a day.
	○ Participant preference for one of the two ECP systems (assuming 35 hours for a full course of ECP)	○ Participant preference for either one of the ECP systems helps validate the Wave PRO as a viable product with the potential of being more accessible for a population that may have limited mobility due to chest pain.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Potential study participants will be recruited per standard practices of the clinical research facility (may include advertising/publicity). Participants will be consented prior to any study related assessments/procedures. Only eligible participants that meet the required criteria (inclusion/exclusion) will be enrolled in the study and subsequently randomized to the ECP devices. Overall study design is shown in **Figure 1**. For the Wave PRO, PPG waveforms will be collected with an independent data acquisition system, BIOPAC (Goleta, CA). The predicate device has onboard data capture and analysis functionalities.

Steps for the Clinical Site for each randomized participant (see Section 6):

- For the Wave PRO: setup (recorded time), rest period (supine, recorded blood pressure and heart rate), pre-compression baseline PPG (recorded on BIOPAC), compression period (automated inflation/deflation tuning, PPG recorded on BIOPAC), post-compression PPG (recorded on BIOPAC), and end of session procedures (recorded blood pressure and heart rate, Wave PRO questionnaire administered).
- For the predicate ACS NCP-2: setup (recorded time, participant profile created), rest period (supine, recorded blood pressure and heart rate), compression period (manual inflation/deflation tuning required, PPG recorded on predicate device), and end of session procedures (recorded blood pressure and heart rate, predicate questionnaire administered).

There will be a 20-minute washout period between the two ECP device sessions, requiring the participant to walk around (no strenuous or high-intensity activities). An observation period will be required after the last test session. A final questionnaire will be conducted during the follow-up call the next day.

Signal Processing steps include (see Section 6):

- For the Wave PRO: average DA ratio will be measured using an R script that processes the BIOPAC waveform data at the 8th minute of compression (i.e., minute 7 to minute 8 of compressions). Average systolic amplitude of the last 10 waveforms of baseline before compressions and the average amplitude of the systolic amplitude of the first 10 waveforms during compressions will be recorded for systolic unloading calculations.
- For the predicate ACS NCP-2 device: average DA ratio in the 8th minute of compressions will be calculated using an R script that processes the waveforms collected by the ACS software. The predicate device only allows for analysis of 8-second time strips at a time. No systolic unloading calculation for the predicate device.

During Signal Processing, the evaluator will be blinded to the paired participant testing (i.e., blinded to the participant ID). The blinded evaluator will not be able to match a participant's test on the Wave PRO with that of the predicate device. However, given the nature of the data collected, the evaluator will not be blinded to which ECP device the data pertains to. The

blinded evaluator will record the DA ratio in the CRF for each tested ECP device. For the Wave PRO, the blinded evaluator will also record the average systolic amplitudes.

Statistical analysis steps include (see Section 9)

- An ANOVA model for crossover design will be performed and the pairwise difference between two treatments DA ratios (Wave PRO – predicate ECP) in the treatment least square mean and its 95% CI will be constructed. Non-inferiority margin will be set at -0.15.
- Descriptive analysis will be conducted for all secondary endpoints.

During Statistical analysis, the statistician will be provided the DA ratio values (per ECP device) matched to each participant ID.

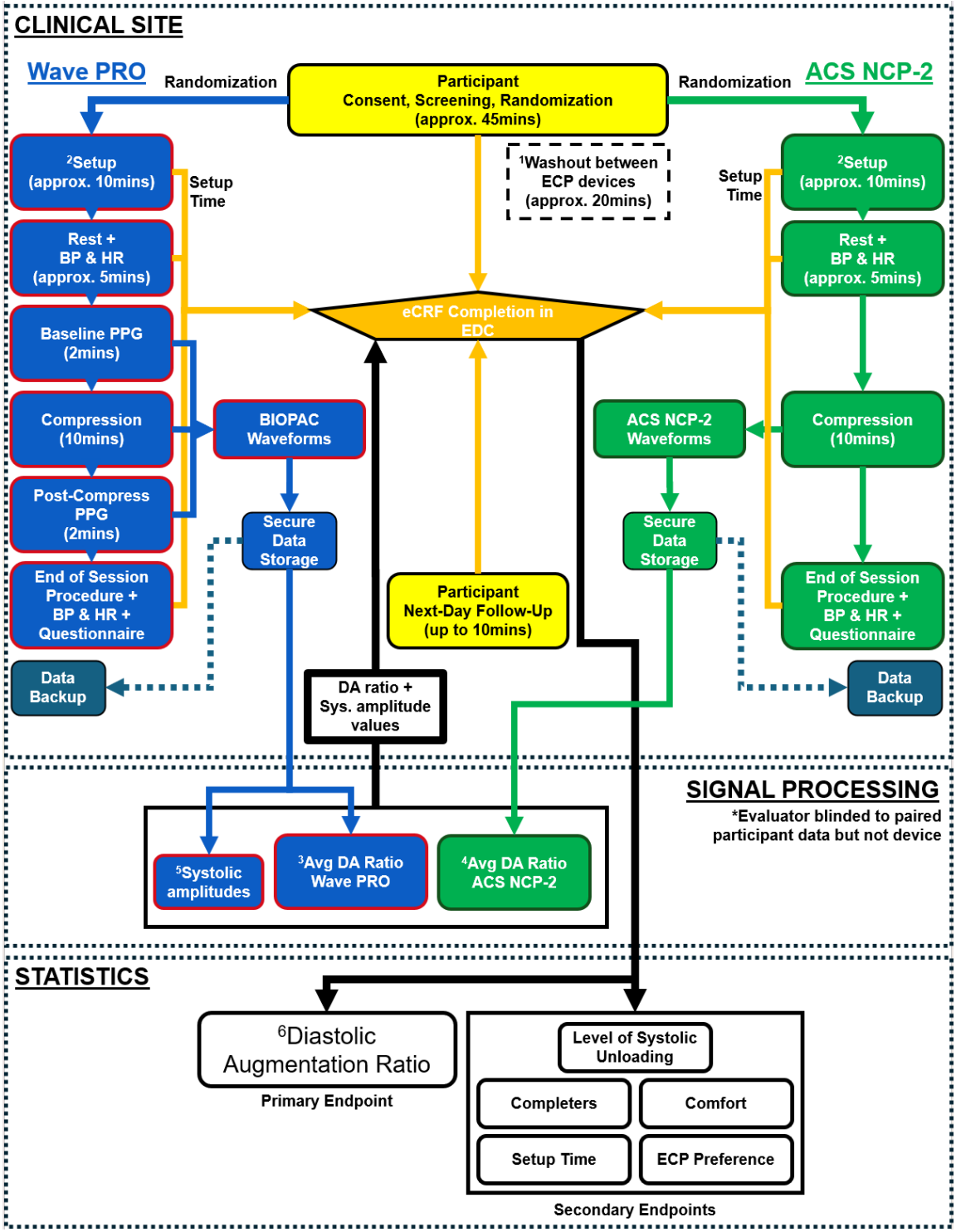

Figure 1: Study design schematic, including steps at the Clinical Site, Signal Processing, and Statistics. *[1]Washout period between the ECP devices for each randomized participant will include walking around, [2]Duration of setup will be recorded, [3]Average DA ratio in the 8th minute of compressions (BIOPAC data, R script analysis), [4]Average DA ratio in the 8th minute of compressions (ACS NCP-2 data, R script analysis), [5]Average systolic amplitude of the last 10 waveforms of baseline and the systolic amplitude of the first 10 waveforms during compressions, [6]Compared to non-inferiority margin (see stats description).*

4.2 JUSTIFICATION OF STUDY DESIGN

As the purpose of the study is to demonstrate substantial equivalence of hemodynamic effect of the Wave PRO ECP system to a predicate ECP device, the study is intended to test the two devices in head-to-head fashion.

