Clinical Investigation Plan:

Clinical Investigation Plan (CIP) Title:	Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study
Short Title	Instylla HES™ Hypervascular Tumor Pivotal Study
CIP Number: **Version Date:**	INY-P-20-001, Rev I 26January2024
Investigational Device:	Instylla Hydrogel Embolic System (HES) including Instylla Delivery Kit and Instylla Microcatheter Note: Instylla Delivery Kit and Instylla Microcatheter are 510(k) cleared in the US
Universal Trial Number:	NCT04523350
FDA IDE Number:	G200149
Sponsor:	Instylla, Inc. 201 Burlington Rd, North Building Bedford, MA 01730 USA
Sponsor Contact:	Clinical Operations Email: Clinical@Instylla.com O: +1 781-790-4860

Confidentiality Statement

INVESTIGATOR AGREEMENT

Clinical Investigation Plan Title:	Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study
Clinical Investigation Plan Number:	INY-P-20-001, Rev I

I agree to conduct the above referenced clinical investigation plan (CIP) of the Instylla Hydrogel Embolic System (HES) including Instylla Delivery Kit and Instylla Microcatheter sponsored by Instylla, Inc. (hereinafter "Study Sponsor") in accordance with the design and specific provisions as designated in this CIP, and conditions of approval imposed by the reviewing country specific regulatory agency/competent authority and Institutional Review Board (IRB)/ local ethics committee (EC), 21 CFR 812 and any other applicable FDA regulations. Modifications to the CIP are acceptable only in the form of a CIP amendment. I agree to await EC/ IRB, Regulatory Authority (as required) and Study Sponsor's approval for the CIP, informed consent and documentation to be presented to subjects before initiating the study; to obtain informed consent from subjects prior to their enrollment into the study; to collect and record data as required by this CIP and case report forms; to report non serious and serious adverse events that may occur for any subject participating in this study under my care; to report device deficiencies or malfunctions for any of the devices utilized in this CIP; and to maintain study related documentation for the period of time required. I have read and understand the contents of this CIP. I agree to follow and abide by the requirements set forth in this document.

I agree to supervise all use of the investigational device. The rights, safety, and well-being of clinical investigation subjects shall be protected consistent with the ethical principles laid down in ISO 14155 and U.S. Code of Federal Regulations (CFR), specifically, 21 CFR Part 50. This shall be understood, observed, and applied at every step of the investigation.

I understand that this investigation will be monitored by Study Sponsor and/or a designee. This monitoring will involve remote or in-person periodic inspection of my investigational site and ongoing review of the data that is submitted by me to Study Sponsor. I am also aware that I may be inspected by regulatory authorities/agencies to verify compliance with applicable requirements related to clinical research on human subjects. I am aware that my contact for all matters related to this investigation is Instylla at +1 781-209-6516 or e-mail Clinical@Instylla.com.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time. In the event that I decide to discontinue my participation as an Investigator in this study, I will notify Study Sponsor 30 days prior of my intent to discontinue. I understand that I am obligated to complete the follow up of the subjects already participating in the investigation.

Any data generated as a result of this investigation will be the exclusive property of Study Sponsor who retains all rights of publication. I understand that Study Sponsor encourages me to pursue independent publications related to my experience with this investigational device with the understanding that Study Sponsor reserves the right of prior review of these publications.

I agree to provide to Study Sponsor a current curriculum vitae and medical license (or equivalent) along with the curriculum vitae and medical license (or equivalent) of those physicians at this institution who will be using this investigational device or participating in this study as sub-Investigators under my supervision. These CVs include the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of a Study Sponsor, this institution's EC/IRB, or a regulatory agency.

I understand that this investigation, protocol, and trial results are confidential, and I agree not to disclose any such information to any person other than a representative of Study Sponsor or a regulatory authority without the prior written consent of Study Sponsor.

I will provide financial information as requested by the Study Sponsor and 21 CFR Part 54.

I understand the information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to me, which is indicated as privileged or confidential.

I understand that I cannot participate in this study until I have signed this agreement.

Signed:_____ Date:_____
Investigator

Print Name:_____

Site #: ____

SYNOPSIS

Clinical Investigation Plan (CIP) Title:	Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE) / Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study
CIP Number:	INY-P-20-001, Rev I
Study Objective	To determine whether Instylla HES has the ability to effectively embolize targeted arterial segments of hypervascular tumors as well as (i.e., is non-inferior to) standard of care (SOC) transarterial embolization/ conventional transarterial chemoembolization, while resulting in an acceptable risk of device and procedure-related serious adverse events.
Indication for Use	The Instylla Hydrogel Embolic System (HES) is indicated for embolization of hypervascular tumors in vessels ≤ 5mm.
Study Design	This is a subject and evaluator blinded, prospective, randomized, parallel arm, multicenter study to investigate whether Instylla HES is as effective (i.e., non-inferior) as SOC TAE/cTACE for occluding targeted arterial segments of primary or metastatic hypervascular tumors. It is anticipated that at least 150 men and women with hypervascular tumors will be treated. Randomization to Instylla HES or the Institutional SOC TAE/cTACE (2:1) will be performed intra-operatively after a satisfactory pre-embolization angiogram and will be stratified by investigational site and tumor location (hepatic or non-hepatic). Following the embolization procedure, subjects may be admitted for overnight observation and will be evaluated at discharge, 30, 90 and 180 days following the Index Procedure. The 90-day visit will be considered the completion of the clinical investigation (e.g., for the purpose of submission to regulatory authorities). End of study is defined as the last subject's last visit which will occur at the 180-day visit. At the 30- and 90-day visits, subjects will undergo a physical assessment (vitals only), hematological and chemical laboratory testing and follow-up tumor imaging. An in-person visit is preferred, but a remote (e.g. over the phone or via telehealth) visit can be substituted for select components of the follow-up. Tumor characteristics at baseline and local response following

treatment will be assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST 1.1. guidelines using CT (Multiphasic CT for hepatic tumors) or magnetic resonance imaging (MRI) with images reviewed by an Imaging Core Laboratory. The same imaging modality/protocol (same machine preferred) is to be used throughout the study. At the 180-day visit, subjects will complete the quality of life questionnaire remotely and a series of questions to evaluate concomitant medications and adverse events.

Throughout the duration of the study, subjects will be clinically evaluated and assessed for adverse events using the grading of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). Severity of complications will be further classified in accordance with Society of Interventional Radiology (SIR) guidelines.

Interim review of safety data by an independent Data Monitoring Committee (DMC) will be performed following accrual of 20 HES treated subjects. The study will continue uninterrupted if the stopping safety rule is not met.

Additionally, the study will incorporate an adaptive design in which an interim analysis will be performed for purposes of sample size re-estimation. The ultimate sample size for the trial will be adaptively determined based upon a review performed once 70% of the planned number of target vessels have been evaluated for the primary effectiveness endpoint and 70% of the planned number of evaluable investigational group (HES) subjects have been evaluated for the primary safety endpoint (whichever occurs later).

Safety data will be reviewed and adjudicated by a Clinical Events Committee. The DMC will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analyses.

This study will be conducted at up to 30 sites in the United States, plus up to 10 sites outside the United States (Australia, and Canada). All sites will have access to an interventional suite. A minimum of 50% of the subjects and total number of sites will be located within the United States. It is anticipated that enrollment will take approximately two (2) years and that the full clinical investigation will take approximately 2.5 years.

Primary Safety Endpoint	The primary safety endpoint will be freedom from major adverse events (MAE) through 30 days post-index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG). The following events will be considered MAE if deemed by the CEC to be definitely device and/or procedure-related or probably device and/or procedure related and satisfies the severity criteria for a Grade ≥ 3 event, classified in accordance with the 2017 Society for Interventional Radiology (SIR) Guidelines (1) • Death • Non-target embolization (NTE) of the index procedure, e.g., severe intractable abdominal pain, gastroduodenal ulceration, intestinal ischemia, pancreatitis, cholecystitis **AND** angiographic/CT evidence of NTE • Unintended target tissue ischemia (defined as symptomatic healthy/non-diseased tissue ischemia in the target organ) • Pulmonary embolism • Vascular injury requiring surgical/endovascular intervention • Renal failure defined as increase in serum creatinine of ≥ 2mg/dL above baseline that persists to the Day 30 visit • Hepatic failure (Grade 3+ asterixis, encephalopathy) that persists to the Day 30 visit • Abscess in target organ/tissue: defined as clinical symptoms of infection (fever, leukocytosis, bacteremia), imaging consistent with the diagnosis of abscess, and a positive drainage culture • Toxic and/or Allergic reactions to the HES hydrogel manifested as immediate anaphylaxis or acute kidney injury (AKI - severe azotemia, oliguria and/or anuria) with no other apparent etiology; e.g., contrast sensitivity.
Primary Effectiveness Endpoint	Delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by an independent radiologist via comparison of the pre and final post procedure angiograms. Subjects may contribute more than one endpoint evaluation, i.e., it is anticipated that on average the number of target vessel embolizations per subject will be 1.5. Target vessels are defined as a single discrete vascular bed. If a greater number of embolizations are performed, this will increase the power for the endpoint evaluation.

	Note: All pre-, intra- and post-procedure diagnostic images (CT/MR) and fluoroscopy/angiograms captured during the conduct of this study must be de-identified and provided to the Sponsor.
Inclusion Criteria	1. Male or female subjects age ≥ 22 years old 2. Subjects with confirmed finding of hypervascular tumor on CT and/or MRI for whom TAE or cTACE is medically indicated, including but not limited to: a. Subjects with unresectable primary or metastatic hepatic cancer b. Subjects with primary, metastatic or benign renal tumors c. Subjects with bone metastases d. Subjects with adrenal tumors e. Subjects with other hypervascular tumors 3. Subjects with at least one target lesion that is well-delineated such that, in the Investigator's opinion, the lesion can be measured in at least one dimension as 1 cm or more, suitable for remeasurement, and demonstrating definitive arterial enhancement. (Note: Pre-operative tumors do not need to meet this criterion.) 4. Subjects with at least one target vessel ≤ 5mm and Instylla HES can be delivered to the target vessel(s). 5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2 (PS 0-1 for metastatic disease) 6. Subject or authorized representative have been informed of the nature of the study and has provided written informed consent approved by the appropriate local Ethics Committee/Institutional Review Board and agrees to comply with all protocol-specified follow-up appointments. 7. Expected life expectancy ≥ 6 months after Index embolization
Exclusion Criteria	Subjects who meet any of the following criteria are not eligible for participation in the study: 1. Embolization for lesions other than hypervascular tumors such as arteriovenous malformations. 2. It is anticipated that not all target vessels requiring embolization during the index procedure can be embolized with either HES alone or the SOC embolization agent as assigned. 3. Undergoing radioembolization or DEB-TACE for Index procedure 4. Undergoing a planned secondary procedure the same day as the Index Procedure 5. Requires TAE/cTACE for liver tumors via extrahepatic collateral artery(ies)

	6. Prior radioembolization of the target tumor lesion/vascular bed within 30 days of the Index Procedure. 7. For subjects with HCC or undergoing embolization to the liver: Child-Pugh Class C or presence of complete portal vein thrombosis. 8. Tumor lesions > 8 cm in diameter (in one direction) or >50% tumor volume burden of the target organ 9. If subject was treated with Avastin, last dose is within 4 weeks of the planned procedure. 10. Known severe atheromatosis or vascular anatomy that precludes catheterization 11. Presence of bilioenteric anastomoses and/or prior biliary stenting/drainage or any violation of the biliary sphincter, including sphincterotomy for embolization of liver tumors 12. Target lesion supplied by the pulmonary artery, coronary artery, or cerebral or cerebellar artery (requiring embolization of these arteries) or the artery to be embolized has connections to these arteries via a collateral pathway 13. Known allergies (based on history) to PEG, ferrous compounds, tert Butyl Hydroperoxide, contrast media or procedural sedatives/anesthetics that is not amenable to pre-medication 14. Uncorrectable impaired clotting: Platelet count <30,000/μL or International Normalized Ratio (INR) > 1.5 15. Serum creatinine > 2 mg/dL 16. Serum bilirubin level > 3 mg/dL 17. Serum albumin < 2.5 g/dL 18. Any contraindication to angiography or embolization protocol utilized at treating institution. 19. Pregnant or breast-feeding or females planning on becoming pregnant with the next 3 months (*women of child-bearing potential must undergo a pregnancy test performed in accordance with local institutional requirements*). 20. Other concurrent conditions including an ongoing adverse effect or complication of prior therapy or adverse drug reactions, that in the opinion of the Investigator or Clinical Events Committee, would be unlikely to receive clinical benefit from the study procedure or participation in the study may compromise subject safety or study objectives (including but not limited to ongoing acute infection, renal dysfunction, morbid obesity, severe cardiac disease). 21. Enrollment in a concurrent study in which the study treatment may confound the evaluation of the study device
Study Procedures	Men or women for whom vascular embolization is clinically indicated and who appear to meet eligibility criteria will be consented for the study.

