CorPath®GRX with ReMOTE Proof of Principle Protocol

CorPath®GRX with ReMOTE: First in Human

Rev. A
August 20, 2018

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Protocol Signature Page

I have read and understand the contents of this protocol. I agree to follow and abide by the guidelines set forth in this document.

_____

Investigator Name (print)

_____ _____

Investigator Signature Date

Sponsor Summary

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Monitoring:	Corindus Vascular Robotics, Inc. 309 Waverley Oaks Road, Suite 105 Waltham, MA 02452
Study Product:	CorPath®GRX + ReMOTE Proof of Principle (POP) System
Protocol Number:	2018-001

GRX with ReMOTE Proof of Principle (POP) Study Summary

Title:	**CorPath GRX with ReMOTE Proof of Principle (POP): First in Human**
Short Title:	GRX with ReMOTE: First in Human
Device:	CorPath®GRX + ReMOTE Proof of Principle System (CorPath GRX POP System) consists of: • CorPath GRX Bedside Unit (Extended Reach Arm, Robotic Drive and single-use Cassette) • Local and Remote Control Station
Regulatory Status:	The CorPath GRX System (Bedside Unit and Remote Workspace) was granted CM Mark approval on February 29, 2016 and was granted US Food and Drug Administration on October 27, 2016. The Local and Remote Control Station is a validated working prototype.
Indication for Use:	The CorPath GRX System is intended for use in the remote delivery and manipulation of coronary guidewires, rapid exchange balloon/stent catheters and remote manipulation of guide catheters during percutaneous coronary interventional (PCI) procedures.
Study Objective:	To evaluate the safety and performance of CorPath GRX POP System, in the ReMOTE (location outside hospital) delivery and manipulation of coronary guidewires and stent/balloon catheters, and manipulation of guide catheters during PCI procedures.
Study Design:	Prospective, single-arm, single center, non-randomized feasibility study of the CorPath GRX POP System to examine its performance during remote angioplasty (ballooning) and stenting and patient outcomes through 48 hours post-PCI procedure hospital discharge, whichever occurs first.
Principal Investigator:	Tejas Patel, M.D.
Sample Size:	Up to 5 subjects shall be treated in the study.
Investigational Sites:	One (1) international OUS investigative site will participate in this study.
Study Duration/ Follow-up Period:	The anticipated enrollment period is one (1) month. All subjects will be followed post ReMOTE CorPath PCI through 48 hours post-procedure or hospital discharge, whichever occurs first.

Subject Population: Subjects with coronary artery disease and with a clinical indication for PCI.

General Inclusion Criteria: Candidates will be included in the study only if all the following conditions are met:

1. Age ≥18 years;
2. Patients with coronary artery disease with clinical indication for PCI;
3. Patient deemed appropriate for robotic-assisted PCI; and
4. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.

Angiographic Inclusion Criteria:

1. Study lesion is a single *de novo* native coronary artery lesion (i.e. a coronary lesion not previously treated).
2. The lesion reference vessel diameter is between 2.50 mm and 4.0 mm by visual estimate.
3. Study lesion length less or equal to 20 mm by visual estimate.
4. The study lesion length can be treated with one stent. The stent should be able to cover the whole length of the lesion with at least 2mm of normal segments on proximal and distal edges of the lesion.
5. Study lesion diameter showing significant stenosis of at least 50% by visual estimate.

NOTE: Patient may have additional lesions requiring treatment using standard PCI (i.e. without utilization of the CorPath device) prior to actual enrollment in the study to perform treatment of study lesion using CorPath device. These non-study lesions must be in different vessel(s) than the study lesion. If non-study lesion(s) are treated on the same day of the index procedure, non-study lesion(s) must be successfully treated prior to the treatment of the study lesion

General Exclusion Criteria: Candidates will be excluded from the study if any of the following conditions are present:

1. Failure/inability/unwillingness to provide informed consent; or
2. The investigator determines that the patient or the coronary anatomy is not suitable for robotic-assisted PCI.

Angiographic Exclusion Criteria:

1. Target lesion that cannot be fully covered by a single stent.
2. Subject requires treatment of multiple lesions
3. Any previous stent placement within 5 mm (proximal or distal) of the target lesion

4. The study lesion requires planned treatment with DCA, laser, rotational atherectomy, or any device except for balloon dilatation prior to stent placement
5. The study vessel has evidence of intraluminal thrombus or moderate to severe tortuosity (> 90°) proximal to the target lesion
6. The study lesion has any of the following characteristics:
   a. Total occlusion
   b. Within 2mm of a side branch > 2.0 mm vessel diameter
   c. Not ostial in location
   d. Is located at ≥ 45° bend in the vessel
   e. Is severely tortuous
   f. Is severely calcified
   g. Severe calcification at the part of the vessel proximal to target lesion
   h. Target lesion that is located in a native vessel distal to an anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass and is approached through the by-pass graft
7. Unprotected left main coronary artery disease (an obstruction greater than 50% diameter stenosis in the left main coronary artery)

Primary Feasibility Endpoint:

Device Technical Success:
Defined as successful completion of the ReMOTE robotic-assisted PCI absent ***unplanned*** conversion to manual for guidewire or balloon/stent catheter inability to navigate vessel anatomy or poor guide catheter support.

Primary Safety Endpoint:

In-Hospital MACE:
MACE that occurs within 48 hours of the procedure or prior to hospital discharge, whichever occurs first, in a subject treated with ReMOTE delivery and manipulation of guidewires, balloon catheters and guiding catheters used with the CorPath GRX POP System.

Secondary Feasibility Endpoints:

Clinical Procedural Success:
Defined as less than 30% residual stenosis (visual estimate) post PCI in the lesion(s) treated with the CorPath GRX POP System (without an unplanned switch to the manual procedure) in the absence of device-related SAE, either within forty-eight (48) hours of the procedure or prior to hospital discharge, whichever occurs first.