This study is a randomized crossover study enrolling up to 50 participants in order to have 44 completing participants. Each participant will receive ECP compressions from the Wave PRO device and from the predicate (ACS NCP-2) ECP device, one at a time, and with the sequence of device use randomized to control bias. Pression has utilized accepted biostatistical study design principles to calculate the sample size of the clinical study to reach adequate power to prove substantial equivalence (non-inferiority) of the DA ratio achieved by the Wave PRO compared to the predicate ECP device.

The Diastolic Augmentation (DA) ratio, also referred to as Diastolic/Systolic (D/S) ratio and Effectiveness Ratio (ER), noninvasively characterizes the hemodynamic effect, and thus the clinical effectiveness, of ECP treatment. Predicate device Instructions for Use (IFU) and ECP literature direct medical professionals to utilize this metric to optimize the treatment: “The treatment aims to create an enhanced [DA ratio] during cardiac diastole” and “[DA] ratio [is] monitored using standard finger photoplethysmography [PPG]” [9]. Medical professionals delivering ECP treatment are further trained to recognize permutations of the PPG waveform that indicate whether a treatment is being effectively delivered or whether the treatment parameters require adjustment. The hemodynamic impact of these adjustments is measured solely by way of the PPG waveform.

While the predicate device has built-in functionality to capture PPG waveforms, the Wave PRO has no onboard PPG waveform capturing capability. Therefore, for the purposes of this study, a dedicated and independent data acquisition system, BIOPAC, will be used.

DA ratio will be calculated by a qualified blinded evaluator (blinded to participant ID and ECP session pairing). A computer containing the ACS software (provided by Pression) will be used to review the ACS NCP-2 data and capture screenshots of the data, enabling the R script (provided by Pression) to process the data and calculate DA ratio, in accordance with the IFU. For the Wave PRO, raw data obtained from the dedicated BIOPAC data acquisition system will be evaluated using a seperate custom R-script code (which Pression will provide). In effect, the same DA ratio calculation of the eighth minute of compressions for both systems will be conducted.

Internal testing has demonstrated that diastolic augmentation can be observed almost immediately at the start of an ECP session. The initial response of the participant to the ECP device can be assessed after the first 5 minutes of compression, so the 10 minute compression time is appropriate.

Per the ACS NCP-2 IFU regarding compression pressures on the first day (to be set by the operator at the clinical site), pressures will be set to 3PSI, from a maximum of 6PSI. Pressures are typically set to however much patients are able to tolerate, and more pressure does not always equate to higher augmentation in the predicate ECP device.

4.3 END OF STUDY DEFINITION

There will be approximately 10 minute observational period at the conclusion of the second ECP device session. The participant will be provided a post-session questionnaire regarding their ECP experience after each ECP device test. Once the participant has received their +1-day follow-up phone call and questionnaire, they will be considered exited from the study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Each participant must meet all of the following Inclusion Criteria to be considered eligible for the study.

- Age 35 years or greater
- History of mild to moderate coronary artery disease (CAD), as evidenced by one or more of the following:
  - Angina pectoris
    - Canadian Cardiovascular Society (CCS) Angina classes I or II
  - Prior confirmation of CAD from invasive or noninvasive studies
  - Prior myocardial infarction (MI)
  - Prior coronary artery bypass graft (CABG) surgery
  - Prior cardiac stents
- Able to ambulate without assistance (no cane or walker)
- Able to lay down (approximately 5 degree angle) for the duration of the protocol required procedures
- Able and willing to give informed consent
- Able and willing to participate in the clinical study and complete all questionnaires provided

5.2 EXCLUSION CRITERIA

Participants must not meet any of the following Exclusion Criteria to be considered eligible for the study.

- Unstable angina within prior 3 months
- Canadian Cardiovascular Society (CCS) Class III or IV Angina
- Moderate to severe peripheral arterial disease (PAD)
  - ABI < 0.8
- Myocardial infarction in the past 3 months
- Coronary artery bypass grafting (CABG) in the past 3 months
- Any major surgery within the past 3 months
- Decompensated heart failure
- Cardiac catheterization or arterial femoral puncture in the past 2 weeks
- Presence of mechanical circulatory support (MCS) device
- Pacemaker or other implantable pulse generating device
- Valve disease, including aortic insufficiency
- Abdominal or thoracic aortic dissection or aortic/cerebral aneurysms requiring clinical intervention
- Severe pulmonary disease
- Bleeding diathesis
- Patients undergoing warfarin anti-coagulation therapy, or with PT-INR > 2.5, or who have routine INR or prothrombin time tests Active thrombophlebitis
- Uncontrolled hypertension (greater than 180/110 mmHg)
- Baseline heart rate > 120 beats per minute or < 40 beats per minute
- Arrhythmia and/or abnormal heart rhythm

- Major hand injuries or amputation that would interfere with finger PPG
- Unhealed wounds/fractures below the waist or lower limb amputation, major lower body musculoskeletal injuries
- Lower body vascular stents (arterial/venous)
- Currently undergoing ECP treatment
- Pregnancy
- Currently participating in any other clinical study of an investigational device or drug where treatment has not yet been completed
- Any medical condition that, in the opinion of the principal investigator (PI), would present undue risk to the participant

5.3 RECRUITMENT STRATEGIES AND CONSIDERATIONS

The recruitment efforts by the clinical study site will aim for a representative population with the following enrollment targets:

- Randomize no more than 60% of one sex
- Randomize no more than 50% White participants

Additional considerations for the day of the Study Visit:

- Participants must remove all nail polish or artificial nails on their hands to ensure that the PPG sensor can accurately detect the participant's pulse and blood volume changes.
- Participants must not eat on the test day prior to their visit.
  *Extended fasting may be required if a later test time is scheduled.
- Participants must abstain from alcohol and caffeine by 8PM the night before their scheduled test day.
- Water is permitted.
  *Compressions may induce the urge to urinate; regulated water consumption is recommended.
- Participants must not take diuretics the morning of the visit if it is scheduled in the morning. If it is scheduled in the afternoon, the diuretics can be taken as usual in the morning. Any other changes or modifications to any dosing schedules should be at the direction of the participant's physician.
- Participants should wear or bring loose-fitting clothing to be worn during the visit
  - For clothing tops, loose shirt or blouse is required to enable placement of EKG leads to enable the operation of the ACS NCP-2 predicate ECP device.
  - For clothing bottoms: shorts are required to allow better interfacing with the inflation cuffs/sleeves.
    - Ensure that clothing bottoms do not have non-removable buckles or metal/hard plastic accessories.
  - Cotton stockinettes will be made available to cover exposed skin on the legs.
- Participants should bring a written list of all current medications; dosage information included.

5.4 SCREEN FAILURES

In order for an individual to participate in the study, the participant must meet all Inclusion Criteria and none of the Exclusion Criteria. The participant must also be able to comply with the additional considerations listed in Section 5.3. Failure to meet eligibility will result in the individual being a Screen Failure. The reason for Screen Failure will be documented for each prospective participant.