See also Schedule of Assessments **(Table 1)**	The consent will be obtained prior to any study specific procedures. It is expected that all subjects will undergo pre- and post-embolization imaging using CT (Multiphasic CT for hepatic tumors) and/or MR as part of standard of care. Following determination of eligibility and a satisfactory pre-embolization angiogram, qualifying subjects will be randomized to receive treatment assignment. Subjects will be considered enrolled at the time of randomization. Embolization will be performed in accordance with the standard practices of the institution and in accordance with the embolic agent's manufacturers' instructions. Using a conventional transfemoral or transradial approach, an appropriately sized catheter will be introduced into the vasculature of the target embolization site. Pre-embolization angiography will be performed to evaluate the vascular anatomy in the targeted embolization area. The procedure will be discontinued 1) if the vascular anatomy precludes catheter placement; or 2) safe embolization is not possible. If it is determined that the subject cannot undergo embolization, the subject will be considered an intra-operative (secondary) screen failure.
Screening/Baseline Visit: (within 45 days prior to Index Procedure, except for baseline imaging for benign tumors which can be within 60 days of Index Procedure)	• Demographic information: date of birth (or age at time of consent), gender, race, ethnicity • Indication for embolization • Disease features: tumor etiology, tumor location, tumor staging, number and dimension of tumor lesions (cm) • Medical/Surgical History/Current status: concomitant medical conditions, prior medical conditions, prior surgeries, prior therapies • Baseline CT (Multiphasic CT for hepatic tumors) or MR imaging (does not have to be repeated if performed within 45 days of planned index-procedure date and there has been no clinical indication of disease progression for malignant tumors or 60 days of planned index-procedure date for benign tumors) • Targeted Physical Examination: including vitals (sitting blood pressure, pulse, respiratory rate, temperature, height and weight) • Laboratory testing: CBC with platelet count, International Normalization Ratio (INR), albumin, creatinine, glucose, AST/ALT, bilirubin, and alkaline phosphatase (for liver tumors) and Alpha-fetoprotein (AFP) levels in subjects with hepatic malignant tumors • ECOG Performance Score • EORTC QLQ-C30 and EORTC QLQ-HCC 18 (as applicable) • Child-Pugh classification (for subjects with liver disease) • NYHA classification (for subjects with cardiac disease)

	• Pregnancy test for women of child-bearing potential.
Intra-operative Treatment Assignment	Envelope based randomization to be stratified by investigational site and tumor location (hepatic or non-hepatic tumor).
Index Procedure: Instylla HES/SOC Administration	• Angiography performed to evaluate tumor lesion and to confirm absence of significant arteriovenous and arterioportal shunting or numerous extrahepatic collateral feeding arteries • Access to target blood vessel with appropriate catheter system • Identification of vessels targeted • Selective embolization procedure until stasis is achieved. The following to be recorded: o Number of tumor feeding vessels targeted o If randomized to HES: Volume of HES embolic material delivered (total volume of both precursors, excluding priming volume) for each vascular area embolized. o If randomized to Control: Chemotherapeutic agent/particulate embolization details for each vascular area embolized o Embolization time (duration of time from initiation of embolic agent injection to final injection) for each vascular area embolized o Embolization Procedure time (duration of time elapsed between placement of the commercially available microcatheter into access vessel for delivery of embolic agent to completion of final angiography) for each vascular area embolized o Cumulative Fluoroscopy Time (in minutes) and dose o Overall Procedure Time (from insertion to removal of the arterial sheath) o Vessels canalized, number and size of tumor lesions treated o Number of times HES, TAE or cTACE syringes are filled o Presence or absence of vessel spasm during procedure o Instances when the catheter is repositioned due to non-embolization • Post-procedure angiography to document technical success at the conclusion of the procedure • Overall Ease of Embolic Delivery (5-point Likert scale from difficult to easy) • Device observations • Adverse Events per NCI Common Terminology Criteria for Adverse Events (CTCAE Version 5.0) and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity

	Classification (1). Note: if subject is experiencing pain, the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represents the worst-possible pain.
Discharge Assessment	• Vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight) • Concomitant medications • Adverse Events per NCI CTCAE Version 5.0 and severity rated in accordance with the SIR guidelines.
Follow-up on Day 30 (±7 days) and Day 90 (±14 days) Post-embolization	• Vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight) • ECOG Performance Score • Child-Pugh classification, for subjects with liver tumors • Target Tumor Response/HES persistence via contrast-enhanced CT (Multiphasic CT for hepatic tumors) or MRI (imaging modality/protocol consistent with baseline imaging (only for non-resected subjects); same machine is preferred): Hypervascular tumor response characterized via modified RECIST or RECIST 1.1 • Laboratory testing (Only for non-resected subjects): CBC with platelet count, albumin, creatinine, AST/ALT, bilirubin, and alkaline phosphatase and Alpha-fetoprotein levels in HCC subjects • EORTC QLQ-C30 and EORTC QLQ-HCC 18 (as applicable) • Adverse Events per NCI CTCAE Version 5.0 and severity rated in accordance with the SIR guidelines. • Concomitant medications Note: An in-person visit is preferred, but a remote (e.g. over the phone or via telehealth) visit can be substituted for select components of the follow-up.
Follow-up on Day 180 (±30 days) Post-embolization	• Adverse Events per NCI CTCAE Version 5.0 and severity rated in accordance with the SIR guidelines • EORTC QLQ-C30 and EORTC QLQ-HCC 18 (as applicable) • Concomitant medications Note: this visit to be conducted via remote (e.g. over the phone or via telehealth) visit unless the Investigator assesses that comments brought up during the remote visit warrant an in-office visit. Note: the duration of subject participation in this study is expected to be about 6 months post-embolization; however, subjects may be consented for a 1 and 2 year follow-up visit.

VERSION HISTORY

Version	Description	Impact on performance, effectiveness, safety, or other endpoints	Affected Documents	Originator
A	Original Issue	N/A	N/A	A. Fagnant (consultant) B. Mastrorio C. Reinhold
B	A detailed summary of the protocol changes for Rev B are located in Appendix 9	Not applicable at this revision	Not applicable at this revision	C. Reinhold
C	A detailed summary of the protocol changes for Rev C are located in Appendix 9	Not applicable at this revision	Not applicable at this revision	C. Reinhold
D	A detailed summary of the protocol changes for Rev D are located in Appendix 9	Not applicable at this revision	Not applicable at this revision	C. Reinhold
E	A detailed summary of the protocol changes for Rev E are located in Appendix 9	Not applicable at this revision	Not applicable at this revision	C. Reinhold
F	A detailed summary of the protocol changes for Rev F is located in Appendix 9	Removed other endpoint: Parent vessel patency at conclusion of embolization procedure	ICF, eCRF	B. Mastrorio
G	A detailed summary of the protocol changes for Rev G is located in Appendix 9	Clarified exclusion criteria of prior radioembolization	eCRF	C. Reinhold
H	A detailed summary of the protocol changes for Rev G is located in Appendix 9	Increase in number of sites in US. There is no impact on performance, safety, effectiveness or other endpoints	eCRF, ICF	S. Dasari
I	A detailed summary of the protocol changes for Rev I is located in Appendix 9	Separation of the analysis populations to maximize subject retention. Correction of a calculation error in the maximum enrollment. There is no impact on performance, safety, or effectiveness.	SAP	N. Rissman

LIST OF ABBREVIATIONS, ACRONYMS AND TERMS

AE	Adverse Event
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBC	Complete Blood Count
CBCT	Cone Beam Computerized Tomography
CCG	CRF Completion Guidelines
CIP	Clinical Investigational Plan
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CT	Computerized Tomography
cTACE	Conventional transarterial chemoembolization
CTCAE	Common Terminology Criteria for Adverse Events
DSA	Digital Subtraction Angiography
EC	Ethics Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Score
eCRF	Electronic Case Report Form
EE	Per protocol Effectiveness Evaluable
eGFR	Estimated Glomerular Filtration Rate
FDA	United States Food and Drug Administration
FIH	First In Human
GCP	Good Clinical Practice
H&E	Hematoxylin and Eosin staining
HCC	Hepatocellular Carcinoma
HES	Hydrogel Embolic System
IC/ICF	Informed Consent / Informed Consent Form
IFU	Instructions for Use
IMM	Independent Medical Monitor
INR	International Normalized Ratio
IRB	Institutional Review Board
IVE	Index Vascular Embolization

MAE	Major Adverse Event
MI	Myocardial Infarction
mL	Milliliter
MR / MRI	Magnetic Resonance / Magnetic Resonance Imaging
mRECIST	modified Response evaluation criteria in solid tumors
NCI	National Cancer Institute
NPO	Nil per os
NTE	Non-target embolization
NYHA	New York Heart Association
PEG	Polyethylene glycol
PS	Performance Score
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RMA	Return Materials Authorization
s	Seconds
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SE	Per protocol Safety Evaluable
SIR	Society of Interventional Radiology
SOC	Standard of Care
SOP	Standard Operating Procedure
TACE	Transcatheter arterial chemoembolization
TAE	Transcatheter arterial embolization
USADE	Unanticipated Serious Adverse Device Effect

1 TABLE OF CONTENTS

Table of Tables

Table of Figures

Clinical Investigational Plan

2 INTRODUCTION

2.1 BACKGROUND

Vascular embolization is a technique in which an occlusive agent is delivered via selective catheter placement and with image guidance to achieve ischemic devascularization of target tissue. Vascular embolization, more specifically, transcatheter arterial embolization is an established treatment for benign and malignant hypervascular tumors of various etiologies. Transcatheter arterial embolization (TAE) has a particularly important role for patients with liver-dominant hepatic primary and metastatic malignancies (e.g., metastatic neuroendocrine or colorectal cancer) in patients with limited progressive disease not responsive to systemic therapy, surgically unresectable or inoperable disease; palliation, or as a bridge or downstage to liver transplantation or ablation. (2) (3).

Two main approaches for embolization are traditionally recognized: transarterial chemoembolization (TACE) (with chemotherapy injection) and bland TAE. The goal of TACE is to fill the tumor with a chemotherapeutic drug (e.g., doxorubicin, epirubicin, cisplatin, or mitomycin C) using a carrier agent, often followed by a physical embolic to stop blood flow. Historically, the carrier agent has been Lipiodol (ethiodized oil) – referred to as conventional TACE or cTACE, but more recently drug-eluting beads (DEB) have been employed; however, drug-eluting beads have yet to be approved by the Food and Drug Administration. No drugs are injected during TAE, rather the goal is to achieve super-selective vascular embolization to deprive the tumor of its blood supply and invoke tumor necrosis.

While many centers routinely use TACE for intermediate hepatocellular carcinoma, there is a paucity of robust data in favor of a clear superiority of TACE over bland embolization (4) (5). Therefore, either TAE or TACE could be considered effective in the management of patients with HCC. Indeed, a recent meta-analysis supports the non-superiority of TACE with respect to TAE, however TACE resulted in a significantly higher rate of post-embolization syndrome and systemic adverse events (liver abscess, liver failure, gastrointestinal hemorrhage, leukopenia, ischemic biliary stricture, spontaneous bacterial peritonitis, septic shock, allergic dermatitis, and severe alopecia) (6). In a systematic review, Katsonos and colleagues evaluated a network of evidence including 55 randomized controlled trials representing a clinical experience for 5763 patients with preserved liver function and intermediate to advanced stage HCC. The evaluation was performed to compare outcomes associated with different approaches to transarterial embolization including bland TAE, conventional TACE and DEB-TACE. The authors cited no survival benefit of the transarterial chemoembolization modalities over TAE alone. Estimated median survival was 13.9 months in control (best supportive care), 18.1 months in TACE, and 20.8 months with bland TAE (7). In a

large series of 322 patients undergoing bland TAE for HCC with a median follow-up of 20 months, 1-, 2-, and 3-year overall survival rates were 66%, 46% and 33% respectively. When patients with extra-hepatic disease or portal vein involvement were excluded, overall 1-, 2- and 3-year survival rates rose to 84%, 66% and 51%, respectively, and median survival was 40 months (8).

Bland TAE also plays an important role for the treatment of renal tumors. The technique has been demonstrated to be effective in decreasing intra-operative blood loss and reducing blood transfusion requirements when performed prior to resection of hypervascular tumors, particularly in patients with renal cell carcinoma (RCC) (9) (10). Renal artery embolization has also been demonstrated to be very effective for palliation of symptoms in the setting of nonoperative advanced stage renal cell carcinoma. Further, this technique plays a large role in the management of angiomyolipomas (AMLs) that are symptomatic or at risk of spontaneous rupture (11) . Due to the minimally invasive, effective, and rapid acting mode of action, embolization has also been used successfully for palliative treatment for symptomatic bone metastases (12) and for palliative, debulking or hormone suppression for adrenal artery tumors (13).