Serious Adverse Events:

All Serious Adverse Events (SAEs) from the start of the Re-MOTE CorPath procedure until the end of the study will be summarized.

Fluoroscopy and/or X-ray Time:
As recorded by an X-ray system utilized during the procedure.

Patient Radiation Exposure Time:
Dose-area-product (DAP) and cumulative dose, as recorded during the procedure.

Contrast Fluid Volume:
Total amount of contrast used during CorPath GRX procedure.

Overall Procedure Time:
Defined as the time measured from the insertion of the hemostasis sheath until procedure complete (guide catheter removed).

PCI Procedure Time:
Defined as the time measured from the insertion of the guide catheter until the removal of the guide catheter.

CorPath GRX Procedure Time:
Defined as the time measured from the exit of the guide wire from the guide catheter until the guidewire is retrieved into the guide catheter.

Revision History

Version	Version Date	Summary of Changes
A	TBD	• Initial release

1.0 Introduction

1.1 Device Name

CorPath®GRX + ReMOTE Proof of Principle System (CorPath GRX POP System)

1.2 Background

The use of surgical robotics is growing immensely. Part of the reason for this growth is the amount of benefits afforded by robotics that are absent in traditional operative methods. For example, robots offer stability, accuracy, integration with modern imaging technology, greater range of motion, telesurgery, in addition to multiple other benefits inherent to individual surgical specialties [1]. Since the introduction of robotic surgery, many advances have been made in the field. One such advancement is using robots to perform operations remotely over long distances. In 2001, surgeons working in New York successfully used remotely controlled robots to laparoscopically remove a gall bladder from a 68-year-old woman in Strasbourg, France. The doctor moved a (remote) control in his hand in New York that sent a signal to (France) to move the robotic arm. So, when the doctor moved the robotic hand (using the remote control) in New York, the hand moved in the patient in France [2].

The CorPath GRX System is the second generation of the CorPath platform. With CorPath GRX, workflow is streamlined by the addition of an easily positioned extended reach arm. The new arm incorporates a "touchscreen". The benefits of the touchscreen allow the tableside user to visualize the instructions. Workflow enhancements also include a redesigned cassette to allow for active guide management. The clinical improvements consist of the addition of Active Guide Management, faster guidewire rotation and improved measurement accuracy. These improvements have the potential to allow for greater robotic procedural control for the primary operator and, perhaps a reduction in not only operator but also patient and Cath Lab team radiation exposure.

Currently the CorPath GRX consists of a bedside unit cabled to the robotic arm in the room of a procedure suite. The cabling is short enough to allow the physician operator to transmit intricate movements of the guidewire, balloon or stent with minimal latency. The Strasburg, France case above has set the stage for remote robotic-PCI. Today's LAN/MAN/WAN communication infrastructure is robust enough to allow remote medical procedures to become commonplace. Although robotic PCI has not yet been performed with an operator located off-site, the recently published REMOTE-PCI study demonstrated the feasibility of such an approach [3].

This study will evaluate the CorPath GRX POP System which will be modified to work remotely over larger distances utilizing LAN/MAN/WAN connectivity. Currently the CorPath GRX has two major components: a cockpit and a robotic arm (which are connected via several cables). This system allows an interventional cardiologist to advance and deploy coronary balloons and stents while sitting at the cockpit instead of standing at the side of the procedure table. After modifying the system to work remotely, the interventional cardiologist with be advancing and deploying balloons and stents remotely while the patient is in another room or tertiary care center (kilometers away).

The CorPath GRX POP System contains two identical workspaces, a local (Cath Lab) workspace designed for bedside use, and a remote workspace, designed for use by an off-site interventionalist. In this study, the primary Cath Lab will have a workspace, and this is the location of the secondary physician operator, scrub technologist and patient. The primary physician operator will be offsite at another location with access and control of the second workspace. The two workspaces equipment will communicate through LAN/MAN/WAN connectivity. The two workspaces will be outfitted with a telepresence system that will allow for real time audio and video between the primary Cath Lab and off-site primary operator during the remote PCI procedure.

This study will examine the feasibility of the CorPath GRX POP System during remote robotic-assisted PCI.

2.0 Intended Use & Device Description

2.1 Intended Use

The CorPath GRX System is intended for use in the remote delivery and manipulation of coronary guidewires, rapid exchange balloon/stent catheters and remote manipulation of guide catheters during percutaneous coronary interventional (PCI) procedures. The Local and Remote Control Station is a validated working prototype.

2.2 Device Description

The CorPath Bedside Unit consists of three components: (1) Extended Reach Arm, (2) Robotic Drive and (3) single-use Cassette (“Cassette”). The Extended Reach Arm supports the Robotic Drive, which houses the Cassette. The joysticks on the Control Console remotely deliver signals through a communication cable to the Robotic Drive that operates the Cassette. After the

selected guidewire and catheter are loaded into the Cassette, the Cassette translates the signals from the joystick manipulations into the linear and rotational movements of the guidewire and guide catheter and the linear movements of the balloon/stent. The Cassette has a Y-connector holder which holds the guide catheter hub and is attached to the drive gear and CoPilot. The drive gear enables guide catheter rotation.

The CorPath GRX POP System is comprised of the CorPath GRX Bedside Unit and the addition of two workspaces. One workspace is a local (Cath Lab) workspace designed for bedside use, and the second is a remote workspace, designed for use by an off-site interventionalist. Each workspace is comprised of two major subsystems: a robot control subsystem, and a telepresence subsystem.

The robot control subsystem contains a control console, housing a touch-screen and three joysticks (one joystick for balloon/stent manipulation, one joystick for guidewire manipulation and one joystick for guide catheter manipulation). The balloon/stent joystick allows for precise control of linear motion (advancement and retrieval) of its respective devices. The guidewire joystick allows for both linear and rotational movement (clockwise and counterclockwise) of the guidewire. The guide catheter joystick allows for precise control of linear motion (advancement and retrieval) and for rotational movement (clockwise and counterclockwise) of the guide catheter. The devices are controlled independently, which allows operations to be performed individually (by using one joystick at a time) or simultaneously (by activating multiple joysticks at once). For precise, discrete manipulation, the balloon/stent, guidewire and guide catheter can also be manipulated in discreet 1-mm increments via the touch-screen buttons on the Control Console.

