FLUIDX
MEDICAL TECHNOLOGY

Evaluation of a Simple-Prep Controlled Embolic (GPX Trial)

Clinical Study Protocol

[redacted]

Revision: A

Fluidx Medical Technology, Inc.
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Sponsor Signatures

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Study Director (CRO)
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FLUIDX MEDICAL TECHNOLOGY	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Fluidx Study Number:** [redacted]
Study Title	Evaluation of a Simple-Prep Controlled Embolic (GPX Trial)
Identifying Regulatory Numbers	FDA IDE number – G230321 Clinicaltrials.gov – *to be assigned*
Study Objective	To evaluate the safety and effectiveness of the GPX® Embolic Device when used as indicated for embolization requiring distal vessel penetration.
Device Description	The GPX Embolic Device comprises two pre-coupled syringes that each contain 0.5 mL of GPX Embolic Material, a water-based solution of two oppositely charged polymers and tantalum (for radiopacity). When delivered into the bloodstream, the GPX Embolic Material begins to immediately solidify as it fills the targeted region, forming a durable occlusion. The GPX Embolic Device is compatible with commercially available delivery devices, such as microcatheters. The GPX Embolic Device is provided sterile (gamma irradiation).
Proposed Device Indications for Use	The GPX Embolic Device is only intended for distal embolization in the peripheral vasculature including vascular tumors (e.g., renal angiomyolipoma, renal cell carcinoma, bone tumors, bleeding tumors, and other vascular tumors), renal embolization, and portal vein branches. It is not intended for embolization of active bleeding sites, veins other than the portal vein, aneurysms, endoleaks, vascular malformations, or vessels for flow redistribution.
Study Design	The investigation is a single-arm, open-label, non-randomized, prospective, multicenter, multinational pivotal study.
Number of Sites & Subjects	The study will be conducted in up to 25 investigational sites in the USA, New Zealand, and Canada; a minimum of 50% of the sites will be in the USA. The study will enroll up to 114 subjects. Each site will be capped at a maximum of 25% of total enrollment. A minimum of 50% of subjects will be enrolled from sites in the USA.
Study Population	The population for this study is adult subjects who present with a need for distal embolization in the peripheral vasculature including vascular tumors (e.g., renal angiomyolipoma, renal cell carcinoma, bone tumors, bleeding tumors, and other vascular tumors), renal embolization, and portal vein branches.

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FLUIDX MEDICAL TECHNOLOGY	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Fluidx Study Number:** [redacted]
Primary Safety Endpoint	Freedom from major adverse events (MAEs) through 30 days post-index procedure. MAEs are defined as device-related serious adverse events, as adjudicated by the Clinical Events Committee (CEC), comprising the following types: • Nontarget embolization with ischemia in an unintended anatomical area • Systemic allergic and/or toxic reaction to the GPX Embolic Device • Catheter entrapment and/or breakage • Culture-proven abscess in target organ/tissue • Embolization-related death
Primary Effectiveness Endpoint	Delivery of the GPX Embolic Device to the target vessel embolization site(s) determined by the investigator at the time of enrollment, and successful occlusion of flow immediately beyond the target vessel embolization site(s), as determined by the core lab via comparison of the pre- and final post-embolization images.
Secondary Endpoints	The secondary endpoints for the study are the occurrence of: • Device-related adverse events (AE) through 30 days post-index procedure • Adjunctive embolization agent usage during the embolization procedure • Catheter occlusion due to the GPX Embolic Material
Ancillary Data	The following ancillary data will be collected: • Device performance assessment

Study Eligibility Criteria	Patients must meet all the following <u>inclusion</u> criteria:
	1. Age ≥18 years on the date of consent
	2. Expected post-procedural lifespan of at least 30 days, in the opinion of the investigator, to allow for participation in all follow-up visits
	3. Presents with need for peripheral embolization where there is a desire for distal vessel bed penetration including:
	  ○ Vascular tumors (e.g., renal angiomyolipoma, renal cell carcinoma, bone tumors, bleeding tumors, and other vascular tumors)
	  ○ Renal embolization
	  ○ Portal vein branches
	4. Informed consent granted by the patient or legally authorized representative
	5. Willing and able to comply with the protocol-specified procedures and assessments

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FLUIDX MEDICAL TECHNOLOGY	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Fluidx Study Number:** [redacted]
	Patients must not meet any of the following exclusion criteria: *General exclusion criteria:* 1. Requires embolization for any of the following applications: a) Neurovasculature b) Coronary vasculature c) Hemorrhage due to trauma d) Non-tumoral focal/active bleeding sites (e.g., gastrointestinal tract, urinary tract, lung) e) Veins other than portal vein f) Aneurysms g) Endoleaks h) Vascular malformations i) Vessels for flow redistribution 2. Has undergone an embolization procedure within 30 days prior to consent 3. Presents with need for embolization where the risk of clinically significant infarction outweighs the benefit of distal penetration (e.g., gastrointestinal, uterine) 4. Embolization target is only intended for temporary occlusion (e.g., bioresorbable biologic embolic agents) 5. Known allergy or hypersensitivity to contrast media that cannot be adequately medicated 6. Pregnant, planning to become pregnant during the study period, or breastfeeding 7. Unresolved systemic infection or localized infection in the targeted region 8. Pre-operative laboratory tests and/or physical examination indicate abnormal results, which, in the opinion of the investigator, would clinically confound the study primary endpoints 9. Existing medical condition which, in the opinion of the investigator, may cause the subject to be intolerant of an occlusion procedure or non-compliant with the protocol or may confound the data interpretation 10. Subject is participating in another device, drug, or procedure clinical investigation and has not completed the study treatment or the other investigation clinically interferes with the endpoints of this study (post-

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	approval registries are allowed as long as the investigator determines there is no clinical interference with study endpoints) 11. Vulnerable subject populations (e.g., incarcerated or cognitively challenged adults) 12. Patients with drug or alcohol dependency (within 6 months prior to study entry) that, in the opinion of the investigator, would interfere with safe delivery of the study treatment or with the interpretation of study results *Intra-procedural exclusion criteria:* 13. Presence of persistent, flow-limiting vasospasm that is not responsive to chemical or mechanical interventions 14. Presence of collateral pathways potentially endangering normal territories during embolization 15. Blood flow precludes safe delivery of embolic material (e.g., arteriovenous shunting or high, unpredictable flow exists) 16. Anatomy that precludes advancement of the delivery device to target vessel embolization site or delivery of embolic material 17. Dissection in the target vessel 18. The delivery device has already been used with an ionic contrast agent (e.g., Conray® (iothalamate meglumine injection USP 60%), Guerbet)
Study Duration	Enrollment is expected to take approximately 18 months. Each study subject will actively participate in the study through 30-day follow-up. The overall study duration, from screening the first patient to the final follow-up visit, data analysis, and final report, is expected to be approximately 24 months.
Study Sponsor[1]	Fluidx Medical Technology, Inc. 2500 South State Street, Suite D246 Salt Lake City, Utah 84115 USA Contact: Libble Ginster, President and CEO [redacted] Email: Libble.Ginster@fluidxmedical.com
Contract Research Organization (CRO)	[redacted]

[1] Detailed contact information is maintained in a separate Sponsor Contact List managed by the CRO

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1.0 ABBREVIATIONS

The following is a list of abbreviations used in the body of this document. Abbreviations solely used in tables (e.g., table headers) are described in the table footer and are not included below.

ADE	Adverse device effect
AE	Adverse event
AML	Angiomyolipoma
CBC	Complete blood count
CEC	Clinical events committee
CFR	Code of Federal Regulations (U.S.)
CRF/eCRF	Case report form / electronic CRF
CRO	Contract Research Organization
DMSO	Dimethyl-sulfoxide
DSMB	Data and safety monitoring board
EDC	Electronic data capture database
FDA	Food and Drug Administration (U.S.)
GCP	Good clinical practice
HDEC	Health and Disability Ethics Committee (New Zealand IRB)
ICF	Informed consent form
ICH	International Conference on Harmonization
IFU	Instructions for use
INR	International normalized ratio
IRB	Institutional review board
ISO	International Organization for Standardization
MAE	Major adverse event
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal investigator
QI	Quality improvement
RAE	Renal artery embolization
RCC	Renal cell carcinomas
REB	Research Ethics Board (Canadian IRB)
SAE	Serious adverse event
SAP	Statistical analysis plan
SIR	Society of Interventional Radiology
UADE	Unanticipated (serious) adverse device effect

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2.0 CLINICAL BACKGROUND

Embolization is an important and commonly performed procedure used in interventional radiology and interventional oncology to stop blood flow in a vessel or vascular territory. The procedure is used in numerous and diverse clinical conditions and scenarios, including vascular injury, vascular malformations, varicosities, aneurysms, pseudoaneurysms, tumors, and excessive bleeding due to trauma.

Embolization can be achieved by delivering an embolic agent to create a mechanical occlusion or by creating a physical reaction in the vessel to initiate formation of thrombus. The resulting embolization can be temporary or permanent, depending on the agent used. It may be a complementary therapy or an important preparation for another therapy (e.g., pre-operative embolization). Embolization procedures are minimally invasive and can often be performed under conscious sedation. The patient's condition may be emergent in some cases and elective or non-urgent in others. Physicians must be flexible and pragmatic in choosing the right course of action for each patient (Kessel & Ray).

An important goal of embolization procedures is to deliver effective treatment while minimizing damage to adjacent structures. Physicians need access to a wide variety of embolic agents, each with different characteristics and properties, so that embolization procedures can be tailored to the clinical diagnoses, patient anatomy, and the desired goal of the procedure. The three types of embolic agents currently used for peripheral embolization procedures include vascular plugs or coils; microspheres or particles; and liquid or conformable embolics.