6 STUDY DESCRIPTION

6.1 STUDY ECP DEVICE ADMINISTRATION – WAVE PRO SYSTEM

6.1.1 WAVE PRO ECP DEVICE DESCRIPTION

The Pression Wave PRO External Counter-Pulsation System applies compression to the calves, timed to peripheral diastole, to positively affect the patient's blood flow. It utilizes a pair of calf sleeves worn by the patient that are attached by tubing to a mobile compression control system, which houses the pneumatic, mechanical, electrical components, and an easy-to-use touch screen control interface. The patient's cardiac cycle is monitored by a pulse photoplethysmography (PPG) sensor worn and secured on the patient's finger by a clip and connected to the compression control system.

The calf sleeves inflate and deflate in synchrony with the phases of the patient's cardiac cycle, which is detected by the finger PPG sensor. These calf sleeves have a series of five inflatable bladders that are inflated sequentially, distally to proximally, towards the heart in the timeframe between heart beats. This compression generates retrograde arterial flow back to the heart, thus augmenting coronary flow during ventricular diastole.

6.1.2 WAVE PRO DEVICE TEST SESSION

This section pertains to the test session using the Wave PRO device with a participant that has been randomized.

- **Setup (approx. 10mins):** Time needed to get the participant ready for compressions will be recorded
  - Participant will be lying on the clinical bed with their back propped head-up at approximately 5° angle
  - Cotton stockinettes will be placed around the participant's legs between the knees and the ankles (if not already)
  - The clinical operator/technician will ensure that the Wave PRO is connected to an air supply source in the session room.
    - Clean air rated at 55 ± 1PSI.
  - Timer to record setup time will be started
  - The compression sleeves (with tubing attached) will be fitted around the participant's calves by a clinical operator/technician
    - The sleeves are differentiated by a left and a right sleeve
    - There are three different sleeve sizes (small, medium, large)
    - The sleeves are placed between the participant's ankles and knees
      - with the compression bands wrapped around the calf muscle
      - with the tubing ports on the medial side of the legs, pointing towards the feet
  - The compression sleeves should be snug against the participant's legs (tight but comfortable)

        - The clinical operator should not be able to fit an index finger between the Compression Sleeve and the legs, but should not be so tight that the participant can feel their pulse through their leg
- **Rest (supine), blood pressure and heart rate (approx. 5 mins):** Participant should be completely set up and then asked to lie back and relax
    - Amount of time it took to set up will be recorded
    - The participant's systolic/diastolic pressures and heart rate will be recorded
- **Baseline PPG (2 mins):** With the Wave PRO system powered ON and on standby (not compressing), recording will be conducted to capture baseline PPG waveforms using the dedicated BIOPAC data acquisition system
    - Two PPG sensors will be placed on the participant's hand:
        - One for the Wave PRO
        - One for the dedicated Data Acquisition System
        - The sensors should be placed on the index (Wave PRO) and middle fingers (BIOPAC) on the right hand (if the Data Acquisition System signal is noisy, the sensor can be switched to another finger on the same hand)
    - The User Pause Button will be given to the participant to hold in the left hand
        - The User Pause Button allows the participant to temporarily stop the compressions at any time.
- **Compression (10 mins):** Participants will be asked to relax and minimize all movement and the operator will begin compressions
    - To be able to start compressions, the clinical operator should make sure of the following:
        - The E-Stop on the front panel is disengaged
        - System Check checklist items on the screen all have blue checkmarks
        - "Next" button has been pressed.
        - 60 minutes Treatment Time has been selected
        - "Start Treatment" button has been selected
    - PPG waveform data will be recorded on the BIOPAC data acquisition system.
        - Mark pre-compression baseline PPG start and end using the study laptop
        - Mark compression start and end using the study laptop
        - Mark post-compression PPG start and end using the study laptop
- **Stop compressions:** The clinical operator/technician will stop the delivery of compressions after 10mins has elapsed by pressing the "Cancel Treatment" button.
- **Post-Compression PPG (2 mins):** At the conclusion of the 10 minute ECP session, a post-compression PPG signal will be recorded
    - Participant will be asked to relax and minimize all movement.
- **End-of-Session procedure, blood pressure and heart rate, device-related questionnaire:** The clinical operator/technician will perform the following:
    - The participant's systolic/diastolic pressures and heart rate will be recorded
    - Participant questionnaire related to the ECP device will be conducted
    - Wave PRO system will be turned off (if applicable)

- Air supply line to the Wave PRO system will be disconnected (if applicable)
- Sensors will be removed from the participant's fingers
- Compression sleeves will be removed from the participant's calves
- If this is the second test session, an observation period of approx. 10 minutes should be made available for each participant

6.2 PREDICATE ECP DEVICE ADMINISTRATION – APPLIED CARDIAC SYSTEMS (ACS) NCP-2 EXTERNAL COUNTER-PULSATION (ECP) SYSTEM

6.2.1 ACS NCP-2 ECP DEVICE DESCRIPTION

The Applied Cardiac Systems (ACS) NCP-2 is an FDA cleared ECP system (K042413) indicated for the treatment of chronic stable angina. The ACS system is similar to other commercially available ECP devices on the market. It utilizes three inflation cuff sets (calf, thigh, buttocks) to deliver sequential compressions timed to the cardiac cycle. Compressions are timed to the patient's EKG and treatment efficacy is measured using a PPG sensor.
The user interface of the ACS NCP-2 device requires the clinical operator/technician to input inflation and deflation timing of the cuffs and must input pressure settings manually. As a result, the clinical operator/technician must have an understanding of EKG and PPG waveform shapes to ensure the input parameters are appropriately set.

6.2.2 ACS NCP-2 (PREDICATE) DEVICE TEST SESSION

This section pertains to the test session with the predicate ACS NCP-2 device with a participant that has been randomized.

- **Setup (approx. 10 mins):** Time needed to get the participant ready for compressions will be recorded
  - Participant will be lying on the ACS NCP-2 bed with their back propped head-up at 5° angle
  - Cotton stockinettes will be placed around the participant's legs between the knees and the ankles (if not already)
  - The ACS NCP-2 system will be powered on (if not already) along with the connected computer and monitor
  - The ACS NCP-2 software must be loaded once the boot-up sequence is complete
  - Participant profile must be created before starting new treatment session
    - Profile must not contain identifying information
      - Treatment ID (see Treatment_ID_LookupSheet) will be used for both name and participant ID on the ACS software query
      - For the birthday query, use 01/01/19XX, where XX is the participant's actual birth year
  - Treatment session screen should be opened
  - Timer to record setup time will be started

- The clinical operator/technician will attach three EKG electrode pads on the participant
  - Refer to the ACS NCP-2 training packet for electrode placement
- With the participant lying down, the compression cuffs (with tubing attached) will be fitted around the participant's calves, thighs, and hips by a clinical operator/technician
  - The compression cuffs are differentiated by left and right.
  - The compression cuffs are positioned such that the tubing ports are on the medial side of the legs, and the ports are pointing towards the bed.
  - There are two different sizes of cuffs (small, large)
  - All compression cuffs should be snug around the participant's legs and hips (snug but comfortable)
    - Operator should not be able to fit two fingers inside the cuffs at the top edge (thigh and calf)
  - The clinical operator/technician will connect the EKG leads to the electrode pads based on the lead labeling.
  - The clinical operator/technician may need to loosen the cuff around the hips to place one of the EKG leads on the participant's left lower rib.