The robot control subsystem also includes monitors for hemodynamic data and fluoroscopic video, providing the operator enhanced visualization of the PCI procedure.

The telepresence system contains local and remote cameras, monitors, and conferencing hubs, which are independent from the robot control subsystem, and provide human-to-human communication. The telepresence subsystem enables full bi-directional audio and video communications between the remote interventional cardiologist, and the Cath lab team. A real-time data stream allows seamless and instantaneous collaboration between the local and remote teams.

CorPath Use Technique

The operator should refer to the CorPath GRX System Operator's Manual for a detailed description of the system and relevant techniques.

To obtain proper data for analysis, the following procedure, with associated data collection milestones, is recommended, but in no case, dictates use of the CorPath GRX POP System in a manner different from that presented in the Operator's Manual.

Note that control of the system is identical whether operated from the local or remote workspace. Only one workspace can be active at a time.

3.0 Objectives, Feasibility and Safety Endpoints

3.1 Primary Objective

The primary objective of the GRX with ReMOTE Study is to evaluate the safety and performance of the CorPath GRX POP System, in the ReMOTE delivery and manipulation of coronary guidewires and balloon/stent catheters, and manipulation of guide catheters during PCI procedures.

3.2 Feasibility and Safety Endpoints

The following primary and secondary endpoints will be evaluated in patients enrolled in the CorPath GRW POP Study. Parameters are subject-based or lesion-based.

3.2.1 Primary Feasibility Endpoint – Device Technical Success

Defined as *successful* completion of the ReMOTE robotic-assisted PCI absent ***unplanned*** conversion to manual for guidewire or balloon/stent catheter inability to navigate vessel anatomy or poor guide catheter support.

3.2.2 Primary Safety Endpoint – In hospital MACE

MACE is defined as cardiac death, clinically relevant MI after coronary revascularization (Q-wave or non-Q-wave myocardial infarction), or clinically driven target vessel revascularization (TVR) by PCI or CABG. Clinically relevant MI after coronary revascularization is defined as:

- Patients with normal baseline cardiac biomarkers
  - CK-MB ≥10x ULN or cTn (I or T) ≥70x ULN, or
  - CK-MB ≥5x ULN or cTn ≥35x ULN plus new Q-waves in ≥2 contiguous leads or LBBB
- Patients with elevated baseline cardiac biomarkers
  - Baseline biomarkers are stable or falling:
    - CK-MB ≥10x ULN or cTn (I or T) ≥70x ULN of **most recent pre-procedure level**, or
    - CK-MB ≥5x ULN or cTn ≥35x ULN of **most recent pre-procedure level** plus new Q-waves in ≥2 contiguous leads or LBBB
  - Baseline biomarkers have not been shown to be stable or falling: CK-MB (or cTn) rises by an absolute increment equal to those recommended above plus new ST-

segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Note: Post PCI collection of biomarkers is left to the discretion of the investigator based on local practice patterns and clinical indication and is not mandatory by protocol.

3.2.3 Secondary Feasibility Endpoint – Clinical Success

Defined as less than 30% residual stenosis (visual estimate) post PCI in the lesion(s) treated with the CorPath GRX POP System (without an unplanned switch to the manual procedure) in the absence of device-related SAE, either within forty-eight (48) hours of the procedure or prior to hospital discharge, whichever occurs first.

3.3 Safety Measure

A safety-based measure will also be utilized to confirm the overall safety of the procedures involving the CorPath GRX POP System. This measure will include:

3.3.1 Serious Adverse Events

All Serious Adverse Events (SAEs) from the start of the ReMOTE robotic-assisted PCI procedure until the end of the study will be summarized.

3.4 Procedural Characteristics

The objective of this study is to demonstrate remote angioplasty (ballooning) and remote stenting with the use of the CorPath GRX POP System.

3.4.1 Overall Procedure Time Measure

Defined as the time measured from the insertion of the hemostasis sheath until the removal of the guide catheter

3.4.2 PCI Procedure Time

Defined as the time measured from the insertion of the guide catheter until removal of the guide catheter.

3.4.3 Fluoroscopy Time

Total fluoroscopy utilized during the PCI procedure, as recorded by an imaging system.

3.4.4 Patient Radiation Exposure

DAP (dose-area-product) and cumulative dose/air kerma, as recorded during the PCI procedure.

3.4.5 Contrast Fluid Volume

Total volume used during the PCI procedure.

4.0 Investigational Plan

4.1 Overview

This is a prospective, single-arm, single center, non-randomized feasibility study of the CorPath GRX POP System to examine its performance during remote angioplasty (ballooning) and stenting and patient outcomes through 48 hours post-PCI procedure.

The study population will consist of up to five (5) staged subjects undergoing a PCI procedure with the CorPath GRX POP System who provide informed consent.

The study will be conducted at one (1) international (OUS) site with an enrollment of up to 5 subjects. This study protocol does not dictate the therapeutic decisions of the operator.

All enrolled patients will be followed post- ReMOTE robotic-assisted PCI procedure through hospital discharge or 48 hours, whichever occurs first.

4.2 Enrollment Plans

Each staged patient undergoing a ReMOTE robotic-assisted PCI procedure will be enrolled in the study after providing written informed consent for the provision of data.

4.3 Informed Consent Procedures

When a suitable candidate presenting for a percutaneous coronary intervention meets the eligibility criteria for enrollment in this study, the Investigator (or designee) will explain the risks and benefits of data provision to the subject. If the subject agrees to participate in the study, an approved study-specific informed consent form must be signed.