Planning for any given embolization procedure requires difficult decisions about which embolic agents to use and the most effective way to use them. With a growing variety of available embolic agents, it may be a challenge for interventional radiologists to be acquainted with all tools and best practices. Key factors to consider include (Kessel & Ray; Golzarian; Lubarsky):

- Size and shape of the target vessel
- Speed of flow in the vessel
- Length of time needed for vessel occlusion (i.e., permanent or temporary)
- Desired outcome for tissue viability (i.e., tissue viability maintained or tissue death)
- Level of vascular occlusion necessary for effective treatment

In all cases, "the over-riding principle is always to use the safest, most readily controlled, effective agent" (Kessel & Ray).

Currently marketed embolic products have a host of clinical challenges related to ease of use and predictability, including the following:

- **Plugs & coils:** Inconsistent embolization; recanalization; time and costs associated with the need for multiple coils to achieve desired occlusion; risk of migration
- **Microspheres & particles:** Off-target embolization; proximal reflux; catheter clogging; poor visualization

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- **Liquid embolics:** Meticulous and time-consuming preparation (e.g., change gloves; measure and mix solutions; agitate 20 minutes on a shaker); toxicity of solvents (e.g., dimethyl-sulfoxide, DMSO); complex delivery techniques; catheter entrapment; obstruction of the catheter tip; unpredictable distribution of delivered embolic
- **Conformable embolics:** Limited to delivery through larger microcatheters and proximal embolization targets, and unpredictable distribution of delivered embolic material

To address these clinical needs, Fluidx has developed a novel liquid embolic called GPX® Embolic Device, a gel-like, solid embolization device that is delivered as a fluid material into the body. The device contains no toxic solvents, and it can be mixed and ready to use in less than 30 seconds. The liquid embolic material is controllable, radiopaque (both pre- and post-delivery), begins to solidify immediately upon delivery independent of the patient's coagulation situation, and provides for durable, long-term occlusion. The GPX Embolic Device is compatible with the smallest microcatheters.

In pre-clinical testing and a feasibility study conducted in New Zealand, the GPX Embolic Device demonstrated that it may have significant clinical value for use in durable or pre-operative embolization procedures where there is a desire for distal penetration (Holden). The GPX Embolic Material flowed deep, following the flow of blood into distally flowing vessels and vessel beds, to provide an effective and durable occlusion. A detailed description of pre-clinical testing and clinical experience is provided in the Investigator's Brochure.

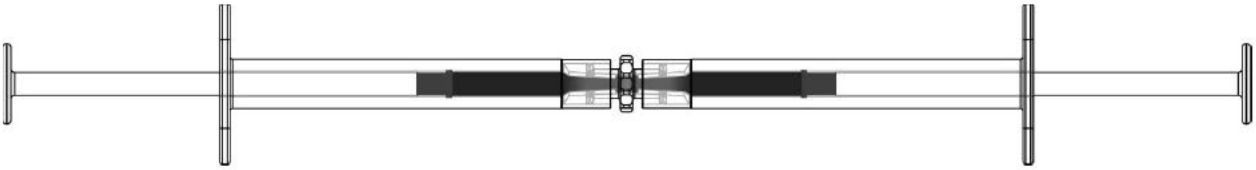
Based on this initial testing, the GPX Embolic Device is expected to provide precise control during delivery of embolic material, permitting distal embolization with low rates of complications, including nontarget embolization. This pivotal clinical study will further evaluate the safety and effectiveness of the GPX Embolic Device to support regulatory applications for market authorization.

3.0 TREATMENT DESCRIPTION

3.1 Device Description

The GPX Embolic Device (**Figure 1**) comprises two pre-coupled syringes that each contain 0.5 mL of GPX Embolic Material, a water-based solution of two oppositely charged polymers and tantalum (for radiopacity). When delivered into the bloodstream, the GPX Embolic Material begins to immediately solidify as it fills the targeted region, forming a durable occlusion.

Figure 1: GPX Embolic Device



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The GPX Embolic Device is provided sterile (gamma irradiation) and is compatible with many commercially available delivery devices, such as microcatheters, with a minimum inner diameter (ID) of 0.019 inches (0.48 mm).

3.1.1 Device Manufacturer

The GPX Embolic Device is manufactured by the study sponsor, Fluidx Medical Technology, Inc. (Salt Lake City, Utah, USA).

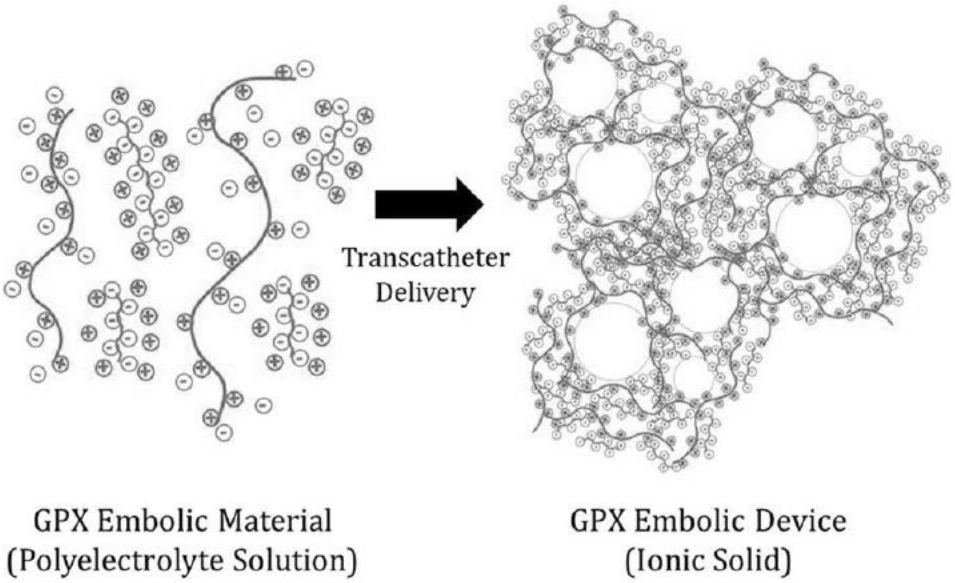
3.1.2 Device Labeling / Instructions for Use

The device instructions for use will be provided with each investigational product.

3.2 Principle of Operation / Mechanism of Action

GPX Embolic Material is a water-based ionic solution comprised of a polycation polymer, a polyanion polymer, and tantalum (suspended in the solution for visualization under fluoroscopy and imaging), premixed and contained within a syringe. While contained in the syringe, the oppositely charged polymers remain separate and dissolved. This results in a polyelectrolyte solution that can be delivered into the bloodstream as a fluid. Within the bloodstream, the small ions present in the water-based ionic solution dissipate. This leads the oppositely charged GPX polymers to bond together, forming the GPX Embolic Device, a gel-like, self-bonding, solid embolus that contains the constituent tantalum (**Figure 2**).

Figure 2: GPX Mechanism of Action



3.3 Proposed Indications for Use

The GPX Embolic Device is only intended for distal embolization in the peripheral vasculature including vascular tumors (e.g., renal angiomyolipoma, renal cell carcinoma, bone tumors,

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bleeding tumors, and other vascular tumors), renal embolization, and portal vein branches. It is not intended for embolization of active bleeding sites, veins other than the portal vein, aneurysms, endoleaks, vascular malformations, or vessels for flow redistribution.

4.0 OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of the GPX Embolic Device when used as indicated for peripheral embolization procedures that require distal vessel bed penetration.

5.0 ENDPOINTS

5.1 Primary Safety Endpoint

The primary safety endpoint for the study is freedom from major adverse events (MAEs) through 30 days post-index procedure. MAEs are defined as device-related serious adverse events, as adjudicated by the Clinical Events Committee (CEC), comprising the following types:

- Nontarget embolization with ischemia in an unintended anatomical area
- Systemic allergic and/or toxic reaction to the GPX Embolic Device
- Catheter entrapment and/or breakage
- Culture-proven abscess in target organ/tissue
- Embolization-related death

5.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for the study is delivery of the GPX Embolic Device to the target vessel embolization site(s) determined by the investigator at the time of enrollment, and successful occlusion of flow immediately beyond the target vessel embolization site(s), as determined by the core lab via comparison of the pre- and final post-embolization images.

5.3 Secondary Endpoints

The secondary endpoints for the study are the occurrence of:

- Device-related adverse events (AE) through 30 days post-index procedure
- Adjunctive embolization agent usage during the embolization procedure
- Catheter occlusion due to the GPX Embolic Material

5.4 Ancillary Data

The following ancillary data will be collected:

- Device performance assessment

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5.5 Rationale for Study Endpoints

The primary effectiveness endpoint directly measures successful embolization of the target vessel, consistent with quality improvement (QI) standards published by the Society of Interventional Radiology (Dariushnia; Angle). The Dariushnia 2021 QI standards article provides a general definition of success (i.e., "... defined broadly as the immediate angiography result and is typically evaluated with completion angiography"). The definition for the present study is conservatively set to require occlusion such that no clinically significant contrast enhancement is seen.

The primary safety endpoint includes events of specific interest in embolization procedures, defined in agreement with FDA, and is, therefore, an appropriate metric to assess the safety of the embolization device.

Effectiveness will be assessed immediately post-procedure and safety assessments will occur at 30 days, which represents a realistic test of an embolic device, with sufficient time to identify and assess risks.

6.0 STUDY DESIGN

6.1 Overall Design

The investigation is a single-arm, open label, non-randomized, prospective, multicenter, multinational pivotal study.