- **Rest, blood pressure and heart rate (approx. 5 mins):** Participant should be completely set up and then asked to lie back and relax
  - Amount of time it took to set up will be recorded
  - The participant's systolic/diastolic pressures and heart rate will be recorded
- **Compressions (10mins):** The clinical operator/technician will begin compressions.
  - The ACS NCP-2 PPG sensor will be placed on the participant's right pointer finger
  - The clinical operator/technician will adjust the device pressure and the inflation and deflation timing based on the red and blue colored marker bars, respectively, on the monitor
    - The timing (red and blue colored marker bars) needs to be adjusted to generate a PPG waveform that has the appropriate shape (refer to IFU for inflation and deflation timing and resulting PPG waveform shapes)
    - As a starting point, the red colored region should start at the peak of T-wave (inflation) and the blue colored region should terminate just prior to the subsequent P-wave (deflation)
    - The 10 minutes of compressions start once the "Start Pump" button has been clicked (i.e., includes timing search)
  - PPG waveform data will be recorded on the ACS NCP-2 software (waveforms are only recorded when the pump is running)
  - Compression pressure will be increased in small increments until a maximum of 3 PSI is reached, per the ACS software readout
    - In accordance with pressure settings for the first day of ECP treatment per the predicate device IFU
    - 3 PSI will be reached as fast as possible along with the correct inflation/deflation timing

- **Stop compressions:** Compressions will be concluded by pressing the “Pump Start” button again after 10 mins have elapsed
  - Proper steps to exit out of the treatment screen will be followed to prevent loss of data
  - The participant’s profile will be revisited immediately to ensure that the test data was saved (Full Disclosure screen)
- **End-of-Session procedure:** The clinical operator/technician will perform the following:
  - The participant’s systolic/diastolic pressures and heart rate will be recorded
  - Participant questionnaire related to the ECP device will be conducted
  - ACS NCP-2 will be turned off (if applicable)
  - EKG leads and electrodes will be removed from the participant
  - Sensors will be removed from the participant’s finger
  - The three compression cuff sets will be removed from the participant
  - If this is the second test session, an observation period of approx. 10 minutes should be made available for each participant

6.3 DATA ACQUISITION WAVE PRO

6.3.1 BIOPAC MP35 DATA ACQUISITION SYSTEM DESCRIPTION

The BIOPAC MP35 Data Acquisition system paired with the BSL 4.1 software will serve as the dedicated PPG waveform and data extraction system to acquire waveforms that will subsequently be used to calculate DA ratio and select secondary endpoints as a result of Wave PRO compressions. The MP35 is a four channel system with a 24-bit A/D sampling resolution. The MP35 is capable of recording 100,000 samples per second.

The BIOPAC SS4LA PPG Transducer, which connects to the 9-pin female DSUB connector on the MP35, will be attached to the participant’s finger using the built-in hook-and-loop strap to capture PPG signals. The SS4LA is a reflectance type PPG sensor that utilizes a matched infrared emitter and photo diode to detect changes in blood density due to blood pressure fluctuations. The emitter/detector wavelength is 860nm ± 60nm, with a built-in low pass filter cutoff wavelength of 800nm.

6.3.2 PREPARATION AND UTILIZATION

Baseline data as well as compression session data will be captured using the dedicated BIOPAC data acquisition system. A laptop running Windows OS will be provided containing the BSL 4.1 software bundle. To launch the software, double click on the BSL 4.1 (BIOPAC) software icon on the desktop.

- The operator will load a pre-set template located on the study laptop
- During data capture, the clinical operator/technician can use specific function keys to tag events during the ECP session, including:
  - F1 key to tag Start Baseline,

    - F2 key to tag End Baseline,
    - F3 key to tag Start of Wave PRO compressions,
    - F4 key to tag End of Wave PRO compressions
    - ESC key to tag any other miscellaneous notes deemed necessary such as irregular PPG waveform due to participant movement
    - NOTE: All keys are labeled with their function on the keyboard itself
- The clinical operator/technician will save the entire session with the following naming convention:
    - RA-C01_TreatmentID
        - (see Treatment_ID_LookupSheet)

  A dedicated directory on the desktop will be used to save the Wave PRO data for each participant
- Data will be backed up on to a dedicated secure data storage for the study

6.3.3 SIGNAL PROCESSING

Signal processing will be conducted by a blinded evaluator working under the requirements of an Analysis Charter. The laptop provided for the data acquisition and processing will be equipped with RStudio integrated development environment software as well as the R script used to extract DA ratio and systolic amplitude values.

- The evaluator will load the data from the secure data storage
- The evaluator will extract waveforms using the BSL 4.1 software and process the waveforms using a custom R script
- The evaluator must run the script and answer the prompts in the Console tab to have the script calculate the DA ratio
    - This script analyzes PPG data from .csv files, prompts the user for key waveform features, and outputs DA ratio values and systolic amplitude, as well as the PPG waveform graphs

An Analysis Charter will be used to guide the evaluator through the process of extracting the DA ratio and systolic amplitude values. The DA ratio and systolic amplitude values will be uploaded via CRF to the EDC.

6.4 DATA ACQUISITION ACS NCP-2

6.4.1 ACS DATA ACQUISITION SYSTEM DESCRIPTION

The ACS NCP-2 software (NCPPLUS) records participant PPG and EKG waveforms throughout the duration of compressions. The ACS software will serve as the dedicated PPG waveform and data extraction system to acquire waveforms that will be used to calculate DA ratio as a result of ECP compressions on the ACS NCP-2.

The ACS PPG sensor is a transmission type PPG sensor that utilizes an infrared emitter and photo diode to detect changes in blood density due to blood pressure fluctuations.

6.4.2 PREPARATION AND UTILIZATION

A computer running Windows OS will be provided to the clinical research site containing ACS software. To launch the software, double click on the NCPPLUS program icon on the desktop.

- Before data capture, the clinical operator/technician must create a patient profile
  - No participant identifying information will be logged on the software
    - For patient I.D. use the treatment ID (see Treatment_ID_LookupSheet)
    - For patient name use treatment ID (see Treatment_ID_LookupSheet)
    - For patient's sex use participant's sex
    - For patient's birth date, use 01/01/19XX, where XX is the participant's actual birth year.
- Data capture begins when the operator/technician starts the pump on the control console and the software starts recording
- The entire session will automatically save with the following naming convention:
  - NCP_T_ParticipantID
    - In this instance, ParticipantID is TreatmentID (see Treatment_ID_LookupSheet)
- A dedicated directory on the trial site desktop will contain ACS data for each participant, categorized by the Participant ID (which is treatment ID, in this instance)
- The operator/technician must copy this directory in its entirety to the provided USB drive
  - Data should be backed up after every participant
- Data will be backed up to a dedicated secure data storage for the study

6.4.3 SIGNAL PROCESSING

After the ACS NCP-2 sessions are complete, data extraction will be conducted by the Statistician and data processing will be conducted by a blinded evaluator. Both the Statistician and blinded evaluator will be working under the requirements of an Analysis Charter.

- The Statistician will load the data from the secure data storage
- The Statistician will open each participant's ACS data file in the ACS NCP-2 Software (NCPPLUS)
- The Statistician will load the Full Disclosure page to access the test data
- The Statistician will use built-in Augmentation Cursor Screen capture all the waveforms within the 8th minute (i.e., minute 7 to minute 8) via screenshots
  - The onboard analysis tool uses 8-second strips. Each of these strips will need to be captured within the 8th minute
- The Statistician will upload the captured data to the secure data storage
- The evaluator will load the captured data from the secure data storage
- The evaluator must run the script and answer the prompts in the Console tab to have the script calculate the DA ratio
  - This script isolates PPG data from the screenshot files, analyzes the PPG data, prompts the user for key waveform features, and outputs DA ratio values, as well as the PPG waveform graphs

An Analysis Charter will be used to guide the evaluator through the process of extracting the DA ratio. The DA ratio values will be uploaded via CRF to the EDC.