During the informed consent discussion, the background of the proposed study and the benefits and risks of the study should be explained to the subject, per the site's Informed Consent Process. This discussion should highlight the fact that the patient is being asked solely to share the data collected from their procedure and any related events through 48 hours post-procedure or discharge, whichever occurs first.

Once the subject signs the EC-approved consent form, they are considered enrolled in the study. Failure to obtain signed informed consent renders the subject ineligible. Copies of the signed informed consent shall be kept in the subject's medical records and study files. A copy of the fully executed informed consent form must be given to each subject enrolled in the study.

Modifications to the GRX with ReMOTE Study Informed Consent must have written approval by Corindus and the EC prior to use, as required.

4.4 Screen Failure

A subject who signs an informed consent form (ICF) and does not have a ReMOTE robotic-assisted PCI or is enrolled in the study but withdraws their consent will be considered a screen failure.

4.5 Patient Selection

Subjects with coronary artery disease with a clinical indication for PCI and deemed appropriate for PCI with the CorPath GRX POP System, and who have signed the ICF for data collection will be enrolled into the GRX with ReMOTE study.

General Inclusion Criteria:

1. Age ≥ 18 years;
2. Patients with coronary artery disease with clinical indication for PCI;
3. Patient deemed appropriate for the CorPath GRX POP System; and
4. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.

Angiographic Inclusion Criteria:

1. Study lesion is a single *de novo* native coronary artery lesion (i.e. a coronary lesion not previously treated).
2. The lesion reference vessel diameter is between 2.50 mm and 4.0 mm by visual estimate.
3. Study lesion length less or equal to 20 mm by visual estimate.
4. The study lesion length can be treated with one stent. The stent should be able to cover the whole length of the lesion with at least 2mm of normal segments on proximal and distal edges of the lesion.
5. Study lesion diameter showing significant stenosis of at least 50% by visual estimate.

NOTE: Patient may have additional lesions requiring treatment using standard PCI (i.e. without utilization of the CorPath device) prior to actual enrollment in the study to perform treatment of study lesion using CorPath device. These non-study lesions must be in different vessel(s) than the study lesion. If non-study lesion(s) are treated on the same day of the index procedure, non-study lesion(s) must be successfully treated prior to the treatment of the study lesion.

General Exclusion Criteria:

1. Failure/inability/unwillingness to provide informed consent; or
2. The investigator determines that the patient or the coronary anatomy is not suitable for robotic-assisted PCI.

Angiographic Exclusion Criteria:

1. Target lesion that cannot be fully covered by a single stent.
2. Subject requires treatment of multiple lesions
3. Any previous stent placement within 5 mm (proximal or distal) of the target lesion.
4. The study lesion requires planned treatment with DCA, laser, rotational atherectomy, or any device except for balloon dilatation prior to stent placement.
5. The study vessel has evidence of intraluminal thrombus or moderate to severe tortuosity (> 90°) proximal to the target lesion.
6. The study lesion has any of the following characteristics:
    a. Total occlusion
    b. Within 2mm of a side branch > 2.0 mm vessel diameter
    c. Not ostial in location
    d. Is located at 45° bend in the vessel
    e. Is severely tortuosity
    f. Is severely calcified
    g. Severe calcification at the part of the vessel proximal to target lesion
    h. Target lesion that is in a native vessel distal to an anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass and is approached through the by-pass graft.
7. Unprotected left main coronary artery disease (an obstruction greater than 50% diameter stenosis in the left main coronary artery).

4.6 Data to be Collected

4.6.1 Baseline data

The following baseline data *should* be collected for all subjects prior to staged index-procedure (usually routinely done for patients with PCI):

- CK & CK-MB and/or Troponin (within 7 days, select the lab value closest to the CorPath PCI)

Additionally, the following baseline data should be collected for all subjects within 30 days prior to the staged index procedure (usually routinely done for PCI patients):

- Patient Eligibility Criteria
- Medical history
- Clinical assessment & physical examination
- Non-cardiac laboratory tests (Creatinine, Hemoglobin)

4.6.2 CorPath GRX PCI Procedure

Peri-Procedure Study Medication Regimen

Follow standard institutional and/or stent manufacturer's guidelines for recommended anticoagulation regimen.

Data to be collected prior to initiating CorPath:

- Arterial access site
- Procedure start time (Sheath insertion)
- PCI Start Time (Guide Catheter Insertion)
- Lesion Classification

Data to be collected during the CorPath procedure:

- CorPath time (guidewire activation to guidewire retraction)
- Fluoroscopy time
- Patient radiation exposure (DAP and AK/CD)
- Contrast volume
- Procedure end time (Guide Catheter out)
- Guide catheter manipulation attempts (guide catheter reengagement with CorPath GRX)

CorPath Use Technique

The operator should refer to the CorPath GRX System Operator's Manual for a detailed description of the system and relevant techniques.

To obtain proper data for analysis, the following procedure, with associated data collection milestones, is recommended, but in no case, dictates use of the CorPath POP System in a manner different from that presented in the Operator's Manual:

1. Obtain access using conventional percutaneous catheterization techniques.
2. Once arterial access is obtained, insert a standard guide catheter using conventional techniques. The guide catheter and guidewire of the physician's choosing shall be used.
3. Manually advance and engage the guide catheter in the coronary artery.
4. Perform angiography to assess the target lesion(s).
5. Record target lesion characteristics such as percent diameter stenosis, etc.
6. For Remote operation, the remote Interventional Cardiologist (IC) workstation must be enabled. In general, select which workspace (local or remote) is to be used for the procedure. Only one workspace can have control at a time.

To enable exclusive control:

For the local (Cath lab) side, the local operator should click or tap “Enable All” from the control console. This will lock out access by the remote (IC) operator, and gray out controls on the remote (IC) side. To release control, the local (Cath lab) operator should subsequently click or tap “Disable all”.

For the remote (IC) side, first the IC workstation must be enabled. The remote operator should click or tap “RCL Disabled” (Remote Cath Lab) from the control console. This will lock out access by the local (Cath lab) operator, and gray out controls on the local (Cath lab) side.