6.2 Number of Sites & Subjects

The study will be conducted in up to 25 investigational sites in the USA, New Zealand, and Canada; a minimum of 50% of the sites will be in the USA.

The study will enroll up to 114 subjects. Each site will be capped at a maximum of 25% of total enrollment. A minimum of 50% of subjects will be enrolled from sites in the USA. Detailed sample size calculations and statistical methods are contained in the statistical analysis plan (SAP).

6.3 Study Population

The population for this study is adult subjects who present with a need for distal embolization in the peripheral vasculature including vascular tumors (e.g., renal angiomyolipoma, renal cell carcinoma, bone tumors, bleeding tumors, and other vascular tumors), renal embolization, and portal vein branches. Based on clinical literature, the anticipated age range for these procedures is 38 – 87 (Karalli; Rimon; Wright; van Lienden). In addition, consistent with prior studies, the feasibility clinical evaluation of the GPX Embolic Device was conducted in 17 subjects who ranged in age from 22 to 85 years (mean 54.3, median 58).

The investigation population is representative of the target population and does not include any sex, racial, or ethnic origin restrictions. Pregnant and breastfeeding patients are excluded due to

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the potential risks of radiation exposure incurred during the angiographic procedure. Vulnerable subject populations are not included in this study.

6.4 Study Duration

Enrollment is expected to take approximately 18 months. Each study subject will actively participate in the study through 30-day follow-up. The overall study duration, from screening the first patient to the final follow-up visit, data analysis, and final report, is expected to be approximately 24 months.

6.5 Subject Eligibility Criteria

6.5.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria:

1. Age ≥18 years on the date of consent
2. Expected post-procedural lifespan of at least 30 days, in the opinion of the investigator, to allow for participation in all follow-up visits
3. Presents with need for peripheral embolization where there is a desire for distal vessel bed penetration including:
    a. Vascular tumors (e.g., renal angiomyolipoma, renal cell carcinoma, bone tumors, bleeding tumors, and other vascular tumors)
    b. Renal embolization
    c. Portal vein branches
4. Informed consent granted by the patient or legally authorized representative
5. Willing and able to comply with the protocol-specified procedures and assessments

6.5.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

General exclusion criteria:

1. Requires embolization for any of the following applications:
    a. Neurovasculature
    b. Coronary vasculature
    c. Hemorrhage due to trauma
    d. Non-tumoral focal/active bleeding sites (e.g., gastrointestinal tract, urinary tract, lung)
    e. Veins other than portal vein
    f. Aneurysms
    g. Endoleaks
    h. Vascular malformations

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i. Vessels for flow redistribution

2. Has undergone an embolization procedure within 30 days prior to consent
3. Presents with need for embolization where the risk of clinically significant infarction outweighs the benefit of distal penetration (e.g., gastrointestinal, uterine)
4. Embolization target is only intended for temporary occlusion (e.g., bioresorbable biologic embolic agents)
5. Known allergy or hypersensitivity to contrast media that cannot be adequately medicated
6. Pregnant, planning to become pregnant during the study period, or breastfeeding
7. Unresolved systemic infection or localized infection in the targeted region
8. Pre-operative laboratory tests and/or physical examination indicate abnormal results, which, in the opinion of the investigator, would clinically confound the study primary endpoints
9. Existing medical condition which, in the opinion of the investigator, may cause the subject to be intolerant of an occlusion procedure or non-compliant with the protocol or may confound the data interpretation
10. Subject is participating in another device, drug, or procedure clinical investigation and has not completed the study treatment or the other investigation clinically interferes with the endpoints of this study (post-approval registries are allowed as long as the investigator determines there is no clinical interference with study endpoints)
11. Vulnerable subject populations (e.g., incarcerated or cognitively challenged adults)
12. Patients with drug or alcohol dependency (within 6 months prior to study entry) that, in the opinion of the investigator, would interfere with safe delivery of the study treatment or with the interpretation of study results

Intra-procedural exclusion criteria:

13. Presence of persistent, flow-limiting vasospasm that is not responsive to chemical or mechanical interventions
14. Presence of collateral pathways potentially endangering normal territories during embolization
15. Blood flow precludes safe delivery of embolic material (e.g., arteriovenous shunting or where high, unpredictable flow exists)
16. Anatomy that precludes advancement of the delivery device to target vessel embolization site or delivery of embolic material
17. Dissection in the target vessel
18. The delivery device has already been used with an ionic contrast agent (e.g., Conray® (iothalamate meglumine injection USP 60%), Guerbet)

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7.0 STUDY METHODOLOGY

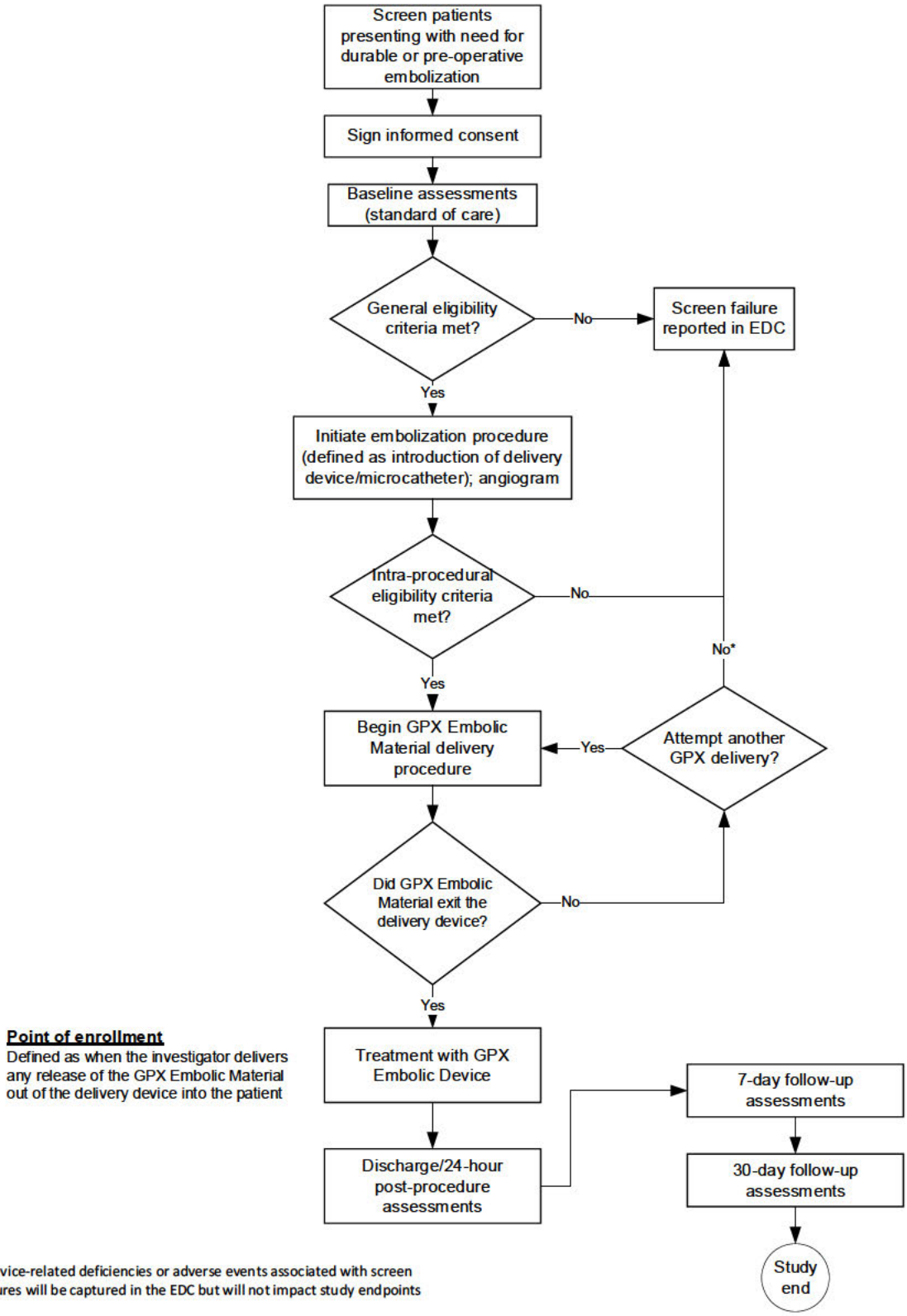
Study assessments and data collection points are visually represented in **Figure 3** and **Table 1** and are described below. To avoid missing data in the study, subjects should be followed for all regularly scheduled visits for safety and effectiveness assessments. Any reason for withdrawal from the study should be documented as described later in the protocol. See **Section 13.0** for definitions of endpoint-related terms used in this section.

Study procedures should be followed carefully as they have been designed to address any known or foreseeable factors that may compromise the outcome of the clinical study or the interpretation of results (e.g., subject baseline characteristics, concomitant medication, the use of other medical devices, and subject-related factors such as age, gender, or lifestyle) and methods for addressing these factors (e.g., subject selection, statistical analysis).

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Figure 3: Study Flow Diagram



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Table 1: Schedule of Study Activities

▼Assessment/Activity	Screening/ Baseline	Treatment Procedure	Pre-Discharge/ 24-Hours Post-Procedure	7 (-3/+7) Days Follow-Up	30 (-7/+15) Days Follow-Up
Visit Type ►	Clinic	Clinic	Clinic	Clinic or phone	Clinic or phone
Eligibility criteria	X	X[1]			
Informed consent	X				
Demographics & medical history	X				
Pregnancy test[2]	X				
Blood labs[3]	X				
Medication assessment[4]	X	X	X		
Procedure angiogram (pre- and post-embolization)		X[5]			
Procedure and device usage		X			
Device performance assessment		X			
Adverse event assessment		X	X	X	X

[1] Assessment of intra-procedural exclusion criteria.