6.5 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.5.1 ACQUISITION AND ACCOUNTABILITY

The study site will receive both ECP devices, the Wave PRO and the ACS NCP-2, from the Sponsor.

The study site will also be provided the BIOPAC MP35 data acquisition system, paired with a BIOPAC SS4LA PPG finger transducer, for capturing PPG data.

A laptop (Windows OS) will be provided and will include the BIOPAC BSL 4.1 software bundle to interface with the BIOPAC hardware. Dedicated digital storage directories will be created to save the data files.

A flash drive storage device will be provided to back up raw data on the laptop on a daily basis.

Data will also be uploaded to a dedicated secure data storage for the study.

Consumables include EKG electrodes, stockinette material (for interfacing the compression sleeves/cuffs to the participants legs), surgical tape, and ultrasound gel (to help interface noisy EKG electrodes) will be provided by the Sponsor.

The Sponsor will also provide an air compressor that the Wave PRO will connect to, to receive compressed air.

All devices and ancillary supplies will be logged on device accountability form(s).

6.5.2 APPEARANCE, PACKAGING, AND LABELING

Shipping: Both the Wave PRO and the ACS NCP-2 will be shipped to the study site via courier. Pression will custom package all devices and supplies for safe transport. Neither of the ECP systems requires calibration prior to powering up. Installation validation (Pression protocols) will be conducted for both systems prior to participant enrollment.

<u>Labeling for Wave PRO:</u>
CAUTION: Investigational Device – Limited by Federal (or United States) Law to Investigational Use.
This device is manufactured and assembled by Pression LLC, Coatesville, PA 19320.

<u>Labeling for ACS NCP-2:</u>
Per 510(k) Number K042413: ACS Model NCP-2 External Counter-pulsation Device is a noninvasive external Counter-pulsation device intended for the use in the treatment of patients

with stable or unstable angina pectoris, acute myocardial infarction, cardiogenic shock or congestive heart failure*.
*Original indications. FDA reclassified the uses of ECP devices in December 2013: Class II (special controls) when the device is indicated for the treatment of chronic stable angina that is refractory to optimal antianginal medical therapy and without options for revascularization.

Labeling for BIOPAC MP35 Data Acquisition System:
Per BIOPAC Product Sheet:
Safety:
The MP35 satisfies the Medical Safety Test Standards affiliated with IEC 60601-1. The MP35 is designated as Class I Type BF medical equipment

EMC:
The MP35 satisfies the Medical Electromagnetic Compatibility (EMC) Test Standards affiliated with IEC 60601-1-2.

Ancillary supplies:
Laptop: Windows operating system containing BIOPAC BSL 4.1 software bundle for data acquisition and R Studio for data analysis and quantification. This laptop is intended for research use, specifically for the acquisition and quantification of PPG waveforms recorded from the Pression sponsored clinical trial. Only personnel explicitly authorized by Pression LLC will be allowed to access this laptop.
EKG electrode pads: single use, commercially available for EKG leads
Stockinette: cotton interfacing layer that is commercially available to minimize abrasions
Ultrasound gel: to be used in the event of very noisy EKG signal
Surgical tape: to be used in the event of very noisy EKG signal
Flash drive storage: commercially available USB-A flash drive for backing up raw data from the laptop. The flash drive will be used specifically and exclusively for the Pression sponsored clinical study.

6.5.3 PRODUCT STORAGE

All devices and ancillary supplies are to be securely stored at room temperature and only accessed by trained and delegated study personnel. While in storage, all devices should be unplugged (not powered) and kept away from fluids or flammable sources. All devices and ancillary supplies should only be used for the purposes of the Pression sponsored clinical trial. Please contact Pression LLC or the CRO (ABio Clinical) in case of damage or misplacement of all devices and ancillary supplies.

6.6 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Given the analysis methodologies and the data collection methods, the blinded evaluator who analyzes the waveforms for input to the endpoints of DA ratio and systolic unloading will not be

blinded to ECP device, but will be blinded to the participant IDs (only treatment IDs will be provided so that the treatments cannot be paired per participant) and to the sequence of ECP device used (i.e., Wave PRO used first vs. ACS NCP-2 used first). Due to the nature of the devices, participant and operator blinding to the ECP units cannot be performed.

Randomization of ECP device order will be performed within the Electronic Data Capture System once eligibility has been determined. The randomization schedule will be generated using randomly selected small block sizes to minimize bias for the single site.

6.7 STUDY INTERVENTION COMPLIANCE

The Wave PRO System and the ACS NCP-2 ECP device will be operated according to each device's Instructions for Use (IFU), this clinical study protocol, and the training packet (provided by Pression).

Any deviations will be documented on a Protocol Device electronic Case Report Form (eCRF).

6.8 CONCOMITANT THERAPY

Participants must not be currently undergoing ECP treatment or participating in any other clinical study of an investigational device or drug where treatment has not yet been completed.

Participants may need to consult with their primary care physician to discuss their health and safety regarding their participation in this clinical trial.

For participants on diuretics, medications may be taken immediately after the session. Participants are encouraged to check with their primary care physician regarding any deviations in medication scheduling.

7 STUDY PROCEDURE DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY PROCEDURES AND/OR ASSESSMENTS

The site Principal Investigator or study staff may discontinue any of the protocol required study assessments or procedures at any time due to participant safety or other concerns. For any procedures not completed, the reason for discontinuation will be documented, and Protocol Deviation eCRF will be recorded as appropriate.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to withdraw their consent to participate at any time during the study. In addition, the site Principal Investigator (PI) or study staff may remove participants from the study at any time if they feel it is best for the safety and well-being of the participant. Examples include:

- Significant study intervention non-compliance.
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for discontinuation/withdrawal will be documented on the Study Exit eCRF.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant is unable to be contacted by the study site for the follow-up phone call. The following actions will be taken if a participant fails to return the phone call:

- The site must attempt to contact the participant as soon as possible.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods including email). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered "lost to follow up".

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 GENERAL AND ADMINISTRATIVE PROCEDURES

The summary of study assessments, procedures and their timing are also provided in Sections 1.1 and 4.1. Before conducting any non-standard of care assessments or procedures, obtain written informed consent. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a consent log to record details of all participants enrolled and to confirm eligibility or record reasons for screening failure, as applicable.

Demographic and baseline characteristic data will include sex, age, Fitzpatrick skin type, race, and predominant ethnicity. Relevant medical history and current medical conditions and medications will be recorded. Where possible, diagnoses but not symptoms will be recorded. Body weight will be measured in kilograms (kg) and body height will be measured in centimeters (cm).

8.2 EFFECTIVENESS ASSESSMENTS

Data from the investigational devices will be obtained per Sections 4.1, 6.1, 6.2, 6.3, and 6.4.

As discussed above, analysis of the PPG data will be conducted by a blinded evaluator not associated to the study investigators or sponsor and as described in the Analysis Charter. The analysis process is briefly described in section 6.3 and 6.4 and is further detailed in a dedicated data analysis document (provided by Pression).

8.3 SAFETY AND OTHER ASSESSMENTS

Adverse Events/Serious Adverse Events (SAEs) will be recorded on the Adverse Event eCRF from the time the participant signs Informed Consent until study exit. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE in the AE eCRF and remain responsible for following up all AEs.