Once the IC workstation has been enabled the operator should click or tap “Enable All” from the control console. This will allow control of the IC workstation to proceed.

To release control, the remote (IC) operator should subsequently click or tap “IC Enabled”.

During any procedure (whether controlled remotely or locally), to change devices on the robot arm, or to otherwise lock out joystick controls, the bedside operator should click or tap “Exchange Devices” on the robot console, to disable controls.

The remote or local user can click or tap “Disable All” at any time to lock out the joystick controls.

7. Introduce and advance coronary guidewire to the tip of the guide catheter utilizing CorPath GRX POP System.
8. Introduce and advance the therapeutic coronary device (balloon/stent) using the CorPath GRX POP System. The delivery of interventional dilatation and stenting devices to the target lesion (pre-dilation, stent, post dilatation) will be done using the CorPath GRXPOP System. Active guide management may be used to fine tune the placement of or reengage the guide catheter in the ostium of the coronary artery.
9. Retract balloon/stent system using CorPath GRX POP System.
10. Perform completion angiography to assess the target lesion final diameter stenosis and the condition of associated vasculature.
11. Record final fluoroscopy time.
12. Record time of guide catheter removal from the coronary vessel (**procedure end time**).

4.6.3 Conversion to Manual Procedure Data Collection

The Investigator shall determine if it is necessary to convert to standard manual percutaneous techniques to ***complete*** the PCI. The Investigator should make this decision based on his/her medical assessment of the situation in accordance with the best interest of the subject. A second physician will be available at the bedside in the event a conversion to manual is necessary. It is recommended that conversion to manual operation be performed at the discretion of the Investigator or if any of the following occur:

- The inability to navigate the guidewire or balloon/stent catheters using the CorPath GRX POP System as intended.
- Any clinical condition that requires rapid medical intervention.

The reason for conversion to manual should be reported by the operator and documented.

4.6.4 Post-CorPath Data Collection

Acute Post-CorPath Procedure Medication Regimen

Follow standard operator and institutional routines for recommended anticoagulation and antiplatelet regimens.

Post-CorPath Procedure Subject Evaluations

- Clinical assessment and physical examination
- Record of all SAEs
- Hemoglobin and Creatinine (Maximum and 48 hours/Discharge levels)
- If clinically indicated as determined by the investigator,
    - 12-lead ECG
    - CK, CK-MB and/or Troponin

4.7 Follow-Up

The patients will be followed for 48 hours post-procedure or hospital discharge, whichever occurs first. No additional patient contact is required for this study. Data collection must be completed on all subjects before they are discharged from the hospital.

4.8 Schedule of Data Collection

Data collected for all subjects enrolled in this study are listed in the following Schedule of Activities (Table 1), many of which are part of routine data collection for all PCI procedures:

Table 1: Schedule of Activities

	Pre-procedure	Procedure	Post Procedure
Patient Eligibility Criteria[1]	X		
Medical history[1]	X		
Clinical assessment & Physical exam	X[1]		X
Non-Cardiac Laboratory Tests	X[1]		X
Cardiac enzymes	X[2]		X[3]
12-lead ECG			X[4]
Angiography		X	
Procedure Parameters (procedure time, fluoroscopy time, etc.)		X	
Contrast volume		X	
Record of SAEs		X	X
Data for lesion classification		X	

[1] Within 30 days of index procedure.

[2] Pre-procedure cardiac enzymes within 7 days of index procedure, if collected.

[3] Post-procedure cardiac enzyme collection is left to the discretion of the investigator and shall be dictated by the patient's clinical symptoms.

[4] Post-procedure 12-lead ECG: it is recommended that an ECG be performed at the time of discharge but is not required for the protocol.

5.0 Data Collection

5.1 Study Data Requirements

CRFs received from the clinical site will be documented with their date of receipt and entered into the trial database. A database that is compliant with 21 CFR Part 11. If there is missing,

incomplete, unclear or discrepant information recorded on a CRF, a Data Clarification Form (DCF) will be generated. The DCF will be sent to the Investigator for completion and signed by the appropriate site personnel. The DCF will then be sent back to Corindus to update the database.

6.0 Monitoring Procedures

6.1 Investigator/Site Selection

The minimum criteria for selecting a Clinical Investigator/site will include the following:

- Education, experience and interest of the Investigator;
- Expertise in the area of interest;
- Adequacy of resources, facilities and equipment at the investigational center;
- Ability of the Investigator and center to meet activation requirements in a timely manner;
- Patient population of the center and the ability to enroll adequate numbers of subjects;
- Status with regulatory agencies;
- Investigator performance in previous clinical trials;
- Investigator participation in concurrent studies; and
- No known financial conflicts of interest.

6.2 Site Initiation

The following documents must be received prior to clinical trial site initiation/activation and maintained at the site and Corindus, if applicable:

- Signed Clinical Trial Agreement;
- Current Curriculum Vitae (CV) for Primary Investigator(s);
- Corindus and EC approved Informed Consent Form; and
- EC Approval Letter.

Additional items that may be collected prior to activation, but not required at that time:

- Investigator Financial Disclosure Form(s);
- EC Membership List and/or Accreditation Statement; and
- Site Personnel Training Record(s)

6.3 Case Report Form Review

CRFs received from the clinical site will be documented with their date of receipt and entered into the trial database. If there is missing, incomplete, unclear or discrepant information recorded on a CRF, a Data Clarification Form (DCF) will be generated. The DCF will be sent to the Investigator for completion and signed by the appropriate site personnel. The DCF will then be sent back to Corindus to update the database.

6.4 On-site Monitoring

The Clinical Representative will maintain personal contact with the Investigator and staff by fax, phone, mail, and on-site visits. The monitor will require access to all subjects' records at. These may include:

- Clinic charts
- Hospital charts
- Angiograms
- Investigator Administrative Records
- Subject Binders

Monitoring will verify:

- Written informed consent has been obtained for each subject;
- Device Accountability;
- Continued plan and regulatory compliance; and
- Verification of data recorded on Case Report Forms to source documents.