Since the procedure was first described in 1974 (14), a diverse armamentarium of embolic agents has become clinically available for tumor embolization including gelatin sponges/gelatin pledgets, and copolymer embolic particles, including most recently beads constructed with biocompatible polyethylene glycol hydrogels (15). However, no consensus is available on the specific type of embolic material that is superior for the different tumor entities regarding oncological efficacy, complication rate, and biocompatibility (16). An important issue for effective embolization is the embolic agent being capable of reaching the targeted vasculature for complete devascularization (17). Generally, the smaller the diameter of a particulate embolic agent, the deeper its penetration into the tumor/target feeding vessels.

Instylla, Inc., located in Bedford, MA, is an early stage medical device company, formed in March 2017 focused on developing hydrogel biomaterials to address unmet needs in interventional radiology and in particular for arterial embolization including embolization of hypervascular tumors.

Instylla has developed the Instylla Hydrogel Embolic System (hereafter referred to as HES), for the embolization of hypervascular tumors. The Instylla HES is an aqueous, biocompatible, persistent hydrogel produced from polyethylene glycol. The product is a liquid embolic agent provided as a two-part system that forms *in situ* at the target location. The HES is designed to offer controlled, targeted embolization. HES is delivered via the Instylla Microcatheter, with the aid of the Instylla Delivery Kit, and a commercially available outer microcatheter system that enables the delivery of the HES precursors through discrete fluid lumens. One of the precursors (Polymer Precursor) is an aqueous combination of polyethylene glycol (PEG) and a ferrous complex. The second precursor (Initiator Precursor) is a dilute aqueous peroxide solution. Commercially available contrast media is mixed with the precursors to allow fluoroscopic visibility during delivery. The precursors are combined when injected into the subject via a dual catheter (coaxial) delivery system under fluoroscopic guidance. Immediately following injection, the mixed precursors rapidly solidify

to form a biocompatible hydrogel. The formed hydrogel is soft with a modulus similar to vascular tissue and has been designed to be unaffected by natural thrombolytic processes that may cause recanalization.

Similar to other commercially-available embolization devices, such as microspheres, the therapeutic effect of the Instylla HES is to cause tissue necrosis by blocking the feeding blood supply. The HES fills the vessels and prevents further blood flow which causes necrosis of the targeted tumor cells. As the targeted tissue becomes necrotic it encapsulates the embolic material within it. After approximately 6 months the hydrogel completes liquification via hydrolysis, allowing the hydrogel degradation products to diffuse through the necrotic tissue to healthy capillaries where they are taken to the kidneys and cleared from the subject via renal filtration. Animal studies performed to date suggest that the occlusion remains durable and the vessels do not become patent following hydrogel absorption.

The Instylla HES, including Instylla Delivery Kit and Instylla Microcatheter, will be evaluated for embolization of malignant and benign hypervascular tumors. Characteristics of embolic materials that determine their clinical utility for vascular embolization include the following:

- The greater the completeness of embolization of a tumor the more effective is the necrotic effect on the tumor
- Presence of the embolic at a duration sufficient for tumor necrosis to inhibit recanalization
- Embolization that is independent of the subject coagulation status is desirable to decrease procedure time and to additionally limit the potential for non-target embolization
- Selective and super-selective embolization to limit potential damage to non-tumorous/non-target tissue
- Delivery of the embolic with an easy-to-learn procedure is desirable to increase the consistency of procedural performance. There is also the potential to reduce procedure time and thus fluoroscopy time reducing radiation exposure to both staff and subjects
- Compatibility of multi-model therapy that combines embolization with ablation and surgery

Current embolic choices have trade-offs of the above noted desirable characteristics, with each device having its own characteristics that make it less or more ideal for certain clinical situations. Historically, the relatively large and wide standard deviation of the size of embolization microspheres has limited the ability to deeply penetrate target tumors and ensure complete embolization. Smaller microspheres also require very slow and careful delivery of the material to inhibit non-target embolization and to avoid possible reflux of spheres into non-target vessels. This requirement for slow delivery also increases procedural time (typically 45 minutes to an hour) resulting in increased duration of anesthesia, and greater radiation exposure for the patient and

operating room staff. Additionally, the smaller size microspheres can increase the sensitivity of the procedure to the coagulation status of the patient and increase the time needed, and the possibility of non-target embolization with patients who have compromised coagulation through disease or treatment with anticoagulation medications or if injection is too forceful. (15) (18).

Instylla has set out to design the Hydrogel Embolic System in order to offer the potential to achieve embolic effectiveness, safety and procedural reliability by combining the best attributes of currently commercialized embolic devices. Of note, the PEG platform technology utilized for the Instylla HES has a wide history of safe use in implantable medical devices including products that come in contact with the vasculature (Mynx® Vascular Closure Device, AccessClosure, Inc) and sensitive neurological tissues (i.e., DuraSeal® Dural Sealant and DuraSeal Xact® Spinal Sealant, Integra LifeSciences Corp.).

First in Human Study

Eight (8) subjects (3 in Australia, 4 in New Zealand and 1 in Taiwan) were enrolled in the First in Human (FIH) Instylla HES study for evaluation of patients indicated for non-traumatic lesion and end-organ vascular embolization. Instylla HES was well tolerated, safe, and resulted in a 100% embolization Technical Success. No recanalization was seen at imaging at 30 and 90 days, and tumor responses were as anticipated in this population.

All cases in the FIH study had sufficient visibility to achieve 100% technical success, but feedback was provided on the need for improved visualization during the delivery of the HES hydrogel. Based on this feedback Instylla updated the product, which will be used in the pivotal trial. The updated product allows for the incorporation of more contrast media, which will translate into more HES radiopacity, and improve the visual feedback and control during HES procedures. This increase in HES radiopacity in the pivotal trial will implement the improvement opportunity made during the FIH study.

Additional feedback from the FIH study was received regarding preparation and procedural step order. Simplification of instruction and update to the sequence of steps has been incorporated in the HES Instructions For Use.

3 STUDY OBJECTIVES

To determine whether Instylla HES has the ability to effectively embolize targeted arterial segments of hypervascular tumors as well as (i.e., is non-inferior to) standard of care (SOC), transarterial embolization/conventional transarterial chemoembolization, while resulting in an acceptable risk of device and procedure-related serious adverse events.

3.1 PRIMARY SAFETY ENDPOINT

The primary safety endpoint will be freedom from major adverse events (MAE) through 30 days post-index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG) as described in the Statistical Analysis Plan. The composite primary safety endpoint is considered appropriate for characterizing those events of most concern with embolization devices and is adequate for representing the safety profile of the device. See Section **10.3.1** for the Safety Endpoint and Statistical Hypothesis. The following events will be considered MAE if deemed by the CEC to be definitely device and/or procedure-related or probably device and/or procedure related and satisfies the criteria for a Grade ≥ 3 event in accordance with the SIR recommendations.

- Death
- Non-target embolization (NTE) of the index procedure, e.g., severe intractable abdominal pain, gastroduodenal ulceration, intestinal ischemia, pancreatitis, cholecystitis **AND** angiographic/CT evidence of NTE
- Unintended target tissue ischemia (defined as symptomatic healthy/non-diseased tissue ischemia in the target organ)
- Pulmonary embolism
- Vascular injury requiring surgical/endovascular intervention
- Renal failure defined as increase in serum creatinine of ≥2mg/dL above baseline that persists to the Day 30 visit
- Hepatic failure (Grade 3+ asterixis, encephalopathy) that persists to the Day 30 visit
- Abscess in target organ/tissue: defined as clinical symptoms of infection (fever, leukocytosis, bacteremia), imaging consistent with the diagnosis of abscess, and a positive drainage culture
- Toxic and/or allergic reactions to the HES hydrogel manifested as immediate anaphylaxis or acute kidney injury (AKI - severe azotemia, oliguria and/or anuria) with no other apparent etiology; e.g., contrast sensitivity.

3.2 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint for this study is Technical Success defined as the delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by an independent radiologist via comparison of the pre- and final post- procedure angiograms. See Section **10.3.2** for the Primary Effectiveness Endpoint and Statistical Hypothesis. Stasis of flow, as defined above, is an accepted measure of an embolic device per SIR guidelines[1] and is consistent with the indication for use statement proposed for the device.

[1] https://www.jvir.org/article/S1051-0443(10)00648-2/fulltext

Subjects may contribute more than one endpoint evaluation, i.e., it is anticipated that on average the number of target vessel embolizations per subject will be 1.5. Target vessels are defined as a single discrete vascular bed. If a greater number of embolizations are performed this will increase the power for the endpoint evaluation. Sites must capture and provide to the Imaging Core Lab for independent assessment a DSA, having a minimum frame rate of 2 frames per second, from contrast injection through clearance (about 5-10 seconds) before and after embolization. The DSA should include the arterial opacification and complete venous drainage of the intended target vessel.

Note: All pre-, intra- and post-procedure diagnostic images (CT/MR) and fluoroscopy captured during the conduct of this study must be de-identified, appropriately labeled and provided to the Sponsor. A screening image must be sent to the Core Lab prior to the first Index Procedure at each site.

3.3 OTHER DATA COLLECTED

- Embolization Procedure Time (minutes): time elapsed from time of insertion of the outer microcatheter to completion of final angiography
- Embolization Time (minutes): time elapsed from initiation of embolic agent injection through final embolic agent injection (per vessel and per patient)
- Objective Target Tumor Response at all time periods and Duration of Response
- Time to Progression / Survival
- ECOG Performance Score
- QoL (e.g., EORTC QLQ-C30 and EORTC QLQ-HCC 18 as appropriate)
- Cumulative Procedural Fluoroscopy Time and dose
- Overall Procedure Time: from placement to removal of the arterial sheath
- Volume of Embolization Material delivered (excluding priming volume)
- Instances when the catheter is repositioned due to non-embolization
- Number of "assisted embolization" successes (i.e. multiple embolics used during single procedure)
- Embolization Agent Preparation Time (start time, end time)
- Number of times HES/Embolic Agent syringes are filled
- Ease of Embolic Delivery:(5-point Likert scale from easy to difficult where 1= Very difficult, 2=Difficult, 3=Neither easy nor hard, 4=Easy, 5=Very easy)
- Device observations (in both treatment groups as appropriate)

Adverse Events will be documented at all visits per NCI CTCAE Version 5.0 and classified in accordance with the 2017 Society of Interventional Radiologist (SIR) guidelines. Note: if subject

is experiencing pain, the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represent the worst-possible pain.

4 STUDY INTERVENTIONS

4.1 INVESTIGATIONAL DEVICE

4.1.1 Name of Device

Instylla Hydrogel Embolization Device including Instylla Delivery Kit and Instylla Microcatheter

Note: Instylla Delivery Kit and Instylla Microcatheter are 510(k) cleared in the US.

4.1.2 Indication for Use

The Instylla Hydrogel Embolic System (HES) is indicated for embolization of hypervascular tumors in vessels ≤ 5mm.

4.1.3 Device Description

The Instylla Hydrogel Embolic System (HES), manufactured by Instylla Inc. (Bedford, MA USA) is a polyethylene glycol (PEG) hydrogel that rapidly forms *in situ* with the two precursors are combined during the embolization procedure. Prior to use, the precursors are mixed with commercially-available iodinated contrast media to allow for radiopacity. The formed hydrogel acts as a vascular embolic by providing a mechanical barrier to blood flow. The HES embolic remains in place for approximately 6 months. The hydrogel undergoes hydrolysis, with the degradation products being cleared via renal filtration once the embolic liquifies. HES is synthetic with no animal or human derived components. The main components of HES are water and PEG, which has a long history of safe use in medical devices, pharmaceuticals, and cosmetic products. The Instylla Delivery Kit and Instylla Microcatheter are also manufactured by Instylla Inc. The components of the kit are listed below and in the Instructions for Use (IFU).

4.1.3.1 Overview of the Instylla HES System

The HES will be provided in a sterile, single-use package (**Figure 1**). The embolic system will include all component devices necessary for the preparation of the synthetic, hydrogel embolic. For delivery, the Instylla Microcatheter and Delivery Kit will be provided and are intended to be connected to conventional, commercially-available microcatheters.

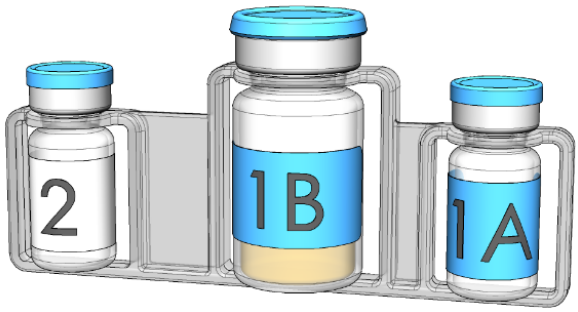
The hydrogel is formed by *in situ* mixing of two precursors, the Polymer Precursor and Initiator Precursor. The Polymer Precursor is prepared at the time of use by mixing an aqueous solution of PEG, an iron complex (referred to as the "Conditioning Solution"), and commercially-available iodinated contrast media which is provided by the procedural site. The Initiator Precursor is a

dilute aqueous peroxide solution combined with commercially-available iodinated contrast media. Since the use of iodinated contrast media is based on physician preference and is readily available within the interventional suite, it is not provided in the HES package, see IFU for contrast information. The resulting HES precursor volume is anticipated to allow for approximately 7.5mL of hydrogel embolic, less any materials required for priming the catheter system. **Figure 1** shows the Instylla HES.