[2] If the subject is female and is of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be completed within 7 days of the treatment procedure and the result must be negative.

[3] Standard of care blood labs to collect: CBC, INR, and creatinine.

[4] Medications assessed: Anticoagulants and antibiotics.

[5] Refer to core lab Image Acquisition Guide for requirements; imaging will be sent to the core lab.

7.1 Screening Visit

The study team will screen patients for the study. Screening is defined as the process of reviewing a patient's medical records against the study eligibility (inclusion and exclusion) criteria to determine if the patient is eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria.

The following eligibility criteria can only be evaluated after the patient has consented for the study: pregnancy testing (when applicable) and intra-procedural exclusion criteria. If a patient meets all but these eligibility criteria, they can be consented for the study. Sites will be required to maintain screen failure information in the electronic data capture (EDC) database, including rationale for subject ineligibility post-consent.

7.1.1 Informed Consent Process

Prior to enrolling subjects in this study, the site will be required to have an Institutional Review Board (IRB) approved informed consent form (ICF). To ensure compliance with informed

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consent requirements, the sponsor or contract research organization (CRO) must review any modifications made to the sponsor's template ICF prior to IRB submission.

Written informed consent will be obtained from the patient (or the patient's legal representative, if applicable) prior to participation as a subject in the study. The investigator (or authorized designee) will explain the nature of the planned treatment and objectives of the study to the patient, along with any costs to the subject, payments for participation, and types of insurance provided (if applicable). The investigator will allow adequate time for the patient to read and review the consent form and to ask questions. When the investigator has reasonable assurance that the patient (or legal representative) has an acceptable level of comprehension and the patient (or legal representative) voluntary agrees to participate, the patient (or legal representative) and the investigator (or authorized designee) will sign and date the ICF. Once consented, the patient is then referred to as a subject.

The site will retain the original signed ICF in the subject's study records and will provide a copy of the signed ICF to the subject. The site will document the consent process (e.g., that the subject was consented, the date on which the consent was obtained, and that a copy of the signed ICF was given to the subject) in the subject's medical records.

Subjects will be informed of any new information that may make them change their mind about staying in the study. Subjects may be asked to sign a new ICF if this occurs.

7.1.2 Vulnerable Population

To preserve the ethical integrity of this study, the sponsor does not intend to enroll vulnerable subject populations (e.g., incarcerated persons or adults with severe cognitive challenges) in this study since such populations may be coerced or compelled to participate in a clinical study without a full understanding or against their will these subjects should be excluded (in consideration of ISO 14155:2020 sections 5.7 and A.6.3).

7.2 Baseline Assessments

Baseline data from the medical record will be entered into the EDC for consented patients who meet eligibility criteria and for whom an attempt was made to *initiate* delivery of the GPX Embolic Material, as well as for enrolled subjects. The following standard of care baseline evaluations and assessments will be performed:

- Eligibility criteria
- Informed consent
- Demographics and medical history
- Pregnancy test, if required (as specified in **Table 1**)
- Blood labs (as specified in **Table 1**)
- Medication assessment (as specified in **Table 1**)

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After the baseline assessments have been completed, the inclusion and exclusion criteria should be reviewed to ensure that the subject continues to be eligible for the study.

7.3 Point of Enrollment & Numbering of Study Subjects

A patient will be considered enrolled as a study subject when the investigator delivers any release of the GPX Embolic Material out of the delivery device into the patient.

- **Note:** If the delivery device is navigated to the target vessel embolization site and the investigator determines that a distal penetrating embolic device is not appropriate (i.e., healthy tissue would be sacrificed to complete the embolization, and the value of maintaining the healthy tissue outweighs its embolization-related loss) or the GPX Embolic Material cannot be delivered from that position, the investigator will provide a rationale on why they could not use the investigational product at that position in the patient's screen-failure documents.

Upon enrollment, the lowest available subject number will be assigned first, then progress sequentially for each enrolled subject thereafter. The CRO will be notified of subject enrollment via the EDC. Screen failures will also be identified and tracked within the EDC.

7.4 Treatment Procedure

Note: Final eligibility for study enrollment is evaluated d*uring* the procedure (refer to the intra-procedural exclusion criteria)

If attempts are made to deliver GPX Embolic Material but the material never exits the delivery device into the patient (i.e., point of enrollment not reached), the patient will be considered a screen failure and any device-related deficiencies and/or adverse events will be reported in the EDC. Screen failures will not impact endpoint assessments.

Treatment will be performed according to the GPX Embolic Device Instructions for Use (IFU); the following are procedural reminders:

- The amount of GPX Embolic Material required to successfully occlude a target vessel varies significantly based on the selected anatomical target volume; this amount will be determined based on investigator discretion.
- GPX Embolic Material must be mixed at least 25 times to resuspend the tantalum and must be delivered within 30 minutes of tantalum suspension, either via initial suspension or re-suspension.
- Benchtop, pre-clinical, or clinical testing has shown compatibility with the following microcatheters: Cantata (Cook), Direxion (Boston Scientific), Lantern (Penumbra), Maestro (Merit), Progreat (Terumo), Pursue (Merit), Soldier (Embolx), Trevo Trak (Stryker), XO Cath (Transit Scientific).
    - The GPX Embolic Device should not be used with Renegade or TruSelect microcatheters (Boston Scientific), as adhesion to these microcatheters has

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been observed. Such adhesion may lead to embolus or embolization of an unintended area.

- Considerations for use of other embolization agents during the treatment procedure:
  - Other embolic agents may be used to direct flow away from, or to protect flow to certain anatomical areas outside of or adjacent to the target vessel embolization site.
  - Other embolic agents should not be used within the target vessel embolization site and should not come into direct contact with the GPX Embolic Device.
- Pre- and post-GPX delivery angiograms should be recorded immediately before and after the GPX Embolic delivery per instructions in the image acquisition guide.
- Additional embolic procedures using the GPX Embolic Device or other embolization agents may be performed within the 30-day period following the index GPX embolization procedure. These treatment decisions are at the discretion of the investigator and must be consistent with standard of care and with device compatibility requirements specified in the GPX Embolic Device IFU.

Enrolled subjects are expected to receive medical care consistent with administration of an embolic device for the procedure that merits its use. This standard of care varies by clinical need; it may involve administration of medication for pain or fever and some days of hospital stay prior to discharge.

The assessments described below will be performed and results will be recorded on the relevant eCRFs.

- Eligibility criteria (intra-procedural exclusion criteria)
- Medication assessment (as specified in **Table 1**)
- Procedure angiogram (pre- and post-embolization)
- Procedure and device usage
- Device performance assessment, to include the following at minimum:
  - Ease of use (e.g., mixing ease, delivery ease)
  - Visibility of the GPX Embolic Material during and post-delivery
- Adverse event assessment

Pre- and final post-GPX Embolic delivery angiographic images will be sent to the core laboratory per provided procedures (refer to core lab Image Acquisition Guide for imaging requirements).

7.5 Pre-Discharge/24-Hour Assessment

The following assessments will be performed before discharge or within 24 hours post-procedure, whichever occurs first, and documented on the relevant eCRFs:

- Medication assessment (as specified in **Table 1**)

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- Adverse event assessment

7.6 7-Day Follow-up Visit

An adverse event assessment will be performed on day 7 [-3/+7 days] at the hospital/clinic or via phone, and results will be recorded on the relevant eCRFs.

Post embolization tumor resection and the required 7-day follow-up visit may be conducted together for subject and research personnel convenience. If the visit is out-of-window, protocol deviations will be recorded.

7.7 30-Day Follow-up Visit

An adverse event assessment will be performed on day 30 [-7/+15 days] at the hospital/clinic or via phone, and results will be recorded on the relevant eCRFs.

Post embolization tumor resection and the required 30-day follow-up visit may be conducted together for subject and research personnel convenience. If the visit is out-of-window, protocol deviations will be recorded.

At the conclusion of the 30-day follow-up visit, subjects will exit from the study via completion of the Study Completion eCRF. Subjects will continue to be followed by their physician per standard of care.

7.8 Unscheduled Visits

Assessments completed during an unscheduled visit will be recorded on the Adverse Event eCRFs.

7.9 Early Withdrawal/Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for several reasons including:

- Subject death
- Subject lost to follow-up
- Subject request for withdrawal (withdrawal of consent)
- Investigator decision (e.g., subject adverse event precludes further participation)

If a subject is withdrawn from the study early, a Study Completion eCRF must be completed to describe the reason for early withdrawal. The investigator should make all attempts to conduct an “Early Withdrawal” visit at the time of the withdrawal from the study. If a subject has withdrawn consent for the study or is lost to follow-up, the completion of this visit is not necessary. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of the adverse event or determination that the subject’s condition is stable.

If a subject chooses to withdraw from the study, the subject will be asked for permission for their medical status to be followed by telephone contact, medical chart review, or by other agreed

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upon method. If the subject withdraws consent for disclosure of further information, no further assessment(s) should be performed, and no additional data collected. The sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

7.10 Handling Subjects Lost to Follow-Up

Every attempt must be made to have all subjects complete the follow-up visit schedule. A subject will be considered lost-to-follow-up when all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone, and if contact via phone is not successful, a certified letter from the principal investigator (PI) or authorized delegate must be sent to the subject's last known address. Both telephone and letter contact efforts to obtain follow-up must be documented in the subject's medical records and on the Study Completion eCRF.

7.11 Handling of Samples Obtained from Subjects

No subject samples will be retained by the sponsor.