6.5 Final Monitoring Visit

At the close of the trial, the Clinical Representative will make a final on-site visit. The purpose of this visit is to:

- Collect all outstanding study data;
- Insure that the Investigator's files are accurate and complete;
- Review record retention requirements with the Investigator; and
- Assure that all requirements are met for the closure of the study.

6.6 Confidentiality and Protection of Study Files

In conducting the study, the investigational site will comply with all applicable federal and regional laws and regulations relating to the confidentiality and security of individually identifiable medical information.

If a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

In accordance with PHI regulations, subject records leaving the facility for purposes of the investigation should be identified by the Subject ID assigned for the study, and should not include the subject's name, whenever practical. Every effort should be made to "black out" subject's name from medical records including films prior to sending to Corindus or the core lab.

All personal information pertaining to subjects will be kept confidential. This study is being conducted in compliance with FDA 21 CFR. Whenever practical, subjects will be identified only by their Subject ID Number and initials. Clinical trial documents and hospital and clinic medical records pertaining to study subjects may be reviewed by Corindus study personnel or their representatives, FDA, or other health inspectors as needed to assure compliance with all study requirements.

Information obtained during executing this study, including still and motion photography, may be presented for regulatory, clinical or educational purposes as long as no subject is identified. The data collected is the property of Corindus.

7.0 Data Quality Assurance

7.1 Clinical Event Handling

This study will collect data on subjects undergoing standard treatments and procedures. The site will be asked to provide documentation of events on the paper CRFs related to specific procedural events and device complications. The Sponsor will identify events associated with the study endpoints and additional event review may be performed, as described below. The site will follow their routine hospital procedures for adverse event handling, as necessary.

7.2 Study Endpoint Event Adjudication

A site independent review of all clinical events associated with the study endpoints will be conducted. Adjudication will be based on narratives and source data supplied by the site. Source data that may be collected for review include, but are not limited to, de-identified angiograms (diagnostic and procedural), catheterization lab report, procedure report, discharge summary, lab reports, and pre- and post-procedure ECGs. The site may be contacted for queries and additional support documentation.

8.0 Statistical Methods

This is a prospective, single-arm, single center, non-randomized feasibility study of the CorPath POP System designed to evaluate the safety and effectiveness of the clinical and technical performance of the CorPath GRX POP System in the REMOTE delivery and manipulation of coronary guidewires and stent/balloon catheters, and remote manipulation of guide catheters for use in PCI. The detailed investigational plan, pre-defined nature of study endpoints, and prospective nature of data collection help provide protection against study bias. The intent of this study is to gather preliminary data of performance and does not have powered pre-specified pass/fail objectives and associated type I error rates. As such, interim analyses may be performed on accruing data during the study.

The sample size of up to 5 subjects will provide a reasonable degree of precision for events that occur during the study. For example, at an assumed success rate of 99%, the expected confidence interval width for the success rate based on a two-sided 95% exact binomial confidence interval will be less than 19%. Similarly, at an assumed safety outcome rate of 1%, the expected confidence interval width for the success rate based on a two-sided 95% exact binomial confidence interval will be less than 19%.

Corindus' standard operating procedures for study monitoring, data editing, data management, computer entry and verification of database accuracy will be implemented prior to study onset. After verification of database accuracy and closure, an examination of the distribution of each numeric variable (i.e. study endpoint) will be performed. Descriptive statistics for each variable will be calculated which will include measures of central tendency, variation, a frequency histogram and a count of the number of missing values.

When the arithmetic mean is found not to be an appropriate measure of central tendency, alternative statistics will be considered (e.g. median). When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches or data transformations may be implemented. Two-sided 95% confidence intervals will be used for means or proportions as appropriate for primary and secondary outcome measures. For proportions, exact binomial confidence intervals will be used. If data transformations are used, they will be specified in the final clinical report.

It is not a planned part of this study to utilize data imputation for missing values. However, should data imputation be used at the time of analysis, the method will be specified in the final clinical report. Exploratory analyses may be performed to better characterize and understand the data.

9.0 Administrative Responsibilities

The GRX with ReMOTE Study will be conducted in accordance with Good Clinical Practice including the study protocol, the fully executed Clinical Study Agreement and all applicable regulations.

9.1 EC Approval

The Clinical Protocol, ICF, and associated documents and any other relevant documentation shall be reviewed and approved by the EC prior to subject enrollment. All proposed changes, including administrative changes, to the protocol, ICF, associated documents and other relevant documentation must be reviewed and approved by Corindus and the EC prior to implementation.

Investigators are responsible for obtaining and maintaining annual renewal of the study by their EC. Evidence of renewal and continued EC approval must be provided to Corindus or their authorized agent prior to continuation of the study at the Investigational Site.

9.2 Confidentiality

All data sent to Corindus or their authorized designee, concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

9.3 Study Registration and Publication Policy

The GRX with ReMOTE Study will be registered with clinicaltrials.gov prior to the start of enrollment.

Prior to publication, Corindus will be given the opportunity to review and comment upon any manuscript that contains data derived from this study.

10.0 Supply of Study Materials

10.1 Supply of Investigational Devices

Corindus will ship investigational devices (Local and Remote Control System) only to the qualified investigational site participating in the clinical investigation after Regulatory Authority approval to begin the study and EC approval to begin the study at the site. Corindus will maintain records pertaining to the shipment of the investigational device. Records of shipment include the name and address of the consignee, type and quantity of device, date of shipment and batch or lot number.

10.2 Tracking, Storage and Disposition of Investigational Devices at the Clinical Site

Investigational supplies must be stored in a secure location segregated from standard hospital inventory. The investigational site will maintain complete, and accurate records pertaining to the receipt and disposition of investigational devices, whether used for a study subject, returned to Corindus, destroyed or discarded. The site primary investigator is responsible for ensuring that investigational devices are made available only to site personnel who are authorized to access them and only to subjects under the Investigator's supervision.