The HES precursors are applied by inserting the 1.2Fr or 1.7Fr Instylla Microcatheter (inner catheter) inside a conventional single lumen microcatheter having a minimum of an inner lumen of 0.021 or 0.027 inch (outer catheter) respectively, effectively creating a coaxial dual lumen catheter system (**Figure 2**). The distal tip with the radiopaque marker of the inner catheter is advanced about 5mm beyond the radiopaque marker of the outer catheter, which prevents plugging by avoiding precursor mixing inside the catheter system. The Initiator and Polymer Precursors are simultaneously injected through the outer catheter and inner catheter, respectively. Outside the catheter tip is where the fluids mix and form the hydrogel within the vessel. Using this delivery system, and unlike conventional liquid embolics, the liquids will not prematurely polymerize and plug the catheter.

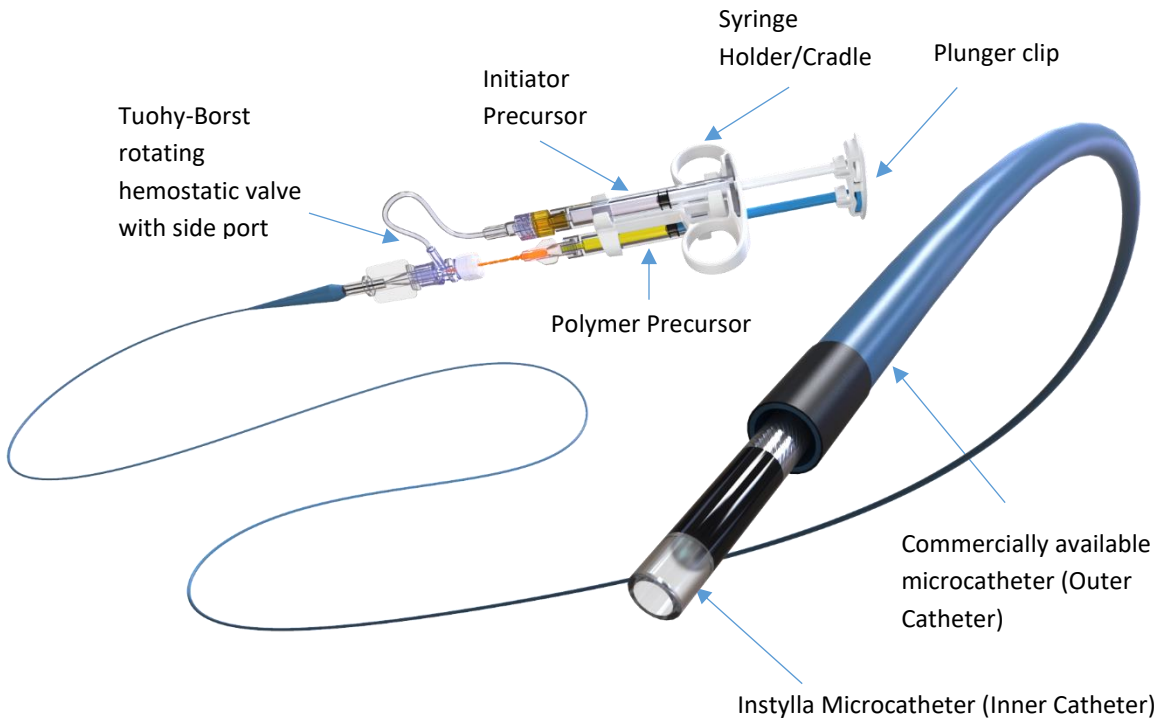
Figure 1. Diagram of the Instylla HES System

Figure 1. Diagram of the Instylla HES System Cont.



Instylla HES System Components	
Packaging	**Component**
HES Precursor Sub-Assembly: Poly/Tyvek pouch placed inside a protective foil pouch	2mL glass vial containing HES polymer solution labeled "1A"
	5mL glass vial containing HES conditioning solution labeled "1B"
	2mL glass vial containing HES initiator solution labeled "2"
	Vial holder
HES Accessory Sub-Assembly: Poly/Tyvek pouch	White 1mL syringe
	3mL syringe
	5mL syringe
	2 small clear vial spikes
	1 large clear vial spike
	Female to female luer lock connector

Figure 2. Diagram of Fully Assembled Instylla HES Delivery System



Instylla Microcatheter and Instylla Delivery Kit	
Kit	**Component**
Instylla Microcatheter	Instylla Microcatheter (122 WL, 142 WL, or 162 WL) WL = Working Length
	Tuohy-Borst rotating hemostatic valve with side port
	Short Catheter Extension Adapter
	Long Catheter Extension Adapter
	Check Valve Connector
Instylla Delivery Kit	1mL Polycarbonate Syringe (Blue)
	1mL Polycarbonate Syringe (White)
	Syringe Holder
	Plunger Clip

The standard technique of vascular access under fluoroscopic imaging (advancing a microcatheter over a guidewire) is used. A specified commercially-available outer catheter is connected to a Tuohy-Borst with side-port having check valve attached, flushed and introduced into the body to the target location. The flushed Instylla Microcatheter is inserted inside the outer catheter with the aid of a guidewire until it is in position, and the guidewire is removed effectively creating a coaxial dual-lumen catheter. The inner and outer lumens are primed with Polymer and Initiator Precursors,

respectively. Two syringes, one filled with the Polymer Precursor (attached to the inner catheter luer/lumen) and the other with the Initiator Precursor (attached to the check valve on the Touhy Borst side port), are assembled to the Syringe Holder/Cradle and Plunger Cap.

Under fluoroscopic imaging, the embolic is delivered with a starting injection rate of approximately 0.05-0.1 mL/second per syringe with pulsatile ("puff") delivery, holding the plunger against any back pressure and adjusting as required, until desired embolization endpoint is achieved. The configuration of the distal tip of the catheter allows for passive mixing of the two precursors beyond the distal opening of the inner catheter resulting in the formation of the hydrogel embolic. The coaxial delivery system has been designed in a manner such that there is optimal delivery of the precursors so that the hydrogel forms in the targeted vessel. In the unlikely cases of high-flow shunting or branches, or in the presence of reflux, the HES precursor is diluted, preventing the gel formation process. This HES characteristic has the potential to minimize the possibility for non-target embolization which can occur, in particular, when established particulate embolics reach non-target areas via intra-arterial communications or collateral vessels.

The Instylla HES and accessory components (i.e., Instylla Microcatheter and Delivery Kit) provided to the institutions participating in this study will be identified by manufacturing lot numbers which are required to be recorded on an individual subjects' Procedure eCRF.

The Instylla HES, Instylla Microcatheter and Delivery Kit have undergone bench and preclinical evaluation which have established the biological safety of the devices under study and have established that the device is appropriately designed for the conduct of embolization procedures. The Instylla Microcatheter and all components of the precursors may be in direct contact with subject's tissues and/or bodily fluids. Design, manufacturing and processing of the Instylla HES System device applied in full or in part with the current standards and guidance documents is outlined in Table 3 of the Investigator's Brochure. Please refer to the Instylla HES Investigator's Brochure for additional details.

4.2 CONTROL INTERVENTIONS

Control interventions will be in accordance with the treating investigator's standard of care and may include bland embolization products, ethanol or conventional TACE in combination with lipiodol. Drug-eluting beads are prohibited from use in this protocol.

Control treatment supplies **will not** be provided by Instylla.

5 STUDY SCOPE AND DURATION

5.1 STUDY DESIGN

This is a subject and evaluator blinded, prospective, randomized (2:1) evaluation to investigate whether Instylla HES is as effective (i.e., non-inferior) as SOC TAE/cTACE (Control) for occluding targeted arterial segments of primary or metastatic hypervascular tumors. Randomization will be performed intra-operatively following a satisfactory pre-embolization angiogram and will be stratified by investigational site and tumor location (hepatic or non-hepatic).

Subjects must have at least one well-delineated tumor such that the tumor can be accurately measured in at least one dimension as 1 cm or more, suitable for remeasurement, and demonstrating definitive arterial enhancement. Pre-operative tumors do not need to meet the 1cm threshold. During the embolization procedure, arterial access will be achieved using either a transfemoral or transradial approach. Celiac and superior mesenteric angiograms will be performed to evaluate tumor vascularity and portal vein patency prior to treatment of liver tumors. Embolization will be performed via catheterization of the arterial branches feeding the tumor followed by delivery of the embolic/chemoembolic agents (Note: embolization for liver tumors should be performed in a segmental or sub-segmental manner). The effectiveness endpoint is delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by an independent radiologist via comparison of the pre and final post procedure angiograms.

For subjects with bilobar hepatic disease, a staged embolization may be performed to treat all targeted tumors. Additionally, repeat treatment may be required in the presence of tumor progression. Unless clinically necessary, such treatments should not be performed prior to the Day 30 assessment. Staged/repeat embolization will be performed using the treating physician's standard of care or Instylla HES if subject was originally randomized to the Instylla HES arm. Subjects will not be randomized a second time.

Following the embolization procedure, subjects may be admitted for overnight observation and will be evaluated at discharge and at 30, 90 and 180 days following the Index Procedure. At the Day 30 and 90 visits, subjects will undergo a physical assessment (vitals only), hematological and chemical laboratory testing and follow-up tumor imaging. An in-person visit is preferred, but a remote (e.g. over the phone or via telehealth) visit can be substituted for select components of the follow-up. The Day 180 visit will be performed remotely unless the Investigator assesses that comments brought up during the remote visit warrant an in-office visit.

Target tumor characteristics at baseline and local response following treatment will be assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST 1.1 guidelines using CT (Multiphasic CT for hepatic tumors) or magnetic resonance imaging (MRI).

The same imaging modality/protocol (same machine is preferred) is to be used throughout the study.

Throughout the duration of the study, subjects will be clinically evaluated and assessed for adverse events using the grading of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). Severity of complications will be further classified in accordance with Society of Interventional Radiology (SIR) guidelines.

Interim review of safety data by an independent Data Monitoring Committee (DMC) will be performed following accrual of 20 Instylla HES-treated subjects (at that time it is estimated that there will be approximately 10 control subjects). The formal stopping rule will be considered reached if 4 Instylla HES subjects experience the following specific device or procedure-related events meeting criteria for a Grade ≥3 event per the 2017 SIR adverse event severity classification (as determined by the CEC): non-target injury, target organ ischemia or serious and severe unanticipated adverse device effect (see **Section 10.7** for details).

Safety data will be reviewed and adjudicated by a Clinical Events Committee. The DMC will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analyses.

At least 150 subjects meeting the eligibility criteria identified within Section 6.1 will be enrolled and randomized in the study to evaluate the primary effectiveness and safety endpoints (100 Treatment: 50 Control). A justification for the sample size is provided in **Section 10.5.** This study utilizes an adaptive design with interim analysis for sample size re-estimation in order to maintain adequate power. The interim analysis will also include a report of instances when the catheter is repositioned due to non-embolization. The ultimate sample size for the trial will be adaptively determined based upon a review performed once 70% of the planned number of evaluable vessels have been evaluated for the primary effectiveness endpoint and 70% of the planned number of evaluable investigational group (HES) subjects have been evaluated for the primary safety endpoint (whichever occurs later). The maximum enrollment will be set to 270 evaluable subjects (or 405 evaluable vessels).

It is planned that up to 30 US sites and up to 10 additional sites outside the US will be used for this study. A minimum of 50% of the subjects and total number of sites will be located within the United States. Each participating center can enroll up to 20% of the total study size.

5.2 SITE REQUIREMENTS AND TRAINING

Investigators participating in this study are expected to meet the following qualifications to be considered for selection.

- Principal Investigator and participating staff are trained in Good Clinical Practice (GCP) within 3 years of the start of their study participation. Documentation of GCP training should be

provided during the startup period or additional training is required to occur prior to site activation.