8.0 STATISTICAL METHODS

8.1 Analysis Data Sets

The primary analysis will consist of all available data on all subjects enrolled, referred to in *ICH E9 Statistical Principles for Clinical Trials* as the "full analysis set." As the study is a treatment-only, single-arm design, comparisons between treatment and control groups are not pertinent, and summaries of results will principally be presented for the entire study population. No interim analyses are planned for this clinical study.

8.2 General Statistical Principles

Continuous data will be summarized using the following descriptive statistics: mean, standard deviation, median, and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For events that can occur more than once in a single subject, such as adverse events (AEs), the percentage will be based on the number of subjects experiencing the event; both subject and event counts will be reported.

All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

8.3 Analysis of Primary Safety Endpoint

The primary safety endpoint will be presented as the proportion of subjects experiencing a major adverse event as defined in **section 5.1**.

The U.S. Food and Drug Administration (FDA) recommended that this trial's primary safety endpoint includes several major adverse events (MAE). Recent literature identified thresholds

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for each of the recommended MAEs. Several events are outlined in the "Society of Interventional Radiology Quality Improvement Standards for Percutaneous Transcatheter Embolization" published in the *Journal of Vascular and Interventional Radiology* (Dariushnia).

The document addresses the quality improvement (QI) standards for embolization in the bronchial, celiac, superior and inferior mesenteric, renal, hypogastric, and prostatic arterial territories. Pulmonary artery embolization, portal vein embolization before an operation, and gonadal vein embolization are discussed as well. The QI standard identifies appropriate thresholds for nontarget embolization, ischemia in an unintended vascular territory, and abscess. An earlier version of the QI standard identified a rate and threshold for procedure-related mortality (Angle). A recent article on the use of liquid agents for embolization (within their approved indication for the occlusion of brain arteriovenous malformations) identified an average rate of catheter entrapment (Triano). The Onyx Liquid Embolic System warnings include a note about hypersensitivity reactions, stating that they are possibly due to the DMSO solvent in the Onyx product; the warning statement only cites one occurrence involving a patient that was treated concurrently for interstitial cystitis (Medtronic). Based on this information, **Table 2** was developed indicating thresholds for each MAE based on current standard of care.

Table 2. Possible Thresholds for MAEs Related to the Primary Safety Endpoint

Major Adverse Event	Threshold
Nontarget embolization of an unintended anatomical area (e.g., colonic or spinal infarction during renal embolization)	10% *
Ischemia in an unintended vascular territory	1.4% †
Allergic and/or toxic reactions to embolic agent	<1% (rare) ‡
Delivery device entrapment and/or delivery device breakage	3.4% §
Abscess in target organ/tissue	2.4% ‖
Embolization-related death	1% ¶

** Dariushnia (ref. Table 3, renal arteries, nontarget embolization).*
† Dariushnia (ref. Table 3, portal vein embolization, portal vein left lobe occlusion).
‡ Medtronic, Onyx Liquid Embolic System Warnings (https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/avm-embolization/onyx-liquid-embolic/indications-safety-warnings.html).
§ Triano. Note that the article describes early reports of device entrapment between 1% and 9.7% in brain arteriovenous malformation (AVM) cases with liquid agents.
‖ Dariushnia (ref. Table 3, splenic, abscess/sepsis (splenic injury)).
¶ Angle (ref. Table 2, complications-general, procedure-related mortality).

The 10% threshold for unintended nontarget embolization is a primary contributing factor in calculating an appropriate safety performance goal for this trial considering that the primary safety endpoint includes multiple major adverse events. This rate is derived from rates of non-target embolization reported by Sam et al. in 2011. While that particular study describes embolizations of iatrogenic bleeding, the actual embolizations studied were performed using a superselective approach targeting the focal bleed and minimizing damage to healthy

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parenchyma. Distal penetration cases for angiomyolipomas (AMLs) and renal cell carcinomas (RCCs) are performed in similar anatomies and follow a similar approach.

Based on the above results, the largest single threshold is 10% while the sum of the various thresholds is 19.2%, but this summation cannot account for double-counting due to the potential for multiple MAEs in a single subject. A conservative definition of the overall safety performance goal is therefore made at 13%.

The primary safety endpoint will be tested against this performance goal using Clopper-Pearson (exact) tests of a single binomial proportion against a fixed null hypothesis.

8.4 Analysis of Primary Effectiveness Endpoint

The primary effectiveness endpoint will be presented as the proportion of subjects with successful embolization as defined in **section 5.2**.

Fluidx identified a QI standard published by the Society of Interventional Radiology (SIR) for percutaneous transcatheter embolization published in the *Journal of Vascular and Interventional Radiology* (Dariushnia). The 2021 SIR guidelines specified a suggested threshold of 75% technical success in renal artery embolization (RAE). However, this rate is specific to RAE in acute or recurrent hemorrhage, which Fluidx recognizes may have a lower success rate than other RAE procedures. GPX-relevant performance thresholds are not provided in the 2021 SIR QI guidelines. However, a previous version of SIR QI guidelines published in 2010 (Angle) does outline technical performance thresholds for GPX-relevant embolization applications. This document lists performance targets of 75% for malignant renal tumors, 90% for non-neoplastic renal tumors, 90% for preoperative renal embolization, and 95% for portal vein embolization.

Fluidx compared these applications against the feasibility trial for the GPX Embolic Device, where 17 distal penetration cases were performed, including embolizations of 5 primary or secondary tumors, 7 renal angiomyolipoma (AMLs), 1 polycystic kidney, and 4 portal veins (Holden). This approximate ratio of feasibility clinical applications has been used to guide selection of appropriate performance goals for this pivotal trial. Using an average of the performance thresholds outlined in the QI guidelines, weighted by the proportion of the procedure types from the fully enrolled GPX Embolic Device feasibility trial, a performance goal of 87% was calculated (see **Table 3**).

Table 3. Statistical Assessment of Primary Effectiveness Endpoint

Performance goal derived from the 2010 SIR QI Guideline, weighted based on a per-case calculation of GPX feasibility study cases		
Procedure	**Cases**	**SIR QI Threshold**
Malignant renal (RCC)	5	75%
Non-neoplastic renal	7	90%
Preoperative renal	1	90%

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Performance goal derived from the 2010 SIR QI Guideline, weighted based on a per-case calculation of GPX feasibility study cases		
Procedure	**Cases**	**SIR QI Threshold**
Portal vein	4	95%
TOTAL	17	---
Weighted Performance Goal		**86.8%**

The primary effectiveness endpoint will be tested against this performance goal using Clopper-Pearson (exact) tests of a single binomial proportion against a fixed null hypothesis.

8.5 Analysis of Secondary Endpoints

Secondary endpoints will be tabulated and reported descriptively using the general principles described in **section 8.2**. No formal hypothesis testing is planned *a priori* for the secondary endpoints; hence, methods of controlling familywise Type I error (e.g., hierarchical testing, multiplicity adjustment) need not be employed. In addition, the results of any *ad hoc* statistical test not prespecified in the protocol or SAP will not be presented in the labeling of the investigational device.

8.6 Safety Analysis

Summary tables and listings will be provided for all reported adverse events, which will additionally be reported by seriousness and relatedness. Such summaries will comprise the number and percentage of subjects with an adverse event and the total number of such events. The proportion of subjects with events will be considered primary for analysis of adverse events.

AEs will additionally be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Multiple occurrences of the same AE will be counted once at the maximum grade and strongest relationship, as appropriate. Adverse events adjudicated by the CEC as *definitely* or *probably* device-related will be considered related adverse events for data analytic purposes. Events adjudicated by the CEC as *possibly*, *unlikely,* or *not related* will not be considered device-related adverse events for data analytic purposes.

8.7 Sample Size

Both the primary safety and primary effectiveness endpoints will be tested against predefined performance goals, as developed and stated in **sections 8.3** and **8.4**, using Clopper-Pearson (exact) tests of a single binomial proportion against a fixed null hypothesis.

Formally, the hypotheses to be tested for the primary effectiveness endpoint are as follows:

H0: $r_E \leq 0.87$

HA: $r_E > 0.87$,

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where r_E is the proportion of subjects experiencing effectiveness success and 0.87 is the corresponding performance goal. Similarly, for safety we test:

H0: $r_S \geq 0.13$

HA: $r_S < 0.13$,

where r_S is the proportion of subjects experiencing a primary safety event and 0.13 is the corresponding performance goal.

The hypotheses above will be tested at a one-sided alpha level of 0.025, and in each case endpoint success will be declared if the performance goal is met (i.e., if the null hypothesis is rejected in favor of the alternative hypothesis). For primary analysis, these endpoints will be tested on all subjects with available data.

Based on the performance goals and hypothesis testing specified above, sample size and power were computed using SAS version 9.4 PROC POWER, assuming an exact test of a single binomial outcome against a performance goal (the null hypothesis). Postulating a primary effectiveness success rate of 95% against a null hypothesis of 87% per the performance goal, a sample size of 108 subjects provides 83% power to meet the primary effectiveness endpoint. Similarly, a primary safety event rate of 5% against a null hypothesis of 13% per the performance goal gives an identical sample size of 108 for 83% power.

Under modest assumptions for missing data on study outcomes (e.g., 5% missingness), to obtain 108 evaluable samples a total of 114 subjects are required to be included in endpoint analyses using the definition of enrollment (release of the GPX Embolic Material into the patient) stated above.

8.8 Subgroup Analyses

All subjects will be treated with the GPX Embolic Device. While their embolizations will involve different anatomical targets, each embolization procedure will still be undertaken with the desire for distal penetration. Subgroup analysis will be completed to analyze the use of the GPX Embolic Device for specific clinical applications.