10.3 Return or Destruction of Trial Supplies

At the completion or termination of the investigation (or the Investigator's participation in the investigation) or at the sponsor's request, an investigator will return to Corindus any remaining

supply of the device or otherwise dispose of the device as Corindus directs. Corindus will perform a final reconciliation of investigational supplies shipped, consumed, and remaining.

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2. Gottlieb, S. (2001). Surgeons perform transatlantic operation using fiberoptic. *BMJ*, 323(7315), pp.713-713.
3. Madder, R., VanOosterhout, S., Jacoby, M., Collins, J., Borgman, A., Mulder, A., Elmore, M., Campbell, J., McNamara, R. and Wohns, D. (2017). Percutaneous coronary intervention using a combination of robotics and telecommunications by an operator in a separate physical location from the patient: an early exploration into the feasibility of telestenting (the REMOTE-PCI study). *EuroIntervention*, 12(13), pp.1569-1576.

APPENDIX A. DEFINITIONS

MACE Definitions

Major Adverse Cardiac Event (MACE): MACE is defined as cardiac death, Q-wave or non-Q-wave myocardial infarction (MI), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods.

Cardiac Death: Death due to cardiac causes. If the cause of death cannot be determined, it will be categorized as cardiac.

Myocardial Infarction (Protocol Definition):

Clinically relevant MI after coronary revascularization is defined as:

- Patients with normal baseline cardiac biomarkers
  - CK-MB ≥10x ULN or cTn (I or T) ≥70x ULN, or
  - CK-MB ≥5x ULN or cTn ≥35x ULN plus new Q-waves in ≥2 contiguous leads or LBBB
- Patients with elevated baseline cardiac biomarkers
  - Baseline biomarkers are stable or falling:
    - CK-MB ≥10x ULN or cTn (I or T) ≥70x ULN of **most recent pre-procedure level**, or
    - CK-MB ≥5x ULN or cTn ≥35x ULN of **most recent pre-procedure level** plus new Q-waves in ≥2 contiguous leads or LBBB
- Baseline biomarkers have not been shown to be stable or falling: CK-MB (or cTn) rises by an absolute increment equal to those recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Target Vessel Revascularization (TVR): Ischemia-driven repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel. A TVR will be considered as ischemia-driven if the target vessel diameter stenosis is ≥50% and any of the following are present:

- A positive functional study corresponding to the area served by the target vessel.
- Ischemic ECG changes at rest in a distribution consistent with the target vessel.
- Ischemic symptoms referable to the target lesion.

In-Hospital MACE: MACE that occurs within 48 hours of the procedure or prior to hospital discharge, whichever occurs first, in a subject treated with the CorPath GRX System.

Other Definitions

Adverse Event Classification

An adverse event is defined as any adverse change in health or undesirable clinical occurrence from the subject's baseline whether it is considered device related or not.
An adverse event is considered serious if it results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is an important medical event which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

Procedure-Related Adverse Event

An adverse event is considered to be procedure-related when, in the judgment of the Investigator, it is reasonable to believe that the event is not associated with the CorPath GRX System use. Instead, other products, surgical techniques, or medications required specifically for the procedure are deemed by Investigator as likely to have contributed to the occurrence of the event.

Abrupt Closure: The occurrence of new severely reduced flow (TIMI flow grade 0 or I) within the target vessel that persisted and required rescue by a non-assigned treatment strategy (including emergency surgery) or resulted in MI or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus or severe spasm. Abrupt closure does not connote "no reflow" (due to microvasculature limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application reversed the closure.

Coronary Dissection - Refers to a split or a tear in the wall of the artery which compresses or compromises the lumen of the artery reducing blood flow.

Coronary Guidewire Dissection - A coronary dissection where a coronary guidewire is inadvertently positioned in a subintimal position or when stiff-tipped or hydrophilic-tipped guidewires are used to cross highly stenosed or totally occluded arteries.

Coronary Perforation - Coronary perforation occurs when a dissection or intimal tear propagates outward sufficient to completely penetrate the arterial wall. This may be caused by pre/post balloon dilatation or post stent deployment where the stent edge causes an edge perforation. Stent edge perforation will range in severity. Ellis classification of coronary perforation:

- Type I - Focal extraluminal crater without extravasation
- Type II - Pericardial or myocardial 'blush' without contrast agent
- Type III - Contrast agent 'jetting' through a frank (>1 mm) perforation

Access Site Complication: A complication occurring at the access site that requires either local intervention or blood transfusion.

Subacute Thrombosis: An abrupt closure of the target vessel that occurs after the index procedure is completed (and the subject has left the catheterization laboratory) and within 48 hours of the PCI.

Threatened Abrupt Closure: A grade B dissection and >50% diameter stenosis or any dissection of grade C or higher.

Bleeding Requiring Transfusion: Any blood loss requiring transfusion of blood products. Transfusion without clinical evidence of bleeding will be recorded separately.

Coronary Artery Bypass Graft Surgery (CABG): Classified as emergent, urgent, or elective as follows:

- **Elective**: the subject is clinically stable, and the overall medical condition does not indicate the need for revascularization within forty-eight (48) hours.
- **Urgent**: the subject is clinically unstable and the condition warrants revascularization within two (2) to forty-eight (48) hours.
- **Emergent**: the subject is clinically unstable, and the condition requires immediate revascularization within two (2) hours.

Cardiogenic Shock: Subject presents with systolic blood pressure <80 mm Hg for more than thirty (30) minutes unresponsive to fluids or requiring intravenous pressures or an intra-aortic balloon pump.

CK: Creatine kinase, or creatine phosphokinase.

CK-MB: An iso-enzyme of creatine phosphokinase (CK) with a distinct molecular structure specific as an indicator of myocardial cell injury. It is used to evaluate possible causes of chest pain, to detect and diagnose acute MI and re-infarction, and to monitor the severity of myocardial ischemia.