- Principal Investigator and participating staff complies with additional local regulatory qualifying requirements as appropriate
- The Principal Investigator and/or relevant staff have experience in Clinical Trials.
- Principal Investigator and participating staff have adequate time and availability to conduct the study related procedures.
- Principal Investigator and/or Sub-Investigator is a physician proficient in performing embolization procedures and will be available to perform study specific medical assessments and evaluation of SAE/AEs.
- The Principal Investigator is able to provide access for the site Monitor to all source documentation expected to be captured for the study.
- The Principal Investigator has adequate access to the protocol described subject population such that trial enrollment can be completed within a reasonable time frame (approximately one year).
- The Principal Investigator has cleared any applicable debarment and exclusion screening.
- The Investigational Site has adequate infrastructure to facilitate the execution of the protocol required assessments including the following equipment requirements below:
    - Access to CT/MRI facilities for subjects to have imaging completed
    - Secured Investigational product room-temperature storage area
    - Access to Interventional Radiology procedure room
    - Access to an Accredited Local Laboratory
    - Ability to ensure subject safety including a hospital infrastructure able to handle potential adverse events.
- The Principal Investigator has access to appropriate storage facilities for Investigational Product and/or related supplies, including review of any relevant IP procedures (storage, destruction etc.)
- The Principal Investigator and relevant staff have experience with Electronic Data Capture (EDC) systems (or can be trained) and the appropriate equipment to access the study-specific EDC site.

- Relevant investigator site staff are able to negotiate a contract and budget within a timeframe that supports the study startup timelines.

In addition to the standard selection criteria listed above, Investigators being considered for this study are required to meet the following study specific criteria:

- Interventionalist, interventional radiologist, interventional oncologist, hepatologist, medical oncologist, urologist
- A sub-Investigator could be a physician assistant or nurse to perform medical assessments or perform the informed consent process according to GCP and site specific procedures
- Can delegate to a sub-Investigator that is an Interventional Radiologist, who has experience performing embolization procedures

Investigators will be fully trained in the proper use of the Instylla HES including delivery via the Instylla Delivery Kit and Instylla Microcatheter. Training will include hands-on use of the system and didactic sessions. In addition, on-site or remote training will be provided to the investigator, co-investigators and other study support personnel before the first treatment at the study site or remotely (e.g. over the phone or via video conference). If necessary, additional training will be provided. Instylla personnel or an Instylla representative will be present on site for every case unless Instylla personnel have determined that case support is not needed due to site proficiency or remote proctoring is deemed necessary.

6 PROTOCOL

6.1 SUBJECT POPULATION

The target patient population are subjects for whom vascular embolization is appropriate and have confirmed finding of hypervascular tumor. To participate, an individual must meet all inclusion criteria and none of the exclusion criteria listed below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1.1 Inclusion Criteria

Subjects must meet the following criteria to be eligible for participation within this study:

1. Male or female subjects age ≥ 22 years old
2. Subjects with confirmed finding of hypervascular tumor on CT and/or MRI for whom TAE or cTACE is medically indicated, including but not limited to:
   a. Subjects with unresectable primary or metastatic hepatic cancer
   b. Subjects with primary, metastatic or benign renal tumors
   c. Subjects with bone metastases
   d. Subjects with adrenal tumors
   e. Subjects with other hypervascular tumors
3. Subjects with at least one target lesion that is well-delineated such that, in the Investigator's opinion, the lesion can be measured in at least one dimension as 1 cm or more, suitable for remeasurement, and demonstrating definitive arterial enhancement. (Note: Pre-operative tumors do not need to meet this criterion.)
4. Subjects with at least one target vessel ≤ 5mm and Instylla HES can be delivered to the target vessel(s).
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2 (PS 0-1 for metastatic disease)
6. Subject or authorized representative have been informed of the nature of the study and has provided written informed consent approved by the appropriate local Ethics Committee/Institutional Review Board and agrees to comply with all protocol-specified follow-up appointments.
7. Expected life expectancy ≥ 6 months after Index embolization

6.1.2 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for participation in the study:

1. Embolization for lesions other than hypervascular tumors such as arteriovenous malformations.
2. It is anticipated that not all target vessels requiring embolization during the index procedure can be embolized with either HES alone or the SOC embolization agent as assigned.

3. Undergoing radioembolization or DEB-TACE for Index Procedure
4. Undergoing a planned secondary procedure the same day as the Index Procedure
5. Requires TAE/cTACE for liver tumors via extrahepatic collateral artery(ies)
6. Prior radioembolization of the target tumor lesion/vascular bed within 30 days of the Index Procedure.
7. For subjects with HCC or undergoing embolization to the liver: Child-Pugh Class C or presence of complete portal vein thrombosis.
8. Tumor lesions > 8 cm in diameter (in one direction) or >50% tumor volume burden of the target organ
9. If subject was treated with Avastin, last dose is within 4 weeks of the planned procedure.
10. Known severe atheromatosis or vascular anatomy that precludes catheterization
11. Presence of bilioenteric anastomoses and/or prior biliary stenting/drainage or any violation of the biliary sphincter, including sphincterotomy for embolization of liver tumors
12. Target lesion supplied by the pulmonary artery, coronary artery, or cerebral or cerebellar artery (requiring embolization of these arteries) or the artery to be embolized has connections to these arteries via a collateral pathway
13. Known allergies (based on history) to PEG, ferrous compounds, tert Butyl Hydroperoxide, contrast media or procedural sedatives/anesthetics that is not amenable to pre-medication
14. Uncorrectable impaired clotting: Platelet count <30,000/μL or International Normalized Ratio (INR) > 1.5
15. Serum creatinine > 2 mg/dL
16. Serum bilirubin level > 3 mg/dL
17. Serum albumin < 2.5 g/dL
18. Any contraindication to angiography or embolization protocol utilized at treating institution.
19. Pregnant or breast-feeding or females planning on becoming pregnant with the next 3 months (*women of child-bearing potential must undergo a pregnancy test performed in accordance with local institutional requirements*).
20. Other concurrent conditions including an ongoing adverse effect or complication of prior therapy or adverse drug reactions, that in the opinion of the Investigator or Clinical Events Committee, would be unlikely to receive clinical benefit from the study procedure or participation in the study may compromise subject safety or study objectives (including but not limited to ongoing acute infection, renal dysfunction, morbid obesity, severe cardiac disease).
21. Enrollment in a concurrent study in which the study treatment may confound the evaluation of the study device

6.2 ENROLLMENT

Potential study participants will undergo screening in the investigator's clinic.

A subject must sign a study-specific IRB/EC-approved informed consent form prior to any testing for eligibility that goes beyond standard care (reference **Section 6.3**). A subject will be tracked

through the screening process using a screening reference number. Adverse events will be captured for subjects starting at the index procedure. Any adverse events that occur prior to the index procedure will be documented in the subject's medical history. Subjects determined to meet all eligibility criteria will be scheduled for the Index Procedure. Subjects will be assigned a unique study identification number including a two-digit site reference number (assigned by Instylla) and a sequential three-digit number, e.g., 01-001. This subject ID number will be used throughout the study on all study related documentation to ensure anonymity of study subjects. In the event that a subject is treated multiple times with Instylla HES, they will maintain the originally assigned subject ID number. Subjects will be considered enrolled at the time of randomization.

Any subjects deemed unsuitable for the vascular embolization procedure during the pre-procedure angiography (i.e., cases where the vessel is too small to be targeted for embolization or cases where acceptable vessel access is not possible) will be considered an intra-operative (secondary) screen failure.

6.3 INFORMED CONSENT PROCESS

The principles of informed consent are described in the ISO 14155: Clinical investigation of medical devices for human subjects – Good clinical practice as well as 21 CFR Part 50.

A written informed consent approved by the central IRB or local IRB/EC shall be obtained from each subject prior to participating in the study or performing any unusual or non-routine procedure that involves risk to the subject. An informed consent form (ICF) template is provided by Instylla. If any institution-specific modifications to the consent form or study-related procedures are proposed or made by the site, the consent must be reviewed by Instylla prior to IRB/EC submission. Once reviewed, the consent will be submitted to the IRB/EC for review and approval.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. The investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial. Before consenting, the subject must be left with ample time to read and understand the informed consent form and to consider participation as well as to ask questions. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical trial at any time and for any reason without prejudice. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing and dating the ICF. The Investigator will sign and date the ICF to verify the consent process has occurred.

The original signed ICF must be maintained in the subject's study record and a copy must be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All active participating subjects must be informed of the new information and provide their written consent if they wish the subject to continue in the study.

6.3.1 Compensation and Reimbursement of Research Participants

Subjects may receive compensation of a set amount determined by the site and Instylla to be an appropriate amount per visit completed. This covers reimbursement for any reasonable travel, parking, and accommodation expenses associated with any research project visit.

6.4 STUDY PROCEDURES AND ASSESSMENTS

6.4.1 Study Schematics

The schematic of the trial is presented in Table 1, which indicates with an "✓" if the assessment is to be performed at a specific visit.

The Screening/Baseline assessments should be performed ≤ 45 days prior to the Index Procedure (with the exception of benign tumor imaging which can be within 60 days prior to the Index Procedure).

Note: Adverse events will not be captured for enrolled subjects until they have reached the index procedure. Any events that occur prior to the index procedure are considered part of the subject's medical history and should be added to the eCRF.

Study visits, tests and/or procedures should occur on schedule per Table 1.

Table 1. Schedule of Subject Assessments

Procedure	**Screening/Baseline Assessment *(within 45 days prior to planned vascular embolization)***	**Index Procedure *(Vascular Embolization)***	**Discharge**	**Follow-up: Day 30 ± 7 days and Day 90 ± 14 days**	**Follow-up: Day 180 ± 30 days (Remote visit unless in-person visit warranted)**
Demographic Information	✓				
Indication for Embolization	✓				
Disease Features[a]	✓				
Med./Surgical History/Current Status including Prior Therapies	✓				

Procedure	Screening/Baseline Assessment (within 45 days prior to planned vascular embolization)	Index Procedure (Vascular Embolization)	Discharge	Follow-up: Day 30 ± 7 days and Day 90 ± 14 days	Follow-up: Day 180 ± 30 days (Remote visit unless in-person visit warranted)
CT Scan (Multiphasic CT for hepatic tumors) / MR at baseline and follow-up for assessment of radiologic response	✓*			✓*	
Targeted Physical Exam or Assessment[b]	✓		✓ (vitals only)	✓ (vitals only)	
EORTC QLQ-C30 and EORTC QLQ-HCC 18 (QLQ-HCC for hepatic subjects only)	✓			✓	✓
ECOG Performance Score/Child-Pugh Classification	✓			✓	
Laboratory Testing [c]	✓			✓	
Pregnancy test for women of childbearing age	✓	✓			
RANDOMIZE		✓			
Angiography		Pre- and Post-Embolization Procedure	If clinically indicated		
Embolization Procedural Details		✓			
Concomitant Medications		✓	✓	✓	✓
Adverse Events (per NCI CTCAE Version 5.0) and severity rated in accordance with SIR guidelines; pain Numeric Rated Scale[d]		✓	✓	✓	✓

*The same imaging modality/protocol is to be used pre- and post-vascular embolization. Also, it is preferred that the same CT or MR system be used for the same subject for the duration of the study. If tumor is benign, baseline imaging can be taken within 60 days of Index Procedure. Images for tumors collected as standard of care prior to the informed consent process but within 45 days (or 60 days for benign tumors) of Index Procedure may be utilized as the baseline imaging.
[a]Tumor etiology, tumor location, tumor staging, number and dimension of tumor lesions (cm)
[b]At baseline, targeted physical examination including vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight). At follow-up: Physical Assessment: including vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight) to evaluate for changes from baseline. An in-person visit is preferred, but a remote (e.g. over the phone or via telehealth) visit can be substituted for select components of the follow-up if necessary.
[c]At baseline, complete blood count plus platelets, albumin, glucose, creatinine, AST/ALT, bilirubin, INR and Alpha-fetoprotein levels in subjects with hepatic malignant tumors and Alkaline phosphatase for liver tumors. At follow-up, all baseline labs excluding INR
[d] Note: if subject is experiencing pain the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represent the worst-possible pain

NOTE: If a subject undergoes retreatment with HES, the follow-up schedule will be adjusted to capture a Day 30 visit post-last retreatment if it is later than the subject's 90-day visit. The subject does not need to repeat 90-day visit. The 180-day visit should be completed 6 months after final HES treatment.

6.5 SCREENING & BASELINE ASSESSMENTS

Consented subjects will undergo an initial medical screening to assess preliminary eligibility. This screening is summarized in **Table 1**, **Schedule of Assessments** and includes documentation of demographic data, tumor diagnosis and staging (if applicable), and details of medical and surgical history.