The participant will be asked to complete surveys after each ECP device session and again one day after completion of the study procedures.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device and whether anticipated or

unanticipated. This definition includes events related to the investigational medical device or the predicate, events related to the procedures involved and for users or other persons.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is an adverse event that

a) led to death,

b) led to serious deterioration in the health of the participant, that resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function including chronic diseases, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

All AEs will be assessed by the Investigator(s). Guidelines for Investigators include the following:

- **Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- **Severe:** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

The Investigator, on the basis of his or her clinical judgment, should determine whether there is a reasonable possibility the study device or procedure caused or contributed to the event. Guidelines to assess relatedness of an AE are provided below:

- **Not related:** The adverse event is determined to be solely caused by the underlying disease, disorder or condition of the participant, or attributable solely to other extraneous causes (unrelated to the device, device malfunction, or the procedure).
- **Unlikely related:** The adverse event onset does not follow a sequence of time from procedure for which the event could be attributed to the administration or procedure, and/or can be attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes.
- **Possibly related:** The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure and is more likely than not to be at least partially caused by or aggravated by the use of the device, device malfunction, or the procedure. It must also meet both of the following criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure; and (2) is not fully attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.
- **Probable or highly probable related:** The adverse event is clearly caused by the use of the device, device malfunction, or the procedure. It must meet all the following criteria: (1) has a clear temporal relationship between device exposure and onset of the event; (2) follows a known pattern of response to device use or procedure; and (3) is not reasonably attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.

8.4.3.3 EXPECTEDNESS

Anticipated adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

An **unanticipated** serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment.

An **unanticipated** adverse device effect (UADE) means 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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

8.4.4 ADVERSE EVENT REPORTING

Adverse events will be recorded on the AE eCRF.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

The reporting requirements are as follows:

- In the event of a Serious Adverse Event (SAE) Investigators are required to report to Sponsor within 24 hours of becoming aware of the SAE.
- SAE reporting will be performed per the IRB and any local requirements.
- SAEs will be assessed by the Sponsor to determine if the event is a UADE. Any UADE will be reported to the FDA and IRB as soon as possible, but no later than 10 working days after the Sponsor first learns of the effect, as required by 21 CFR Part 812.

9 STATISTICAL METHODS

9.1 GENERAL CONSIDERATIONS

Data will be summarized using descriptive statistics unless specific hypothesis testing is specified. Means, standard deviation, median and range will be summarized for continuous data and counts and frequencies for categorical data. Data analyses will be performed using a validated statistical software package such as Stata (College Station, TX) or SAS (Cary, NC). No imputation for missing data will be performed other than for the sensitivity analysis of the primary endpoint.

9.2 POPULATIONS FOR ANALYSIS

The study has a single test population that will be enrolled according to the inclusion/exclusion criteria.

Intent-to-treat (ITT): All participants that are randomized.

Modified intent-to-treat (mITT): All participants that are randomized and receive any ECP compressions from either device. Group assignment will be the randomized treatment order even if therapy was delivered not according to randomization.

Safety Cohort: Same as the mITT. Only participants that receive any ECP compressions from either device will be included.

Per protocol (PP): Participants that are randomized and receive any ECP compressions from both devices, are treated as they are randomized, and have no major deviations (i.e., inclusion/exclusion criteria, randomization, affect participant safety or validity of primary endpoint).

9.3 ENDPOINTS AND STATISTICAL ANALYSES

9.3.1 PRIMARY EFFECTIVENESS ENDPOINT

There is a single primary endpoint for this trial for effectiveness. Safety will be summarized under secondary endpoints with no hypothesis testing.

Primary Effectiveness Endpoint:

The average DA ratio will be calculated by a blinded evaluator for the 8th minute (i.e., between minute 7 and minute 8) of treatment with each ECP device tested for each participant via the Waveform Analysis Charter. The 8th minute was selected as the pilot data indicated participants

moved more in the last minute of therapy and more signal noise was present. Each participant will have a single average DA ratio per system (i.e., two values per participant).

The difference of the average DA ratio attained using the Wave PRO and the predicate device will be calculated for all randomized study participants with paired ECP data.

Hypothesis:

Null Hypothesis: Wave PRO is inferior to the predicate ECP device

Ho: μP - μp ≤ - 0.15

Alternative hypothesis: Wave PRO is not inferior to predicate ECP device

Ha: μP - μp > - 0.15,

where μP is the mean diastolic ratio for Wave PRO and μp is the mean diastolic ratio for the predicate ECP, and -0.15 is the non-inferiority margin.

Sample size calculation:

Based on preliminary internal data, the observed mean difference between Wave PRO and the predicate ECP was 0.05 ± 0.23, but we will assume a true difference of 0 with a standard deviation of 0.30 for sample size calculations.

Table 1: Summaries for the predicate and Pression Wave Pro ECP pilot data.

	Predicate ACS	**Pression Wave Pro ECP**	**Difference (Wave Pro– ACS)**
Diastolic ratio (N=7)	0.93± 0.12	0.98 ± 0.19	0.05 ± 0.23

Assuming a true difference of 0 with the inflated standard deviation of 0.30, a sample size of 44 participants is adequate to test the non-inferiority hypothesis with at least 90% power and a 1-sided alpha of 0.025. Allowing up to 12% attrition for missing data, approximately 50 participants may be enrolled and undergo ECP compressions in order to have at least 44 participants with paired data.

Selection of non-inferiority margin:

The non-inferiority margin of -0.15 was selected for the difference in diastolic ratio as it seemed a reasonable number. DA ratio characterizes the hemodynamic effect of ECP and is predictive of CCS angina class improvement. The weighted mean DA ratio calculated using published values for predicate ECP devices is 0.79 ± 0.46 (N = 5600). Pression has utilized accepted biostatistical study design principles to calculate the sample size of the clinical study to reach adequate power to prove substantial equivalence (non-inferiority) of the Wave PRO compared to predicate ECP devices using the literature.

The proposed sample size aligns with the 20-50 number of participants previously suggested by FDA at the Pression pre-submission meeting on 8 November 2021.

Analysis cohort:
The primary analysis will use the participants in the mITT cohort that have paired data (an average DA ratio from each system). The primary analysis will not include any imputation for missing data (see missing data section below for planned sensitivity analysis).
A supplemental analysis of the primary endpoint will be conducted for the participants in the Per Protocol cohort with paired data.

Analysis methods:
Along with descriptive statistics, an analysis of variance (ANOVA) model for crossover design will be performed. This ANOVA model includes sequence, participant within sequence, period, treatment, and period by treatment interaction factors. The least square (LS) mean of each treatment and its 95% confidence interval (CI) will be presented. A pairwise difference between two treatments (Wave PRO – predicate ECP) in the treatment LS mean and its 95% CI will be constructed. If the lower bound of this 95% confidence interval is greater than -0.15, then we will reject the null hypothesis and conclude that Wave PRO is not inferior to the predicate ECP. A *p*-value will be constructed using the LS means parameter estimates and standard error to test the hypothesis.
A simple paired Student's t-test will also be constructed for the difference of Wave PRO – predicate ECP to test if greater than -0.15.

Missing Data and Imputations:
Every effort will be made to obtain required data at each scheduled evaluation from all participants who have been randomized. In situations where it is not possible to obtain all data, it may be necessary to impute missing data for the primary endpoint. Missing mean diastolic ratio for each ECP may need to be imputed and analyzed in a sensitivity analysis.