Vascular Injuries:

- **Dissection:** A tear in a vessel allowing blood to enter the wall of the vessel and split its layers. The result is either an intramural hematoma or aneurysmal dilatation.

Dissection classification per National Heart, Lung and Blood Institute:

- Type A: Radiolucent areas within the coronary lumen during contrast injection, with minimal or no persistence of contrast after dye has cleared.
- Type B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye has cleared.
- Type C: Contrast outside the coronary lumen, with persistence of contrast in the area after dye has cleared.
- Type D: Spiral luminal filling defects frequently with extensive contrast staining of the vessel.
- Type E: New persistent filling defects that may be caused by thrombus.
- Type F: Non-type A-E dissection types that lead to impaired flow or total occlusion of the coronary artery.

No Reflow: Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

Perforation: Perforations are classified as follows:

- **Angiographic perforation**: Perforation detected by the clinical site at any point during the procedure.
- **Clinical perforation**: Perforation requires additional treatment beyond IV fluid administration (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death.

Restenotic Lesion: Defined as lesion in a vessel that had undergone a prior percutaneous treatment.

Thrombus: Discrete, mobile intraluminal filling defect with defined borders with or without staining.

Thrombosis: Academic research Consortium (ARC) definitions:

- **Definite stent thrombosis** requiring the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion**.**
- **Probable stent thrombosis** includes unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.
- **Possible stent thrombosis** includes all unexplained deaths occurring at least 30 days after the procedure.

TIMI FLOW:

- **TIMI 0**: Dye fails to enter the microvasculature. There is either minimal or no ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery indicating lack of tissue level perfusion.
- **TIMI I**: Dye slowly enters but fails to exit the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately thirty (30) seconds between injections).
- **TIMI II**: There is delayed entry and exit of dye from the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e. dye is strongly persistent after three (3) cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).
- **TIMI III**: There is normal entry and exit of dye from the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent at the end of the washout phase (i.e. dye is gone or is mild/moderately persistent after three (3) cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), like that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade III.

Total Occlusion: True total occlusion is a lesion with TIMI 0 antegrade intraluminal flow and 100% diameter stenosis. A functional total occlusion is a lesion with TIMI I antegrade intraluminal flow and 99% diameter stenosis (functional TO) A chronic total occlusion is either of the above that has been present for at least 3 months.

Troponin: a complex of three regulatory proteins, measured levels of which can be used as a test of several different heart disorders, including myocardial infarction.

Unstable Angina: Angina that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset.

Vessel Characteristics:

- **Angulation**: Vessel angle formed by the centerline through the lumen proximal to the stenosis and extending beyond it, and a second centerline in the straight portion of the artery distal to the stenosis measured in a non-foreshortened view.
- **Spasm**: Transient narrowing >50% diameter in a region where a <25% diameter stenosis had previously been.
- **Tortuosity**: Number of bends that must be traversed by a device to reach the target lesion.
- **Haziness**: Presence of radiolucencies within the arterial lumen not satisfying the criteria for thrombosis.

Lesion Characteristics:

- **Anastomotic**: Lesion located at the junction of a bypass graft and native vessel.
- **Aneurysm**: An expansion of the lumen in the region of maximum stenosis that extends with a wide or narrow mouth beyond the apparent normal contour.
- **Aorto-ostial:** A lesion is classified as aorto-ostial when it is located within 3 mm of the origin of the coronary vessels from the aorta.
- **Bifurcation**: Lesion located at the origin, immediately after, or branch that has a diameter ≥ 2mm.
- **Eccentricity**: A stenosis that has one of its luminal edges in the outer one-quarter of the apparent normal lumen.

- **Calcification**: Readily apparent densities noted within the apparent vascular wall at the site of the stenosis. Calcification is classified as none/mild, moderate when densities noted only during the cardiac cycle prior to contrast injection, and severe when densities noted without cardiac motion prior to contrast injection generally involving both sides of the arterial wall.
- **Intimal Flap**: Extrusion of tissue extending from the arterial surface into the lumen.
- **Irregularity**: Lesion borders with abnormal margins based on the presence of an ulceration, aneurysm, or intimal flap.
- **Length**: "Shoulder to shoulder" distance, which is measured from the proximal shoulder to the distal shoulder of a lesion in the projection that shows the most elongated view of the stenosis.
- **Discrete**: Lesion length <10.0 mm.
- **Tubular/Focal**: Lesion length ≥10.0 mm and ≤20.0 mm.
- **Diffuse**: Lesion length ≥20.0 mm.
- **Location**: Designated as ostial, proximal, mid and distal.
- **Ostial**: Lesions that begin within 3.0 mm of the origin of the artery.
- **Ulceration**: A small crater or flap in a lesion.

ACC/AHA Lesion Characteristics (Type A, B and C):

- *Type A Lesions (high success, >85%; low risk)*: Discrete (<10mm length), concentric, readily accessible, non-angulated segment ,45°, smooth contour, little or no calcification, less than totally occlusive, non-ostial in location, no major branch involvement and absence of thrombus.
- *Type B (B1 and B2) Lesions (moderate success, 60 - 85%; moderate risk)*: Tubular (10-20 mm length), eccentric, moderate tortuosity of proximal segment, moderately angulated, 45 - 90°, irregular contour, moderate or heavy calcification, ostial in location, bifurcation lesions requiring double guidewires, some thrombus present and total occlusion < 3 months old. Type B2 lesion classification has more than one characteristic above.

- *Type C Lesions (low success, < 60%; high risk)*: Diffuse (>2 cm length), excessive tortuosity of proximal segment, extremely angulated, > 90^{o}, inability to protect major side branch, degenerated vein grafts with friable lesions and total occlusions > 3 months old.

APPENDIX B. CORPATH GRX OPERATOR'S MANUAL

APPENDIX C. CRFs