Baseline evaluations may be performed in one or more visits; **however, all baseline evaluations must be performed within 45 days prior to the Index Procedure date (with the exception of baseline imaging for benign tumors which can be obtained within 60 days of Index Procedure):**

- Demographic information: date of birth (or age at time of consent), gender, race, ethnicity
- Indication for vascular embolization
- Disease features:
    - Hypervascular Tumors: tumor etiology (if applicable), tumor location, tumor staging, number and dimension of tumor lesions (cm)
    - Planned procedures as applicable (i.e. resection, ablation)
- Medical/Surgical History/Current status: concomitant medical conditions, prior medical conditions, prior surgeries, prior therapies
- Baseline CT (Multiphasic CT for hepatic tumors) or MR imaging (does not have to be repeated if performed within 45 days of planned index-procedure date and there has been no clinical indication of disease progression for malignant tumors or 60 days of planned index-procedure date for benign tumors)
- Targeted Physical Examination: including vitals (sitting blood pressure, pulse, respiratory rate, temperature, height and weight)

- Laboratory testing (at minimum):
    - CBC with platelet count,
    - INR
    - Albumin
    - Glucose
    - Creatinine,
    - AST/ALT,
    - Bilirubin and
    - Alpha-fetoprotein (AFP) levels in subjects with hepatic malignant tumors
    - Alkaline phosphatase (for liver tumors)
- ECOG Performance Score
- eGFR in subjects with moderate to severe renal disease
- Child-Pugh classification
- NYHA classification
- EORTC QLQ-C30 and EORTC QLQ-HCC 18 (as applicable)
- Pregnancy (urine or blood) test for women of child-bearing potential (*timing in accordance with local site requirements*)

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator or designee will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screen failure, as applicable.

For primary Screen Failures: Only the Inclusion/Exclusion and End of Study information should be entered. Baseline data for subjects who do not meet eligibility criteria will not be collected.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new screening subject ID.

For Intra-operative (secondary) Screen Failures: Inclusion/Exclusion, Procedural information captured and End of Study information should be entered.

6.5.1 Computed Tomography / MR Scan

Note: All baseline, procedural and follow-up imaging acquired during the course of the subject's follow-up will be collected and included in the subject's study record. It is preferred that the same CT/MR system/protocol (same machine preferred) be used for the same subject during the course of the study.

CT /MR Scans are typically performed as standard of care pre-procedure for disease status assessment and post-procedure for evaluation of response. CT scans must be Multiphasic for

hepatic tumors. Consistent with standard of care, within this study, imaging will be repeated prior to resection (if applicable; i.e., subject underwent planned resection and resection was not performed the same day as embolization) and for those subjects who do not undergo resection again at Day 30 and Day 90 visits. Appropriately labeled image datasets will be transferred via electronic format to the Imaging Core Lab in order to allow for independent evaluation of disease status.

Subject data presented with the CT/MR are to be coded with the subject identification number, assessment interval and date of CT acquisition.

Note: All images must be de-identified (no subject names or birth dates).

6.6 INDEX PROCEDURE

6.6.1 Pre-procedure

Subjects should follow pre-procedure fasting guidelines per institutional standard of care. INR should be evaluated prior to the procedure and a pregnancy test should be performed for females of childbearing potential. Antibiotic and pain prophylaxis should be considered if subject is at risk of an infarction that may lead to a significant volume of necrotic tissue. The study site should ensure COVID-19 restrictions specific to country and institution are reviewed prior to each procedure as guidelines may change frequently.

6.6.2 Subject Preparation

Subjects will be prepared for the embolization procedure per hospital standard operating procedure. The subject should be assessed to ascertain if there have been any changes in their health status or medications taken since their last protocol assessment.

6.6.3 Embolization Procedure

Note: Mixing chemotherapeutic agents or lipiodol with Instylla HES is strictly prohibited.

6.6.3.1 Pre-embolization Procedure Angiography:

Note: each embolization procedure is to be preceded by a selective contrast injection to ensure the coverage of the entire target, to define the angioarchitecture, to study the pathologic vessels, and to detect any variant anatomy.

A diagnostic angiography of the prescribed location for embolization will be performed using a commercially available microcatheter (i.e., Progreat® or Renegade®) or guide catheter advanced to the prescribed location according to the registered fluoroscopy and plan. Perform a digital subtraction angiography (DSA) (with or without CBCT) to define the angio-architecture of the vascular segment to be embolized. Satisfactory catheter tip position will be confirmed by DSA. Prior to randomization and the initiation of the embolization procedure, the angio-architecture in

the targeted tumor vascular bed is to be surveyed and the absence of any anatomy that would preclude safe embolization is to be confirmed. Subjects deemed unsuitable for vascular embolization due to contraindicative findings will be considered intra-operative (secondary) screen failures. No additional study follow-up will be deemed necessary for intra-operative (secondary) screen failures. Sites must capture and provide to the Imaging Core Lab for independent assessment a DSA, having a minimum frame rate of 2 frames per second, from contrast injection through clearance (about 5-10 seconds) before and after embolization. The DSA should include the arterial opacification and complete venous drainage of the intended target vessel.

Target vessels will be pre-specified by the Interventionalist and entered into the Procedure CRF prior to randomization. The CRF will also capture the vessel diameter and identifier time on DSA for independent assessment reference.

If additional vessels not previously observed on the pre-embolization angiogram are identified for embolization after randomization, such vessels will be treated based on the Interventionalist's discretion and documented within the CRF. However, only those vessels targeted for embolization prior to randomization will be included in the effectiveness analysis.

6.6.3.2 Randomization

Following the completion of all screening and baseline assessments including pre-specifying target vessels (from the pre-embolization Procedure Angiography), subjects will be randomly assigned to the Instylla HES treatment group or control group by an envelope based system intra-operatively, stratified by study site and tumor type (hepatic or non-hepatic). Randomization is to be performed following a satisfactory pre-embolization angiogram. The subject will be considered enrolled at the time of randomization.

6.6.3.3 Blind Break

This is a double-blind study in which subjects and evaluators (independent radiologist from the Imaging Core lab) are blinded to study intervention. The sealed envelope will be retained by the investigator (or designee) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should contact Instylla prior to unblinding a subject's intervention assignment unless this could delay emergency treatment for the subject. If a subject's intervention assignment is unblinded, Instylla must be notified within 24 hours of this occurrence. Once the study is complete, all envelopes (sealed and opened) must be placed in Investigator Site File or the subject's study binder as applicable and inventoried.

6.6.3.4 Control Embolic Preparation and Administration

Subjects assigned to the Control group should be treated with TAE/cTACE per the Institution's standard of care. The following information should be captured:

- Type contrast used

- TAE/cTACE material type
- Volume of TAE/cTACE material injected
- Embolic preparation time (start time, end time)
- Embolization time
- Embolization Procedure time (outer microcatheter in to completion of final angiography)
- Cumulative Fluoroscopy Time and Dose
- Use of intraarterial anesthetic agents or vasodilators
- Overall Procedure Time (from placement to removal of the femoral arterial sheath)
- Technical Success defined as:
    - Delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by an independent radiologist via comparison of the pre and final post procedure angiograms
- Number and size of tumor lesions treated
- Volume of Embolization Material delivered (excluding priming volume when applicable)
- Overall Ease of Embolization (5-point Likert scale from easy to difficult where 1= Very difficult, 2=Difficult, 3=Neither easy nor hard, 4=Easy, 5=Very easy)
- Device observations
- Adverse Events per NCI CTCAE Version 5.0 and severity rated in accordance with SIR classification guidelines.

6.6.3.5 Instylla HES Preparation and Administration

The procedure should be consistent with those listed in the Instructions for Use for each device component. Refer to Warnings, Precautions, and Potential Adverse Events in the Instructions for Use for each device prior to use.

The Instylla HES will be prepared according to manufacturer's guidelines. Advance the Instylla Microcatheter through the commercially-available outer microcatheter forming a coaxial delivery system. Both the inner and outer catheters will be primed with Polymer and Initiator Precursors per the HES IFU. Very small volumes of the HES will be administered under fluoroscopic control at a rate of approximately 0.1mL/sec with 1-2 second pauses in between. The effectiveness endpoint will be delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel via comparison of the pre and final post procedure angiograms. The procedure will be monitored using fluoroscopy. Angiography with or without CBCT will be performed post-embolization to assess residual flow and estimate distribution of contrast plus HES. During the embolization, if contrast power injection is desired it cannot be performed through the Instylla microcatheter. The selective embolization procedure should be performed until stasis is achieved. The following procedural information will be documented:

- Number of tumor feeding vessels targeted
- Lot numbers of device and accessories used
- Type contrast used: *Iodinated contrast media (≥ 300 mgI/mL, viscosity less than 26 cP at 20°C).* Note: use of Visipaque 320 or similar highly viscous contrast cannot be used for mixing with the HES, please refer to HES instructions for use.
- Volume of HES material injected (total delivered volume of both precursors, excluding priming volume)
- HES Preparation time (start time, end time)
- Embolization time (duration of time from initiation of embolic agent injection to final injection) for each vascular area embolized
- Embolization Procedure time (duration of time elapsed between placement of the standard outer microcatheter into access vessel for delivery of embolic agent to completion of final angiography) for each vascular area embolized
- Cumulative Procedural Fluoroscopy Time and Dose
- Use of intraarterial anesthetic agents or vasodilators
- Overall Procedure Time (from placement to removal of the arterial sheath)
- Technical Success defined as:
    - Delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel via comparison of the pre and final post procedure angiograms.
- Number of times HES syringes are filled
- Vessels treated, number and size of tumor lesions treated
- Presence or absence of vessel spasm during procedure
- Ease of Embolic Delivery: (5-point Likert scale from easy to difficult where 1=Very difficult, 2=Difficult, 3=Neither easy nor hard, 4=Easy, 5=Very easy)
- Device observations
- Adverse Events per NCI CTCAE Version 5.0 and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification (1) Note if subject is experiencing pain, the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represent the worst-possible pain.

6.6.3.6 Use of Ancillary Embolics

If a technical success cannot be achieved with the assigned therapy, an ancillary embolic agent may be used to complete the embolization procedure. If an ancillary embolic is required to achieve successful embolization of the target vessel, this will be considered a target vessel technical failure regardless of determination by an independent radiologist. Any use of ancillary embolic agents will be documented in the case report form.

6.6.3.7 Final Angiogram

After the final embolic injection, capture an angiogram (with or without CBCT) to allow for comparison of pre-embolization and post-embolization angio-architecture of the treated area for determination of Technical Success. To the extent practicable, pre- and post-procedure angiograms should be taken from the same location. Sites must capture and provide to the Imaging Core Lab for independent assessment a DSA, having a minimum frame rate of 2 frames per second, from contrast injection through clearance (about 5-10 seconds) before and after embolization. The DSA should include the arterial opacification and complete venous drainage of the intended target vessel. The determination of Technical Success by the Investigational site should be captured on the subject's CRF.

6.6.3.8 Periprocedural Management Regimen

Prophylactic antibiotics, steroids and pain medications are to be administered to all subjects in accordance with institutional requirements. Periprocedural medications will be documented in the eCRF.

6.6.4 Discharge Assessment

The following evaluations should be performed prior to subject discharge:

- Vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight)
- Concomitant medications
- Assessment for adverse events – Note: if subject is experiencing pain, the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represent the worst-possible pain.

Each subject will receive a participant card with the site phone number listed prior to discharge.

6.7 POST-INDEX PROCEDURE INTERVENTIONS

For subjects who undergo subsequent interventions such as surgical tumor or organ resection, liver transplant, or local therapy (e.g., Radiofrequency Ablation) a contrast-enhanced CT (Multiphasic CT for hepatic tumors) or MRI (imaging modality/protocol consistent with baseline imaging; same machine would be preferred) is preferred to be performed to document target tumor status.

Additionally, the following procedures are to be performed prior to, during and after the procedure:

- Before the Post-embolization Treatment:
  - Vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight)
  - CT and/or MRI preferred
  - ECOG Performance Score
  - Adverse Events per NCI CTCAE Version 5.0 and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification (1)

- Target vessel / organ description (extent of devascularization)
- Any evidence of non-target vessel embolization (surgical resection only)
- Procedural details (procedure type and duration, estimated blood loss)
- Procedural complications and Adverse Events per NCI CTCAE Version 5.0 and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification (1)

The vascularity, consistency and macroscopic appearance of the target tumor/embolized area will be characterized by the surgeon.

6.7.1 Pathology/Histology

For subjects undergoing tumor resection/organ removal, macroscopic histopathological analysis of the embolized area is to be performed consistent with the institution's practices. If photomicrographs are taken of sections/slides of the embolized area (including representative photomicrographs demonstrating presence of the HES material), these images are to be appropriately coded with the subject identification number and transferred via electronic format to Instylla.

When applicable, light microscopy will be used to examine sections of the embolized tumor vascular bed for any changes associated with treatment, such as thrombosis, necrosis, inflammation and presence of embolic material. Other parameters may be assessed as deemed appropriate by the pathologist. Note: Instylla HES can be visualized by Hematoxylin and Eosin (H&E) staining typically presenting as translucent to faintly basophilic material within the target vasculature.