A sensitivity analysis will be conducted, imputing missing ECP mean DA ratios utilizing a Markov Chain Monte Carlo multiple imputation procedure using treatment group as a covariate. For this method, 5 imputation datasets will be prepared if more than 10% of data are missing for randomized participants. These data will be analyzed by imputations using the same model described above and will be combined.

If an mITT participant is missing both ECP mean DA ratios (e.g., unable to tolerate ECP therapy of both devices), then the participant will be excluded from all primary endpoint analyses. Any participant unable to tolerate either ECP therapy will be summarized separately.

9.3.2 SAFETY ENDPOINTS

Safety Endpoint 1:
Occurrence of device-related Serious Adverse Events (SAEs) as reported on the case report forms.

Analysis cohort: Safety cohort.

Analysis methods:
The number of events, number of participants and proportion of participants experiencing any device-related SAE will be summarized by treatment arm. There are no hypothesis tests, but 95% CI for the proportion of participants with an event may be calculated.

Safety Endpoint 2:
Rate of device-related Adverse Events (AEs) as reported on the case report forms.

Analysis cohort: Safety cohort.

Analysis methods:
The number of events, number of participants and proportion of participants experiencing any device-related AE (including serious) will be summarized by treatment arm. There are no hypothesis tests, but 95% CI for the proportion of participants with an event may be calculated.

9.3.3 SECONDARY EFFECTIVENESS ENDPOINTS

Secondary Effectiveness Endpoint 1:
The level of systolic unloading will be recorded for the Wave PRO based on the systolic peaks during compressions compared to baseline of the PPG data (before compressions and captured using the independent data acquisition system). Systolic unloading is the ratio of the systolic peak during compressions divided by baseline systolic peak. Previous studies that measured systolic pressure using coronary catheterization found that “peak aortic systolic pressure decreased 11% during ECP” [4]. Based on these findings, systolic unloading is expected to be similar when measured via PPG. Systolic unloading will be calculated as the ratio of the average systolic amplitude of the last 10 waveforms of baseline PPG before compressions divided by the average amplitude of the systolic amplitude of the first 10 waveforms during compressions.

Analysis cohort: mITT participants with paired data.

Analysis methods:
Descriptive statistics will be used to summarize systolic unloading including mean, standard deviation, median, and minimum and maximum. Additionally, the count and percentage of participants who have systolic unloading values >=11%.

Secondary Effectiveness Endpoint 2:
Number of participants that complete 10 mins of each of the ECP devices (Wave PRO and predicate ECP device).

Analysis cohort: mITT participants with an attempt to receive Wave PRO ECP.

Analysis methods:

The count and proportion of participants that successfully completed the planned 10 min of Wave PRO ECP and the predicate ECP device will be summarized.

Secondary Effectiveness Endpoint 3:

Participant comfort level with the Wave PRO and predicate ECP device, assessed at the conclusion of each ECP session (i.e., using a Likert scale).

Analysis cohort: mITT participants

Analysis methods:
Descriptive statistics will be used to summarize the participant's comfort by ECP device.

Secondary Effectiveness Endpoint 4:

Time to set up a participant (i.e., sleeved up and sensors attached) and ready to start treatment.

Analysis cohort: mITT participants

Analysis methods:
Descriptive statistics will be used to summarize the setup time by ECP device.

Secondary Effectiveness Endpoint 5:

Participant preference for one of the two ECP systems (assuming 35 hours for a full course of ECP).

Analysis cohort: mITT participants

Analysis methods:

The count and proportion of participants that selected their preference as the Wave PRO vs all mITT participants.

9.3.4 POOLABILITY

Since enrollment will occur at only one center due to the challenges of the large size of the predicate device, no poolability analysis will be performed.

9.3.5 SUB-GROUP ANALYSES

Descriptive statistics will be used to summarize primary and secondary effectiveness endpoint data by treatment arm and for the difference (Wave PRO – predicate ECP) for the following subgroups:

- Gender
- Age groups (above and below median)

- Race
- Fitzpatrick skin type

9.3.6 EXPLORATORY ANALYSES

None.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Participants may be pre-screened using IRB approved materials prior to informed consent. Participants must be fully counseled and informed of their options, risks and benefits, and should have every opportunity to ask questions about participation in the clinical investigation. This process includes a thorough explanation of the informed consent form that the participant will be asked to sign, acknowledging that they understand and desire to participate in the clinical investigation.

The Investigator is responsible for assuring that written informed consent is obtained from each participant prior to start of study activities. Should the Investigator delegate the responsibility of conducting the informed consent process to a designee, the Investigator must ensure and document appropriate training of the authorized designee. The Investigator will use an approved informed consent form that was prepared in accordance with this protocol, the IRB, and all local regulatory requirements.

While an Investigator may discuss availability of the investigation with a prospective participant without first obtaining consent, informed consent should always be obtained from a participant prior to initiation of any clinical procedures or assessments dictated by the protocol that are performed solely for the purpose of determining eligibility to participate in the clinical investigation unless the procedures or assessments are conducted as part of the participant's routine care and were obtained before signing the ICF.

If new information regarding the investigational device becomes available and/or the clinical investigation plan changes and this information can significantly affect a participant's future health and medical care, participants will be informed of the information and may be asked to sign a revised informed consent form. The Investigator or the Investigator's designee will inform participants that their medical records will be available for review by the Sponsor or appropriate regulatory bodies. The Investigator will explain the conditions of the study, giving the participant sufficient time to ask questions and to consider whether or not they want to participate. If the participant agrees, they shall be given an approved consent form for signature and date. This must be completed by the participant prior to the commencement of study-specific procedures.

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Participant facing materials, including the informed consent, must be approved by the IRB before use with participants.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

A statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained must be entered in the participant's medical record. One signed informed consent copy shall be returned to the Investigator and filed in the participant's case history; the other signed informed consent copy is for the participant to keep.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed following study completion. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRB, the regulatory authorities, as applicable, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

A study site is considered closed after all participants have exited, data analyses have been completed, all required documents and study supplies have been collected, a study-site closure visit has been performed and the IRB has been notified. The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early study closure of a study site by the Sponsor may include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of effectiveness that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Business reasons (e.g., lack of funding)

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment of participants by the Investigator.

10.1.3 CONFIDENTIALITY AND PRIVACY

The clinical trial will be conducted in accordance with the relevant local and national confidentiality and privacy regulations. Participant confidentiality will be maintained throughout the study in a way that assures that data can always be tracked back to the source data. Participants will be assigned a unique participant ID and treatment ID that will be utilized for data analyses and reporting. Only authorized individuals will have access to identifying information and it will require a unique login and password. All data and information collected during this study will be considered confidential by the study sponsor. All data used in the analyses and summary of this study will be anonymized, and without reference to specific study participant names. Access to study participants files will be limited to study sponsor monitors, case support and Sponsor designees, the Investigator, and research staff. In the case of an audit, authorized regulatory authorities have the right to inspect and copy all records pertinent to this study. Any source documents reviewed remotely by the Sponsor or Sponsor designee should be redacted of any participant identifying information wherever possible.

10.1.4 SAFETY OVERSIGHT

A Medical Monitor with licensed medical training will oversee the safety aspects of this study to evaluate any AEs and assist in identifying any USADE or UADE.

10.1.5 CLINICAL MONITORING

The Clinical Research Organization (CRO), ABio Clinical Research Partners, LLC, is responsible for the monitoring of this study. Clinical Research Associates (CRAs) who are employees or contractors of the CRO will monitor each site during the course of the Study. The monitor will contact and visit the Investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries on the CRF and other protocol related documents. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the Study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. ABio's monitoring standards require full (100%) source document verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of AEs and the recording of the main effectiveness and safety endpoints. Additional random checks of the consistency of the source data with the CRFs may be performed.