Specifically, the following subgroup analyses for the primary endpoints are intended for the FAS population and will be used to determine whether covariates can modify the treatment effect of the investigational device. Statistical methods will follow the same as those outlined for poolability of sites (**section 8.9**). Subgroups of interest include the following:

- Age (≥65 years vs. <65 years)
- Ethnicity (Hispanic vs. Non-Hispanic)
- Portal Vein Embolization (Yes vs. No)
- Pre-Existing Liver Disease (Yes vs. No)
- Race (White, Asian, Black, Other)

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- Renal Embolization (Yes vs. No)
- Vascular Tumors (Yes vs. No)
- Sex (Male vs. Female)

The following subgroups of those patients specifically with vascular tumors (i.e., subgroup of subgroups) are also of interest:

- Renal Angiomyolipoma (Yes vs. No)
- Renal Cell Carcinoma (Yes vs. No)
- Bone Tumors (Yes vs. No)
- Bleeding Tumors (Yes vs. No)

Additional subgroups may be examined, but those specified above are of *a priori* clinical interest. The results of any subgroup analysis not prespecified in the protocol and SAP will not be presented in the labeling of the investigational device.

8.9 Pooling of Data

As this investigation is a multicenter study, poolability of the primary effectiveness endpoint will be assessed by testing for heterogeneity of treatment effect by clinical site of enrollment. As the primary endpoints are binomial variables, such testing will be accomplished using Pearson's chi-square test to assess heterogeneity among sites. For this purpose, sites enrolling fewer than 5 subjects will be amalgamated into a single meta-site. A resulting p-value less than 0.15 will be cause for investigation of potential causes of heterogeneity across clinical sites.

8.10 Missing Data

As stated above, the primary analysis of all endpoints will be conducted on the full analysis set (FAS), and every effort will be made to retain subjects for the intended length of follow-up to minimize the incidence of missingness. For the primary endpoints, methods for replacing missing data such as last value carried forward or multiple imputation will not be routinely used; however, sensitivity analyses incorporating imputation will be performed for the primary endpoints including a tipping point analysis.

For the primary safety endpoint, a tipping point analysis will be performed to evaluate the impact of missing data on study conclusion. Every combination of best/worst case values will be imputed to examine under what circumstances the results change. The best/worst case values used for the primary safety endpoint will be the binary success and failure of this endpoint.

In addition, for the primary effectiveness endpoint, a tipping point analysis will be performed to evaluate the impact of missing data on study conclusion. Every combination of best/worst case values will be imputed to examine under what circumstances the results change. The best/worst case values used for the primary effectiveness endpoint will be the binary success and failure of this endpoint.

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8.11 Statistical Analysis Plan

Refer to the Statistical Analysis Plan (SAP) for additional details on statistical design, method, and analytical procedures.

9.0 MEASURES TO AVOID & MINIMIZE BIAS

As this is a single-arm, open-label, non-randomized, prospective clinical trial, the primary factor that could bias the interpretation of results would be an excess of subject withdrawal or loss to follow-up (potentially due to subjects' state of health or age). Inclusion and exclusion criteria have been developed to reduce the impact of these factors as much as reasonable. Modest withdrawal/loss to follow-up has been considered when calculating a sample size for the trial.

The study has several measures that have been implemented to avoid and minimize bias, including the following: use of an independent CRO for study operations management, monitoring, and data management; establishment of an independent Clinical Events Committee and Data and Safety Monitoring Board; and use of an independent angiographic core laboratory for systematic review of images removing any potential for investigator bias.

9.1 Clinical Events Committee & Data and Safety Monitoring Board

Adverse events will be arbitrated by the Clinical Events Committee (CEC). The CEC, which is made up of a minimum of three non-investigator physicians, will adjudicate and classify AEs for severity, seriousness, and relatedness per the CEC Charter. Sites will be expected to provide supporting source documentation as requested to assist with CEC adjudication.

The Data and Safety Monitoring Board (DSMB), which is made up of at least three non-investigator physicians and one non-study statistician, will review summarized safety data and will use stopping rules as defined in the DSMB Charter. The DSMB will assess the clinical outcomes and procedure and study device success after the first 25 subjects are included and complete safety assessments at the 30-day follow-up visit. Unless otherwise required by the DSMB (e.g., due to significant adverse event trends), the study will continue without the need to stop recruitment or terminate the trial.

9.2 Core Laboratory

An imaging core laboratory will be used to provide an unbiased assessment of study imaging. The core laboratory will provide image acquisition and processing instructions to the sites. The core laboratory will follow a core lab charter or similar procedure to systematize their image review in compliance with the study protocol.

Missing imaging is considered a protocol deviation; however, other deviations from the core lab image acquisition and transfer instructions will not be considered protocol deviations at the site.

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10.0 BENEFITS & RISK ANALYSIS

10.1 Potential Benefits of Study Participation

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with a study device may have the following benefits:

- Distal occlusion with low rates of complications, including nontarget embolization of an unintended anatomical area (e.g., renal embolization resulting in nontarget embolization of a non-renal organ)
- Accurate control of delivery to target vessel embolization site
- Minimal preparation required prior to administration
- No DMSO solvent necessary
- Ease of use; no complex delivery technique
- Immediate, permanent occlusion upon delivery
- Compatibility with common embolic delivery catheters

10.2 Alternative Treatment

There is no obligation for a patient to take part in this study. Alternative treatments may include:

- Standard of care treatment using commercially available embolic devices/agents

10.3 Potential Risks Associated with Study Participation

There are no anticipated increased risks associated with using the GPX Embolic Device compared with other embolization devices that are commercially available. As with any interventional procedure, use of the study devices during embolization procedures involves some risks. Risks associated with laboratory testing (i.e., blood draws) and the embolization procedure will be listed in the site's procedure consent form used per their standard of care.

Peripheral embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following:

- Abscess in target organ/tissue
  - Note: Imaging following embolization may reveal intralesional gas in the early post-procedure period. It is important not to mistake this for abscess without additional findings.
- Allergic reaction to contrast media or medications
- Allergic and/or toxic reactions to the embolic agent
- Complications related to placement of the delivery device (e.g., hematoma or bleeding at the site of entry, clot formation at the tip of the delivery device and subsequent dislodgment, vasospasm, and nerve and/or circulatory injuries)
- Computed tomography (CT) artifact in the treatment area following embolization

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- Delivery device entrapment and/or delivery device breakage
- Foreign body reactions (i.e., pain, rash) necessitating medical intervention
- Incomplete occlusion that may give rise to the possibility of development of alternative anatomical pathways, recanalization, or recurrence of symptoms
- Infection necessitating medical intervention
- Non-target embolization, which may result in other complications including paralysis, nerve damage, pulmonary embolism, atrial fibrillation, ischemia and/or tissue necrosis at an undesirable location, and ischemic stroke
- Post-embolization syndrome, which may include transient pain, nausea, vomiting, fever, abnormal changes in laboratory parameters (e.g., elevated liver enzymes), and inflammation
- Target vessel rupture or hemorrhage
- Vasospasm

The frequency and severity of adverse events can vary, and may necessitate additional medical intervention, including surgery. As with any embolization device, patient injury including permanent disability or death may occur as a result of its use.

It is important to note that an embolization procedure may be done in conjunction with another procedure that has a different set of risks of adverse events not associated with the embolization procedure.

10.4 Methods to Minimize Risks

The GPX Embolic Device was subjected to design and user risk assessments as part of the design control process. Results of pre-clinical bench testing, laboratory testing, and a feasibility clinical study have demonstrated that the device is likely to be safe and perform as intended in clinical use. Additional GPX Embolic Device laboratory and clinical experience is summarized in the Investigator's Brochure. Risks will be further minimized through careful subject screening and selection, training of investigators and study staff, adherence to the scheduled assessments, and regular monitoring visits.

10.5 Benefit-to-Risk Rationale

The results from the risk analysis and risk mitigation measures, combined with results of the feasibility study, support reasonable assurance of the safety and efficacy of the GPX Embolic Device, as well its long-term performance, when used in a manner consistent with its labeling and intended use. The evidence supports a clinical benefit-to-risk determination that is favorable for the GPX Embolic Device.

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11.0 ADVERSE EVENTS

11.1 Adverse Event Definitions

Adverse events will be adjudicated for seriousness and for relatedness to the investigational device and study procedure. Refer to **Section 13.0** for adverse event definitions.

11.2 Adverse Event Collection & Documentation

The collection of adverse events will start at the time of the procedure for enrolled subjects and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the severity, seriousness, relatedness, and outcome of the adverse event and to assess whether it meets the criteria for classification as an unanticipated adverse device effect (UADE) requiring immediate notification. All adverse events will be followed until resolution or investigator determination that the subject's condition is stable.

All reported adverse events will be documented on the Adverse Event eCRF. Copies of de-identified source documentation that contain significant information related to the event, such as progress notes, consultations, nurse notes, operative reports, and subject summaries may be requested by the sponsor, CRO, CEC, DSMB, and/or angiographic core lab as needed for evaluation and adjudication.

The following are not considered reportable adverse events for this study:

- Any normal expected post-embolization complaints or symptoms unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary post-embolization care. Expected post-embolization complaints and findings include, but are not limited to edema, nausea, vomiting, fever lasting less than 72 hours and less than 101.5°F, mild or moderate transient pain (excluding chest pain), inflammation, and non-clinically significant abnormal laboratory results (e.g., elevated liver enzymes).
- Any condition that is recorded as pre-existing at baseline, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
- Planned hospitalization for pre-existing conditions (e.g., tumor resection) or a procedure required by the protocol, without serious deterioration in health.

In case of subject death, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the CRO. Any other source documents related to the death should also be provided to the CRO. If no source documents are available, the PI is required to describe the circumstances of the subject's death in written communication (e.g., letter, email).