6.8 FOLLOW-UP EVALUATIONS

6.8.1 Day 30 (± 7 Days) and Day 90 (± 14 Days) Follow-up Visits

The following procedures are to be performed at the Day 30 and Day 90 Follow-up visits (as appropriate):

- Vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight)
- ECOG Performance Score
- Child-Pugh classification
- Tumor recurrence
- Adverse Events per NCI CTCAE Version 5.0 and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification (1) – Note: if subject is experiencing pain the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represent the worst-possible pain.
- EORTC QLQ-C30 and EORTC QLQ-HCC 18 (as applicable)
- Concomitant medications

- If a woman reports possible pregnancy, appropriate tests should be provided. Investigators should ensure that pregnant subjects do not have radiation exposure from study-related procedures.
- Non-resected subjects Only:
    - Target Tumor Response via contrast-enhanced CT (Multiphasic CT for hepatic tumors) or MRI (imaging modality and protocol consistent with baseline imaging; same machine is preferred) with hypervascular tumor response characterized via modified RECIST (19) for HCC and RECIST 1.1 for other hypervascular tumors (See Appendix 1)
    - Durability of occlusion
    - Laboratory testing: CBC with platelet count, albumin, glucose, creatinine, AST/ALT, bilirubin and Alpha-fetoprotein and alkaline phosphatase levels in HCC subjects
- Resected subjects only
    - Incidence of complete or partial response (Path PR and Path CR)

Note: The study site should ensure COVID-19 restrictions specific to country and institution are reviewed prior to each follow-up visit as guidelines may change frequently. An in-person visit is preferred, but a remote (e.g. over the phone or via telehealth) visit can be substituted for select components of the follow-up. A script will be provided to study coordinators to ensure remote visits capture all relevant follow-up and safety information.

NOTE: If a subject undergoes retreatment with HES, the follow-up schedule will be adjusted to capture a Day 30 visit post-last retreatment if it is later than the subject's 90-day visit. Subject does not need to repeat 90-day visit.

6.8.2 Day 180 (± 30 Days) Follow-up Visit

The following procedures are to be performed at the Day 180 Follow-up visit (as appropriate):

- Adverse Events per NCI CTCAE Version 5.0 and all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification (1) – Note: if subject is experiencing pain the severity of pain is to be scored using a Numeric Rated Scale where 0 represents no pain and 10 represents the worst-possible pain.
- EORTC QLQ-C30 and EORTC QLQ-HCC 18 (as applicable)
- Concomitant medications

Note: this visit to be conducted via remote (e.g. over the phone or via telehealth) visit unless the Investigator assesses that comments brought up during the remote visit warrant an in-office visit

Note: the duration of subject participation in this study is expected to be about 6 months post-embolization; however, subjects may be consented for a 1 and 2 year follow-up visit.

6.8.3 End of Study Definition

The end of the study is defined as the last visit of the last subject in the study. A subject is considered to have completed the study if he/she has completed all visits through Day 180 Follow-up visit. The 90-day visit will be considered the completion of the clinical investigation (e.g., for the purpose of submission to regulatory authorities).

Subjects who have completed study participation will receive continued care per standard of care practice.

6.9 UNSCHEDULED VISITS

Any subject may be seen for any reason in the study clinic. Investigators will document the reason for unscheduled visits (including adverse event assessment) in the eCRF.

6.10 STUDY WITHDRAWAL

Study subjects should be encouraged to continue their participation in the study.

A subject may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

A subject may be terminated or withdrawn due to loss to follow-up.

The cause for subject withdrawal, if known, will be recorded in the eCRF. The site will make reasonable efforts to complete relevant forms in the eCRF for any subject who withdraws from the study without violating subject consent. There are no other early discontinuation visits or procedures required. The participant will be permanently discontinued from the study at that time. All data collected until the point of withdrawal will be included in the analysis.

If the participant withdraws for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, they may request destruction of any samples taken at the site and not tested. The investigator must document this in the site study records.

Subjects who withdraw or are lost to follow-up prior to end of study will not be replaced.

6.11 MISSED VISITS

Any study subject who does not attend a scheduled in person or remote (e.g. over the phone or via telehealth) follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). The reason for the missed visit should be determined and documented in

the subject's study records. If the missed visit was due to an adverse event (AE), an AE form must be completed, and any reporting requirement met.

Per ISO 14155 and 21 CFR 812, all subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for and documented.

6.12 LOST TO FOLLOW UP

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the site for a required study visit: the site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

Before the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, telephone calls, and if necessary, a certified letter, as acceptable by local regulations, to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable after 3 documented attempts (including certified mail, as acceptable by local regulations), he/she will be considered lost to follow-up and withdrawn.

A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up.

7 RISK/BENEFIT ANALYSIS

The study protocol has been designed to provide the greatest potential benefit while assuring the safety of participating subjects by mitigating the occurrence, limiting the severity and ameliorating the effects of possible adverse events. The anticipated profile for subjects (e.g., inclusion of subjects undergoing pre-procedure vascular embolization) are such that the potential for benefit has been maximized while minimizing the potential for undue risks.

The following describes the benefits subjects may receive as well as possible adverse events that have been identified as risks and for which subjects will be carefully monitored.

7.1 BENEFITS

It is possible that subjects will not receive any benefits from treatment. Potential benefits for subjects randomized to the Instylla HES is that the embolization may be more targeted, complete, deeper and persistent and will require less procedure time than currently marketed vascular embolic

devices. Shorter procedure time translates to less anesthesia and reduced exposure of ionizing radiation to both the subject and procedure staff. The Instylla HES hydrogel is soft with a modulus of elasticity similar to vascular tissue and has been designed to be unaffected by natural thrombolytic processes that may cause recanalization. Also, the HES liquid precursors and coaxial delivery are designed to not polymerize if diluted below a critical concentration in blood (dilution sensitivity). Therefore, unlike conventional procedures where every solid particle/microsphere that leaves the catheter will occlude, the dilution sensitivity of HES may provide some level of non-target healthy tissue protection in patients where liquid precursors are refluxed or diverted into high flow shunts. In addition, the HES formation is not dependent on the coagulation status of the subject.

Furthermore, preclinical studies suggest that Instylla HES liquid embolic provides a more complete and durable embolization than bland microspheres alone. Findings from these studies may suggest the following potential benefits:

- Deeper vessel penetration
- Less recanalization (restoration of blood flow to the embolized vessel)
- Reduced viable (living) tissue in embolized areas
- Improved tumor shrinkage

In conclusion, from preclinical studies Instylla HES liquid embolic appears to provide unique safety and efficacy benefit potential that differs distinctly from bland embolic microspheres. Potentially, shorter procedure times and reduced rates of non-target embolization may provide safety benefits, while deep, complete liquid embolic penetration may result in improved target tissue necrosis and tumor shrinkage.

7.2 RISKS

7.2.1 Risks Associated with Exposure to Ionizing Radiation

The study involves exposure to radiation. However, since the peri-procedural imaging is consistent with standard of care it is anticipated that the radiation dose will be equivalent to that which the subject would be exposed for any embolization procedure and therefore is not a risk specifically associated with participation in this study. This risk is therefore considered low.

7.2.2 Potential Risks Associated with Contrast

- There is a risk of an allergic reaction to the contrast material being used. Such reactions usually are mild but may include rash, swelling, tightness in the throat or trouble breathing.
- Contrast extravasation
- Some subjects experience discomfort when the contrast material is injected which may include tingling or warmth in the lips or arm, metal taste in the mouth, nausea or headache.

- Contrast-induced nephrotoxicity can occur and therefore subjects with kidney dysfunction are not to be enrolled in this study.

Again, the risk for an adverse response to contrast is not unique to this study but is a risk for any vascular embolization procedure.

7.2.3 Potential Risks Associated with Vascular Embolization Procedure

Vascular 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:

- Post-embolization syndrome
- Capillary bed occlusion with tissue ischemia and resulting tissue damage
- Vessel or tumor rupture and hemorrhage
- Vasospasm
- Infection such as hepatic or renal abscess necessitating medical intervention
- Hepatic dysfunction or failure
- Renal dysfunction or failure
- Intrahepatic biloma formation
- Gastrointestinal toxic effects caused by presence of extrahepatic perfusion
- Cholecystitis
- Nausea or vomiting caused by anesthesia
- Complications related to catheterization (e.g., hematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgment, and nerve and/or circulatory injuries, or vessel trauma [e.g., dissection, perforation, rupture])
- Allergic reaction to medications (e.g. analgesics)
- Air embolism
- Incomplete embolization or recanalization (which may lead to no response or tumor growth)
- Neurological deficits including cranial nerve palsies
- Death

7.2.4 Potential Risks Associated with Embolization Materials

Complications may be associated with the HES liquid embolic and the Control TAE/cTACE embolic. These risks cannot be completely mitigated and are considered residual risks. There are no known unique risks associated with the Instylla HES:

- Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue edema.
- Undesirable reflux or passage of embolic agent into normal arteries adjacent to the targeted tumor or through the tumor into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations
- Pulmonary embolism due to arterial venous shunting

- Thrombosis
- Foreign body reactions necessitating medical intervention
- Infection necessitating medical intervention
- Toxic or allergic reaction to embolic material
- Pain and/or rash, possibly delayed from the time of embolization
- Ischemia at an undesirable location including ischemic stroke, ischemic infarction (including myocardial infarction), intestinal ischemia and tissue necrosis
- Embolization failure or recanalization requiring secondary intervention
- Device malfunction

7.2.5 Potential Risks Associated with Chemotherapeutic Agents

In addition to the risks noted above related to the embolization procedure and/or embolization agent used, there may be additional systemic or local toxicity associated with the chemotherapeutic agent(s) used if cTACE is performed. This will vary depending on the chemotherapeutic agent(s) used but may include marrow suppression, hand-foot skin reaction, weight loss, diarrhea, constipation ascites, hyperbilirubinemia, anorexia, hypertension, fatigue, alopecia, worsening liver function/liver failure or cardiac function, skin discoloration and mucositis.

7.2.6 Potential Risks Associated with Anesthesia

Risks associated with general anesthesia, some of which could be fatal (rarely), include:

- Airway compromise
- Sore throat/vocal cord injury
- Cardiopulmonary complications including syncope, hypertension, bradycardia and respiratory depression
- Neurological complications including stroke
- Embolism
- Allergic reactions to anesthetics
- Drowsiness, confusion, stupor or slurred speech
- Nausea and vomiting

7.3 SUMMARY OF RISK/BENEFIT ANALYSIS IN THE CONTEXT OF ALTERNATIVE TREATMENTS

Based on preclinical testing, First in Human clinical results and the user Failure Modes and Effects Analysis, the HES is anticipated to be an efficacious embolization material that poses no systemic hazard and may allow for shorter procedure time (thus less exposure to anesthetics and less radiation) and with the potential for deeper penetration than conventional embolics which may improve efficacy. Risks have been mitigated appropriately through design and testing. In the event the embolization with HES is not effective, its use does not preclude the use of alternative embolic agents. Based on the existing HES data, it is Instylla's belief that a pivotal study is appropriate as

the potential for clinical benefit appears to outweigh the potential of risk to research subjects who choose to participate in the clinical trial.

7.3.1 Other Alternatives for Vascular Embolization

There are several embolic agents designed for vascular embolization including polyethylene glycol dacrylamide hydrogel microspheres (HydroPearl Microspheres), polymer/platinum composite coils (Azur CX), polyvinyl alcohol (PVA) microbeads (LC Bead or BeadBlock Microspheres) or gelatin pledgets (e.g., Gel Block). Embolization with these alternative materials have a high success rate (generally ranging between 95 to 100%) (20) (21) (22) (23). The most common adverse event associated with vascular embolization is post-embolization syndrome which consists of fever, abdominal pain, nausea, vomiting, leukocytosis, and an increase in liver enzymes lasting for a few hours to a few days. This syndrome, which has widely variable manifestations, is usually self-limited but may be experienced in up to 36% of patients undergoing transarterial embolization (24) and with reports as high as 89% (25).

7.4 RISK MITIGATION

Risks will be minimized by the following:

1. Subject eligibility criteria identified exclude participation of subjects with comorbid conditions that may put them at undue risk with exposure of the investigational device and/or study procedures and have selected subjects who have a more favorable risk / benefit profile for use of the device.
2. Participating Investigative sites were chosen because of proven expertise in the field of interventional radiology and embolization procedures specifically.
3. All investigators will receive specific instruction on the use of the study device and all study procedures.
4. Study subjects will be carefully monitored during the study and the follow-up period. The Investigator will examine and perform various diagnostic tests before, during, and after the procedure at 30 (± 7 days) and 90 days (± 14 days) after the procedure if necessary
5. Extensive pre-clinical, *in vitro* and *in vivo* testing has been performed in order to optimize device safety and function.
6. The HES has been studied in a First In Human trial with no unanticipated adverse events.
7. The main HES constituent, polyethylene glycol – PEG, is based on a platform that has been used in a multitude of medical devices, and the PEG-based platform has been demonstrated to be safe for humans even at higher volumes and when applied near more sensitive tissues (i.e., neuro tissues).
8. Instylla will utilize a Clinical Events Committee (CEC) to provide ongoing review and adjudication of adverse events and review of emerging device performance data. The CEC

will include an Interventional Radiologist. The CEC will be charged with the following responsibilities:

a) Continuous review of all adverse events that occur over the course of the study and the subsequent classification of these adverse events as primarily related to the device, the procedure or unrelated to either.
b) Monitor emerging data with respect to technical success and clinical performance of the HES to minimize exposure to the device in the event product performance is not satisfactory.
c) Provide oversight for issues affecting the general subject welfare, including recommendations on revisions to the protocol if new information is learned that would affect the risk/benefit analysis presented within this clinical investigational plan.