The Investigator and Co-investigators agree to cooperate with the monitor(s) to ensure that any issue detected in the course of these monitoring visits is resolved.

An onsite initiation visit will be performed before the first participant is enrolled. Monitoring visits and contacts will occur at regular intervals thereafter per the study specific Monitoring Plan. A close-out visit will be performed after Study closure.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

All participant data relating to the study will be recorded on electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (i.e., device data). Access to EDC requires a unique login and password and training is required before access is granted. If Site, Sponsor or Sponsor designee has trained to the EDC system previously, that training document may be used as evidence of training.

The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRFs. Guidance on completion of eCRFs will be provided.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source documents.

Monitoring details describing strategy, including definition of study critical data items and processes, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the monitoring plan.

The CRO or designee is responsible for the data management of this study, including quality checking of the data. Details regarding data management will be outlined in a study specific data management plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion or Wave PRO regulatory approval, whichever is longer, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES - GENERAL

Data management and quality control will be performed by the CRO. Data will be entered into an EDC system by the clinical sites. Any data queries will be issued to sites as required for resolution and entered into the database. The EDC system is 21 CFR Part 11 compliant. Only Research Coordinators or PIs trained to the use of the EDC will have access for data entry. Only trained CRAs and Data Managers from the CRO will have access to the EDC for Monitoring and Data Management purposes.

The investigator or his/her delegate will perform primary data collection drawn from original documents (printed, optical or electronic document containing source data). All source documentation must be available for review by the study monitor during monitor visits. Source

data is defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

The investigators shall ensure the accuracy, completeness, legibility and timelines of the data reported in CRF and in all required documentation. Data reported on the eCRF shall be supported by the source documents with any discrepancies being explained. If an item is not available or is not applicable, this fact should be indicated; no space is to be left blank. The investigator who has signed the study protocol signature page or his/her authorized designee is to personally electronically sign the eCRFs to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner after the participant's visit.

10.1.7.2 DATA COLLECTION – SITE DATA

A Participant Screening Log will be maintained, listing all participants screened for this Study. For each participant, regardless of procedures or visits completed, CRFs will be completed and signed by the Principal Investigator or Co-investigator, as applicable. This includes those participants who failed to complete the Study. If a participant withdraws from the Study, the reason should be noted on the Exit/Termination CRF. Surveys will be completed by the participant and collected and entered by the research staff.

10.1.7.3 DATA COLLECTION – DEVICE DATA

In addition to the descriptions in sections 6.3 and 6.4, the following data types are referenced in the Analysis Charter.

Data Collection (during ECP sessions):

- Data collected on the BIOPAC Data Acquisition System is an .acq file type.
- Data collected on the predicate ECP system is an .DAT type

Data Processing Wave PRO (refer to Analysis Charter):

- The .acq file will then be exported as an .csv file type.
- The .csv file path will be used as input within the RStudio integrated development environment.
- Using a custom R script, the .csv file will be used to output graphs of the 8th minute which should be saved as a PDF. Additionally, the script will output the average DA ratio, both systolic amplitude values, and standard deviation in an Excel spreadsheet.

Data Processing ACS (refer to Analysis Charter):

- The .DAT file and the .mdb database file will be saved on a USB flash drive.
- Insert the flash drive into a computer with the ACS NCP-2 software (NCPPLUS) installed. Transfer the .DAT and .mdb files into a folder called "ncpdata" on the computer's (C:) drive.
- Screenshots of the 8th minute, which should be saved as a PNG, will be uploaded to the secure data storage.

- Signal processing will be performed using the custom R script. As DA ratios are gathered, the blinded evaluator will record them via CRF to the EDC.

Raw data will be backed up for each participant on a separate flash drive storage device and uploaded to a dedicated secure data storage.

10.1.7.4 STUDY RECORDS RETENTION

All study records and reports will remain on file at the clinical sites for a minimum of 2 years after completion of the Study or regulatory approval of the device, whichever is longer, and will further be retained in accordance with local and international guidelines as identified in the clinical study agreement.

10.1.8 PROTOCOL DEVIATIONS

Investigators may not deviate from this clinical investigation plan without first receiving approval in writing from the Sponsor, involved IRB(s), and applicable regulatory authorities, except when necessary to eliminate apparent immediate hazards to a participant. All deviations will be documented on eCRFs.
All deviations will be reported to the CRO within 24 hours of the Investigator becoming aware.

With the help of the CRO, the Investigators will also adhere to procedures for reporting deviations to the involved IRB(s) in accordance with their specific reporting policies and procedures.

Protocol deviations regarding Informed Consent procedures, inclusion/exclusion criteria and deviations that affect the primary endpoints are considered major protocol deviations. The monitor is responsible for major/minor classification of the deviations.

10.1.9 PUBLICATION AND DATA SHARING POLICY

Only the independent data evaluator/analyst and trained study personnel explicitly approved by Pression LLC will be allowed to handle the raw and processed data.

During the study, all data will be stored locally on the data acquisition and analysis laptop. Raw data will be backed up after each participant on a separate flash drive and uploaded to a dedicated secure data storage for the study.

Upon completion of the study, access to clinical trial data will be limited to Pression personnel and the clinical study site (for up to 2 years after completion of the Study or regulatory approval of the device, whichever is longer, and in accordance with regulatory guidelines). Sharing of data to external entities and individuals (outside of Pression and the clinical study) will require approval from Pression and a signed non-disclosure agreement (NDA).

All data pertaining to clinical research conducted or sponsored by Pression is proprietary and confidential. Sharing of data from this study requires explicit approval from Pression.
For intentional dissemination of the clinical research data, as is the case for publications and scientific meetings, images, and summaries of collected data can be found in the manuscript/presentation itself, having been peer-reviewed and approved for publication. Specific requests for metadata, source material, design files, and proprietary code will be evaluated internally by Pression. All data and files generated at or for Pression in relation to R&D or clinical research of a product is considered proprietary and confidential. Pression ultimately reserves the right to admit or revoke data access. Intentional dissemination of clinical data collected during research will be anonymized and will not contain personal identifiable information. Data and images showcased in the form of publication and or website showcase will contain disclaimers dictating their condition for use (unless it is intentionally designated as Creative Commons).

10.1.10 CONFLICT OF INTEREST POLICY

The clinical study will be managed and monitored by an independent Clinical Research Organization (CRO) on behalf of Pression LLC.

Principal Investigators (PI) from the research study centers will not have a financial interest in Pression.

A blinded evaluator will be assigned to analyze and score the ECP data recorded during the study. The blinded evaluator will not have a financial interest in Pression.

10.2 NON-SIGNIFICANT RISK (NSR) STUDY

The Wave PRO System does not meet the below definition of significant risk under 21 CFR 812.3(m), and therefore this study will be conducted in accordance with the abbreviated IDE requirements listed in 21 CFR 812.2(b) for non-significant risk (NSR) devices. As defined in 812.3(m), a significant risk device means an investigational device that:

- Is intended as an implant and presents and potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The Wave PRO System is not an implant, is not purported or represented for use in supporting or sustaining human life, and, based on data from prior experience, does not appear to present the potential for serious risk to the health, safety or welfare of a participant.

The abbreviated IDE requirements per 21 CFR 812.2(b) apply to this study.

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	TBD	N/A – Initial Version	N/A

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