11.2.1 Device Deficiencies

An assessment of device performance, including deficiencies, will also be collected. If a device deficiency results in the subject experiencing any untoward medical occurrence, unintended

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disease or injury, or untoward clinical signs, these outcomes will be reported as an adverse event on an Adverse Event eCRF. Any malfunctioning devices will be returned to the sponsor by the site for further evaluation.

11.3 Adverse Event Reporting Timeframes

The investigator is responsible for reporting serious adverse events (SAEs) to the IRB in accordance with the IRB's procedures. Unanticipated adverse device effects (UADEs) have special reporting requirements for both the investigator and sponsor, as described in 21 CFR 812.150:

- **Investigator Report:** If a subject experiences a UADE, the investigator must notify the sponsor/CRO and the reviewing IRB as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
- **Sponsor Report:** UADEs will be reported to the FDA, all reviewing IRBs, and participating investigators as soon as possible, but no later than 10 working days after receiving notice of the UADE.

11.4 Adverse Event Relatedness

The investigator and the CEC will assess the relatedness of the adverse event to the investigational device and the study procedure using the categories listed below (see **Section 13.0** for definitions):

- Definitely
- Probably
- Possibly
- Unlikely
- Not Related

11.5 Adverse Event Severity

The investigator and the CEC will assess the severity of the adverse event using the Society of Interventional Radiology AE classification system (Khalilzadeh); the categories are listed below (see **Section 13.0** for definitions):

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Patient death or unexpected pregnancy abortion

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12.0 ADMINISTRATIVE PROCEDURES

12.1 Records & Reports

12.1.1 Case Report Forms

Worksheets may be used to collect subject data that are not readily available from the source documentation. An EDC database will be used to collect study-required data on electronic CRFs (eCRFs). The principal investigator (PI) at the site is responsible for ensuring the eCRFs are accurate and completed in a reasonable timeframe. The PI is required to review and approve the eCRF on the appropriate page(s) to verify the completeness, accuracy, and authenticity of the recorded data.

12.1.2 Sponsor / CRO Study Records & Reports

The sponsor and CRO are responsible for maintaining study records and reports per applicable ICH good clinical practices (GCPs), FDA regulations, ISO 14155, and applicable standard operating procedures and study specific plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, Statistical Analysis Plan).

Results on all pre-specified study outcomes will be released in interim reports, as needed, and in a final clinical study report that will be released within 6 months after study termination or completion. The release of this information, including negative outcomes (e.g., stopping rules enacted), may be hastened if the study is terminated early.

12.1.3 Investigator Study Records

The investigator will securely maintain the following accurate, complete, and current records relating to their participation in the study:

- All essential correspondence that pertains to the investigation.
- Records of each subject's case history and exposure to the investigational device. Case histories include the CRFs and supporting data including, for example, signed and dated ICFs and medical records (e.g., progress notes of the physician, the individual's hospital chart(s), and the nurses' notes). Such records will include:
  - Documents evidencing the informed consent process. The case history of each individual will document that informed consent was obtained at the appropriate time.
  - All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
  - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates and reasons for each deviation from the protocol.

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- Signed investigator agreements, financial disclosure agreements, investigator signature pages, and curricula vitae.
- IRB approval documents, including approval of the protocol, protocol amendments, and ICF.

12.1.4 Investigator Reporting Requirements

Investigator reporting requirements are noted in **Table 4** below.

Table 4: Investigator Reporting Requirements

Report	Submitted to	Description
Unanticipated Adverse Device Effects (UADEs)	Sponsor/CRO & IRB	Notification as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
Device deficiency that might have led to a serious adverse event (SAE) if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate	Sponsor/CRO	Notification without unjustified delay after the investigator first learns of the device deficiency that might have led to an SAE.
Serious Adverse Events (SAEs)	IRB	Per IRB reporting requirements
Withdrawal of IRB approval	Sponsor/CRO	Notification within 5 working days of withdrawal.
Progress Report	Sponsor/CRO & IRB	Periodic report detailing the progress of the study, occurring at least annually.
Deviations from protocol (CFR 812.150)	Sponsor/CRO & IRB	**Emergency Use:** Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Other:** If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from sponsor the reviewing IRB, and FDA when required.
Failure to obtain informed consent	Sponsor/CRO & IRB	Notification within 5 working days
Final Report	IRB	Submitted within 6 months after termination or completion of the investigation.

12.1.5 Record Storage & Retention

Refer to the Clinical Trial Agreement for trial data storage, access, and retention requirements.

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12.2 Data Management

Correction of missing or unclear data will be requested as necessary throughout the study. The CRO may request additional information including source documentation as needed. The CRO will also be responsible for confirming the overall integrity of the data. Refer to the study Data Management Plan for more details.

12.3 Device Accountability

All GPX Embolic Device investigational products will be labeled with unique lot numbers. Shipment and receipt records will be maintained, and upon receipt of the investigational devices, the site study coordinator (or delegate) will inventory the devices. As each subject receives treatment with the study device, the date of treatment, subject identifiers (site number/subject number), device performance assessment, and device traceability information will be recorded. If a study device is returned to the sponsor, the date of return and reason for the return shall be documented.

The GPX Embolic Device must be stored in a secure location at each clinical site to ensure use only in the study and unused devices must be returned promptly upon study completion or termination. Product labeled as "Limited by Federal (or United States) law to investigational use" must only be used in the clinical investigation.

12.4 Site Qualification & Selection

The sponsor and/or CRO will assess each potential site to ensure the investigators and his/her staff meet the minimum following criteria:

- The site has an interventional radiologist who can act as a principal investigator.
- The investigators are qualified by experience and training to perform super-selective embolization procedures.
- The site has adequate research support staff with the availability to fulfill the clinical study requirements specified in the protocol.
- The site is not participating in another investigational study that is currently enrolling subjects with competing eligibility criteria.
    - Studies that have a sponsor approved plan for ensuring equitable enrollment would not exclude the site from participation in this study.
    - Studies that have completed enrollment and are in the subject follow-up phase would not exclude the site from participation in this study.
- The investigators are not on the FDA disqualified or debarred list.

Additional details are specified in the study-specific Site Qualification Questionnaires used to select eligible sites.

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12.5 Site Training

Training of the clinical site personnel will be the responsibility of the study sponsor and the CRO. Site personnel will be trained per the study-specific Training Plan, which will consider numerous requirements including inputs from the risk assessments described in this protocol. All site personnel will undergo training during a site initiation visit prior to performing any study-related procedures. All training will be documented. Existing site personnel who have been delegated new tasks and new site personnel will undergo training as designated in the Training Plan.

12.6 Site Monitoring

This clinical study will be monitored according to a study-specific risk-based Monitoring Plan that complies with GCP. Monitors will assess for appropriate study conduct and data integrity, including review of eCRFs and parity checks with the source documentation, worksheets, and hospital charts. Periodic site visits will be conducted (either on-site or remotely), including, routine monitoring visits, and a study closeout visit upon completion of the study. At a minimum, all ICFs, the ICF process, serious adverse event data, and device deficiency data will be monitored and compared to source documentation. A minimum of 20% data verification for the study will be completed. Monitoring will include comparison of eCRFs to source documentation for accuracy and appropriateness, study device accountability, review for unreported adverse events, and prompt evaluation of potential UADEs.

12.7 Institutional Review Board (IRB) / Research Ethics Board (REB) / Health and Disability Ethics Committee (HDEC)

The term IRB will be used in this protocol for readability; IRB can be interchanged with Research Ethics Board (REB) for Canadian sites and Health and Disability Ethics Committee (HDEC) for New Zealand sites. The sponsor will contract with a central IRB making this service available to those sites able to use a central IRB.

At a minimum, the CRO must have documented regulatory approval and IRB approval for the protocol and the site-specific ICF prior to site activation to enroll subjects. Identification of the study (study number, protocol title, and version), documents approved (e.g., protocol, ICF), and the date of IRB review should be clearly stated on the IRB approval documentation signed by the IRB. The site will not be activated until a copy of written and dated IRB approval has been received by the CRO and other applicable study activation requirements are complete.

The site must submit any protocol or ICF amendments to the IRB and is required to forward a copy of the written approval to the CRO. An IRB approval of the amended document(s) must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF, if applicable. The IRB should also be informed of any event likely to affect the safety of subjects or the conduct of the study. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

The ICF must be reviewed by the CRO prior to submission to the IRB for approval.

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12.8 Protocol Deviations

A protocol deviation is defined as a circumstance in which the investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Trial Agreement, Investigator Agreement).

Every attempt will be made to adhere to the protocol. However, should an investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the sponsor or CRO and IRB as soon as possible, but no more than 5 working days from the date the emergency occurred. Except for an emergent circumstance, prior approval from the sponsor, the IRB, and FDA (when applicable) is required for any change in, or deviation from, the protocol as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects.

Protocol deviations will be documented on the Protocol Deviation eCRF. Deviations are reportable to the central or the institution's governing IRB during the annual reporting process, unless otherwise directed by the governing IRB requirements.

Repeated protocol deviations will be closely monitored by the CRO/sponsor. If excessive deviations or a failure to reduce deviations is noted, the sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations (21 CFR 812.46(a)).

12.9 Protocol Amendments

Changes to the protocol must be documented in a formal protocol amendment prior to implementation in the study. Amendments to the protocol will be initiated by the sponsor or CRO and must be approved by the IRB prior to implementation at the site.

12.10 Study Suspension or Termination

No formal statistical rule for early termination of this study for insufficient effectiveness of the study devices is defined.

The sponsor reserves the right to terminate or suspend the study for valid scientific reasons or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable risk to the subjects). The sponsor may also terminate or suspend the study if the DSMB stopping rules (as defined in the DSMB Charter) have been met. The sponsor also reserves the right to terminate the study for business reasons. Refer to the Clinical Trial Agreement for specific information regarding study termination (by IRB withdrawal of approval, by principal investigator, or by sponsor).

If the study is terminated prematurely or suspended, the sponsor will promptly inform all investigators of the termination or suspension and the reason(s). The IRB will also be informed, either by the sponsor or Investigator, and provided with the reasons(s) for the termination or suspension. Regulatory authorities will be informed, as required.

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The IRB may choose to discontinue the study at any site for which they granted approval if the research study is not conducted in accordance with the IRB's requirements or the research study indicates unexpected serious harm to subjects.

12.11 Subject Confidentiality

All information and data sent to the CRO concerning a subject or their participation in this study will be considered confidential. The sponsor, CRO, monitors, IRB, and regulatory representatives will have access to these confidential files and have the right to inspect and copy all records pertinent to this study for data verification. All data used in the analysis and reporting of this study will be without identifiable references to a subject. Subject names and contact information may be visible to the sponsor, CRO, and monitors during review of medical records. Source documentation and/or imaging may be available to the core laboratory, CEC, and DSMB. This information should not contain protected health information and will be treated with adherence to professional standards of confidentiality. In addition, upon regulatory request, subject records shall be provided to regulatory agencies.

12.12 Audits & Inspections

Investigators and study sites are required to permit study-related monitoring, audits, IRB review, and regulatory inspection(s) and provide direct access to source data/documents.

12.13 Statements of Compliance

This study is to be conducted in compliance with the study protocol and in accordance with ethical principles that have their origin in the Declaration of Helsinki, as defined in the following U.S. and international standards for good clinical practice:

- International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2) (2016)
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 11, 50, 54 and 56 and 812)
- ISO 14155: 2020
- Guideline on the Regulation of Therapeutic Products in New Zealand, Part 11, Clinical trials - regulatory approval and good clinical practice requirements
- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications (Canada)

12.14 Finance & Agreements

For details on how the clinical investigation is financed and the agreement between the sponsor, investigators, and sites, refer to the Investigator Agreement and Clinical Trial Agreement.

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12.15 Publications & Public Disclosure

Refer to the Clinical Trial Agreement for publications and public disclosure requirements and conditions.

12.16 Study Contacts

Refer to the Study Contact List for detailed contact information, including names, telephone numbers, and email addresses.

13.0 DEFINITIONS

13.1 Adverse Event Definitions

Adverse device effect (ADE): An adverse event related to the use of an investigational medical device. [*ISO 14155 2020, 3.1*]

- Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment [referred to in this study as "delivery"], implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes "comparator" if the comparator is a medical device.

Adverse event (AE): Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. [*ISO 14155 2020, 3.2*]

Adverse Event Severity: Severity of an adverse event will be assessed using the Society of Interventional Radiology AE classification system based on the categories defined below (Khalilzadeh).

Severity	Description
Mild	No therapy or nominal (non-substantial) therapy (post-procedural imaging performed and fails to show manifestation of AE); near miss (e.g., wrong site of patient prepared, recognized, and corrected before procedure; wrong patient information entered for procedure)
Moderate	Moderate escalation of care, requiring substantial treatment, e.g., intervention (description of intervention and result of intervention) under conscious sedation, blood product administration, extremely prolonged outpatient observation, or overnight admission after outpatient procedure not typical for the procedure (excludes admission or hospital days unrelated to AE)

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Severity	Description
Severe	Marked escalation of care, i.e., hospital admission or prolongation of existing hospital admission for >24 hours, hospital admission that is atypical for the procedure, inpatient transfer from regular floor/telemetry to intensive care unit, or complex intervention performed requiring general anesthesia in previously non-intubated patient (generally excludes pediatrics or in circumstances in which general anesthesia would primarily be used in lieu of moderate sedation, e.g., in mentally challenged or severely uncooperative patients)
Life-threatening or disabling event	e.g., cardiopulmonary arrest, shock, organ failure, unanticipated dialysis, paralysis, or loss of limb or organ
Patient death or unexpected pregnancy abortion	--

Adverse event relatedness: The relationship of an adverse event to the investigational device or the study procedure based on the categories defined below.

Relatedness	Description
Definitely	The adverse event follows a strong temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure. This can include an adverse event that occurs after the study procedure.
Probably	The adverse event follows a reasonable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, and the possibilities of other factors, such as underlying and concomitant illness, concomitant medications, or concurrent treatment can be excluded.
Possibly	The adverse event follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying or concomitant illness, concomitant medications, or concurrent treatment are presumable.
Unlikely	The adverse event has an improbable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying or concomitant illness, concomitant medications, or concurrent treatment.
Not related	The adverse event has no temporal sequence to the interventional procedure, the device treatment, or any user handling, or it can be explained by other factors, including underlying disease or concomitant illness, concomitant medication, or concurrent treatment.

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Device deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. [*ISO 14155 2020, 3.19*]

- Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device or the comparator.

Major adverse event (MAE): Device-related serious adverse events, as adjudicated by the Clinical Events Committee (CEC), comprising the following types:

- Nontarget embolization with ischemia in an unintended anatomical area
- Systemic allergic and/or toxic reaction to the GPX Embolic Device
- Catheter entrapment and/or breakage
- Culture-proven abscess in target organ/tissue
- Embolization-related death

[MAE definition guided by FDA in pre-submission notification Q181516-S002 3(g)]

Serious adverse event (SAE): An adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - 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
- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Note: An AE is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

[ref. ISO 14155:2020, 3.45]

Unanticipated adverse device effect (UADE): 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

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unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. [*21 CFR 812.3(s)*]

13.2 Other Study-Specific Definitions

Catheter entrapment: The inability to withdraw the catheter with which the GPX Embolic Device is administered due to adhesion of the GPX Embolic material to the catheter.

Non-target embolization: Embolization with ischemia that occurs outside of the target area of occlusion (e.g., renal embolization resulting in nontarget embolization and ischemia of a non-renal organ).

Successful occlusion: No clinically significant contrast enhancement immediately beyond the target vessel embolization site, as determined by the core lab via comparison of the pre- and final post-procedure images. [*ref. Dariushnia 2021*]

Target Vessel Embolization Site: The vessel targeted for occlusion using the GPX Embolic Device, including all vessels and vessel beds distal to the vessel target.

14.0 REFERENCES

Angle J F, Siddiqi NH, Wallace MJ, Kundu S, et al. Quality improvement guidelines for percutaneous Transcatheter Embolization. *J Vasc Interv Radiol*. 2010;21(10):1479-1486.

Dariushnia SR, Redstone EA, Heran MK, Cramer HR, et al. Society of interventional radiology quality improvement standards for percutaneous Transcatheter Embolization. *J Vasc Interv Radiol*. 2021;32(3):476.e1-476.e33.

Golzarian J, Sapoval MR, Kundu S, Hunter DW, et al. Guidelines for peripheral and visceral vascular Embolization training. *J Vasc Interv Radiol*. 2010;21(4):436-441.

Griessenauer C, Salem M, Hendrix P, Foreman P, et al. Preoperative Embolization of Spinal Tumors: A Systematic Review and Meta-Analysis. *World Neurosurg*. 2016 Mar;87:362-71.

Holden, Krauss M, O'Hara R, Jones J, Smith DK. A First-in_Human Trial of a New Aqueous Ionic Liquid Embolic Material in Distal Embolization Applications. *J Vasc Interv Radiol.*; 2024;35:232-240.

Karalli A, Ghaffarpour R, Axelsson R, Lundell L, et al. Transarterial Chemoembolization of Renal Cell Carcinoma: A Prospective Controlled Trial. *J Vasc Interv Radiol*. 2017 Dec;28(12):1664-1672.

Khalilzadeh O, Baerlocher M, Shyn P, Connolly B, et al. Proposal of a New Adverse Event Classification by the Society of Interventional Radiology Standards of Practice Committee. *J Vasc Interv Radiol*. 2017 Oct;28(10):1432–1437.

Kessel D, Ray C. Transcatheter Embolization and therapy. Springer. 2010.

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Lubarsky M, Ray C, Funaki B. Embolization agents—Which one should be used when? Part 1: Large-vessel Embolization. *Seminars in Interventional Radiology*. 2009;26(04):352-357.

Medtronic, Onyx Liquid Embolic System Warnings. https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/avm-embolization/onyx-liquid-embolic/indications-safety-warnings.html

Rimon U, Duvdevani M, Garniek A, Golan G, et al. Ethanol and polyvinyl alcohol mixture for transcatheter embolization of renal angiomyolipoma. *AJR Am J Roentgenol*. 2006 Sep;187(3):762-8.

Sam K, Gahide G, Soulez G, Girous MF, et al. Percutaneous embolization of iatrogenic arterial kidney injuries: safety, efficacy, and impact on blood pressure and renal function. *J Vasc Interv Radiol*. 2011 Nov;22(11):1563-8.

Triano MJ, Lara-Reyna J, Schupper AJ, Yaeger KA. Embolic agents and Microcatheters for Endovascular treatment of cerebral arteriovenous malformations. *World Neurosurgery*. 2020;141:383-388.

van Lienden KP, van den Esschert JW, de Graaf W, Bipat S, et al. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol*. 2013 Feb;36(1):25-34.

Wright B, Johnson B, Saidian A, Rais-Bahrami S, et al. Trans-arterial embolization of renal cell carcinoma: a systematic review and meta-analysis. *Abdominal Radiology*. 2022;47:2238-2243.

15.0 REVISION HISTORY

Rev.	Description of Changes	DCO #	Effective Date
A	Initial release.	2024-05-003	5/24/2024

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