9. A Data Monitoring Committee (DMC) will be appointed by Instylla. Members of the DMC will be independent of the investigators and will include a statistician, oncologist, interventional radiologist and gastroenterologist/hepatologist. The DMC will be responsible for interim review of safety data and will be responsible for reviewing data from the sample size re-estimation analysis. The DMC may make formal recommendations for protocol changes to mitigate risk of adverse events.

8 ADVERSE EVENT REPORTING / SAFETY MONITORING

The occurrence of all adverse events (AEs) will be documented in all study subjects from the index procedure throughout the study follow-up period. AE information (start and stop date, description of event, severity, relationship to the assigned embolic therapy (as applicable) and associated placement procedure, or other study-related procedures) will be assessed and recorded on eCRFs. All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. The investigator must review the laboratory report(s), document this review, and record any clinically significant changes. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

Whether an AE meets the definition for serious adverse event will be initially determined by the study investigator using the definitions outlined in **Section 8.1** and **Table 2**. AE severity will initially be judged by the investigator according to **Table 3**. Relationship of the AE to the device placement procedure or the HES will be initially judged by the investigator according to **Table 4**.

8.1 DEFINITIONS

Definitions of adverse events are delineated in **Table 2**. Relatedness of adverse events will be categorized in accordance with the current version of MEDDEV 2.7/3.

Table 2. Adverse Event Definitions (ISO 14155)

Term	Definition
Adverse event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject, whether or not related to the investigational medical device. This definition includes events related to investigational medical device, procedures involved and whether anticipated or unanticipated. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a use error or intentional abnormal use of the investigational medical device. For users or other persons, this definition is restricted to events related to the use of the investigational medical device or comparators. Note: If the subject experiences a worsening or complication of a concurrent condition that was present before exposure to the study device, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of "…").
Device Deficiency	Inadequacy of a medical device with respect to it's identity, quality, durability, reliability, usability, safety or performance. 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.
Device Malfunction	All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.
Serious adverse event (SAE)	An adverse event that: • Led to a death, • Led to a serious deterioration in the health of the users, or other persons as defined by one of more of the following:

Term	Definition
	○ a life-threatening illness or injury, or ○ a permanent impairment of a body structure or a body function including chronic disease or ○ in-patient or prolonged hospitalization or ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or function • Led to 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 CIP, without serious deterioration in health, is not considered an AE or serious AE.
Adverse device effect (ADE)	Adverse event related to the use of an investigational device. This term includes any event resulting from insufficiencies or inadequacies in the instructions for use, the deployment of the device, implantation, installation, or operation or any malfunction of the investigational medical device. Also includes any event resulting from user error or from intentional misuse of the investigational medical device. For this clinical investigational plan an adverse event is regarded as related when the investigator classifies it as being possibly, probably or definitely related to the treatment with the investigational device. Note: This includes 'comparator' if the comparator is a medical device.
Serious adverse device effect (SADE)	Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious health threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Unanticipated serious adverse device effect (USADE/UADE)	Any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment. FOR U.S. Sites: An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, 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 application; or any other unanticipated serious problem

Term	Definition
	associated with a device that relates to the rights, safety, or welfare of subjects. Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in this CIP and/or the device labeling.

Event Severity: Event severity will be graded in accordance with the guidelines provided in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0[2] (NCI, Nov. 2017). Additionally, all adverse events are to be graded in accordance with the 2017 SIR Adverse Event Severity Classification (1) - Appendix A/Part A as denoted in Table 3 and relationship to the device and procedure will be classified as outlined in Table 4.

Table 3. SIR Complication Classification

Grade	Definition
1	Mild AE: No therapy or nominal (nonsubstantial) therapy (postprocedural 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)
2	Moderate AE: 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);
3	Severe AE: 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 nonintubated patient (generally excludes pediatrics or in circumstances in which general anesthesia would primarily be used in lieu of conscious sedation, e.g., in mentally challenged or severely uncooperative patients);
4	Life-threatening or disabling event: e.g., cardiopulmonary arrest, shock, organ failure, unanticipated dialysis, paralysis, loss of limb or organ;
5	Patient death or unexpected pregnancy abortion.

Table 4. Adverse Event Relatedness Categories

Term	Definition
Unrelated	No evidence that AE is related to placement procedure or device
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

[2] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Definitely	The event is associated with the investigational device or with procedures beyond reasonable doubt

8.2 RECORDING AND REPORTING OF ADVERSE EVENTS

Study staff are responsible for ensuring that complete safety information has been recorded on the eCRF and in source documents. All Adverse Events (AE) must be documented throughout the study (from the index procedure to the last visit). Medical assessments must be performed during each scheduled study in-person or remote (e.g. over the phone or via telehealth) visit and serve as the primary basis for identifying AEs. Although spontaneous or elicited medical complaints will likely constitute the majority of AEs, any non-scheduled visit to a healthcare provider or the initiation of a new medication should trigger additional questioning as to the occurrence of an AE. It is recommended that the occurrence of AEs should be sought by non-leading verbal questioning of the subject at each in-person or remote visit during the study (e.g. "Have you experienced any problems since your last visit?").

All adverse events will be collected from the Index Procedure and through the end of follow-up. Subjects who experience an adverse event related to the Instylla HES will be followed until the adverse event has resolved (return to baseline status or to "normal") or until the subject has stabilized (no worsening expected by the investigator) or the condition is considered chronic and follow-up care has been transferred to the subject's physician (e.g. primary care, oncologist, specialist).

To the extent possible, the adverse event diagnosis as opposed to event symptoms should be recorded. Please refer to the following examples:

- Fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as an infection only.
- Pain at the catheter insertion site in the presence of a clinically diagnosed infection is to be reported as infection only.
- Concurrent symptoms of fever, abdominal pain, nausea, vomiting in the presence of leukocytosis and increased in liver enzymes should be reported as post-embolization syndrome.

8.3 SERIOUS ADVERSE EVENT REPORTING

Note: planned interventions/surgical procedures to treat concomitant conditions unrelated to the treatment/condition subject of this CIP are not to be documented as SAE's (the intervention/surgical procedure may be scheduled prior to or during the conduct of the CIP).

All serious adverse events and serious adverse device effects shall be recorded and reported to the Sponsor or their representative via electronic Case Report Form (eCRF) within 24 hours of the time the investigator learns of the event. The eCRF should be finalized with all available data within 5 working days of knowledge of the event. At minimum, the date of the adverse event, treatment, resolution (i.e., ongoing or resolved), and assessment of both the seriousness and the relationship to the investigational device should be initially recorded in the eCRF. If requested, the site will also be responsible for submitting relevant source documentation for the SAE. If the subject is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary should also be included with the SAE eCRF. In case of death, the investigator must make every effort to obtain a copy of the death certificate to submit to the Sponsor. When submitting copies of source documentation, all subject identifying information must be redacted and only the unique subject number will be used to label the forms for identification purposes. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including death, at any time after the participant has been discharged from the study, and they he/she considers the event to be reasonably related to the study intervention or participation, the investigator must promptly notify the sponsor.

Instylla (or Instylla's representative) will notify the governing regulatory authorities of any serious adverse events in accordance with regulatory requirements in each country. Copies of any reports to regulatory agencies regarding serious and unexpected AEs will be provided to the investigators for review and submission to the IRB/EC (if required) or directly to the IRB/EC in accordance with local regulatory requirements. The investigator is responsible for informing the IRB/EC of any SAEs and/or USADEs/UADEs in accordance with local reporting requirements. Copies of SAE/USADE/UADE correspondence with the investigators, regulatory authorities, and Sponsor must be retained with study records.

8.4 DEVICE DEFICIENCIES/MALFUNCTIONS AND OBSERVATIONS

8.4.1 Definition of Device Deficiencies and Observations

A device deficiency is defined as an inadequacy of the investigational medical device with respect to its identity, quality, durability, reliability, safety or performance. Deficiencies include malfunctions, use errors, and inadequate labeling.

8.4.2 Recording and Reporting of Device Deficiencies/Malfunctions and Observations

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study.

All device deficiencies/malfunctions and observations will be recorded in the eCRF.

The site will notify the Sponsor or Sponsor's representative within 24 hours from the site becoming aware of the device deficiency by completing the Device Deficiency/Malfunction eCRF. To minimize delays in Sponsor awareness, a phone call to notify Instylla or designee is recommended. A call to Instylla or designee does not eliminate the requirement to complete the Device Deficiency/Malfunction eCRF.

Where a device deficiency/malfunction causes an AE, the AE eCRF must be completed as well. Any device deficiency/malfunction that might have led to an SAE if:

a) suitable action had not been taken,

b) intervention had not been made or

c) circumstances had been less fortunate,

will be reported using the same method and timelines outlined in **Section 8.3** for reporting of SAEs.

8.4.3 Handling of Device Deficiencies/Malfunctions

Any medical device alleged to be deficient must not be used by the Investigator and should be returned to the manufacturer or destroyed as instructed by the manufacturer. Any discrepancies or deficiencies should be reported to Instylla Clinical Affairs, clinical@Instylla.com.

8.5 STUDY OVERSIGHT

8.5.1 Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) has been appointed by Instylla. Members of the DMC are independent of the investigators and will include a statistician, oncologist, interventional radiologist and gastroenterologist/hepatologist. The DMC is responsible for interim review of safety data and sample size re-estimation analysis. The DMC may make formal recommendations for protocol changes to mitigate risk of adverse events. A DMC charter has been prepared.

8.5.1.1 Independent Statistician

An independent statistician has been appointed to interface between the study statistician responsible for routine study activities and the DMC. The independent statistician will be responsible for producing reports/analyses that inform the DMC.

8.5.2 Clinical Events Committee (CEC)

Instylla will utilize a Clinical Events Committee (CEC) to provide ongoing review and adjudication of safety endpoints and adverse events, and review of emerging device performance data. All safety data collected will be summarized and reviewed by the CEC. The CEC is comprised of three physicians with experience with the subject population including an interventional radiologist. The CEC is charged with the following responsibilities:

- Continuous review of adverse events that occur over the course of the study and the subsequent classification of these adverse events as primarily related to the device, the procedure or unrelated to either.
- Provide oversight for issues affecting the general subject welfare, including recommendations on revisions to the protocol if new information is learned that would affect the risk/benefit analysis presented within this clinical investigational plan.

Instylla will meet with the CEC on a regular and ongoing basis. All serious and/or unanticipated adverse device effects will be reviewed with the CEC on an urgent basis.

9 DEVICE ACCOUNTABILITY

Investigators or qualified, trained designees will be responsible for maintaining device accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records) from the time of receipt of product at the clinical site through use or return of product to Instylla or documented destruction. All investigational devices must be accounted for using the Device Accountability Logs designed to keep track of investigational devices in this study. The investigator is responsible for maintaining accurate records of the three transactions key to material transfer in this study:

- Devices received (Sponsor to investigator) and associated lot numbers
- Devices used (investigator to subject) and associated lot numbers
- Devices returned/destroyed per manufacturer's instructions (investigator to Sponsor) and associated lot numbers.

The necessary documents can be found in the Investigator Site File (ISF) binder.

The site monitor will verify accountability of the study devices during routine monitoring visits to the site.

Only subjects enrolled in the study and assigned to treatment may receive study intervention, and only authorized site staff may supply or administer study intervention.

Investigational devices must be stored according to the conditions set forth for the device on the label and in a secure, controlled, locked area with access limited to the investigator and authorized site staff. Documentation of temperature monitoring is not required as the device is stable at room temperature. All device shipment records (packing lists, etc.) must be maintained at the site. Further guidance and information for the final disposition of unused study investigational product are provided in the Return Materials Authorization (RMA) form. The preferred method is to return investigational product to Instylla. If shipping costs or other logistical hurdles exist, instructions will be provided to destroy and document the destruction of the remaining investigational product in a Materials Destruction Log.

10 DATA ANALYSIS

10.1 GENERAL APPROACH

A detailed Statistical Analysis Plan (SAP) has been developed and approved. The following provides a summary overview of analyses to be performed. Analysis details in the SAP may supersede details in the overview below. Refer to the current version of the SAP for detailed analysis information.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, quartiles, standard deviation [SD], minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category. All results will be presented by treatment and appropriate subject populations. All statistical tests will be performed as a one-sided 0.025 level of significance unless otherwise specified below. SAS software version 9.4 or higher will be used for the statistical analysis.

Data listings will be presented and sorted by subject number and treatment. All data will be included in the data listings.

Study days will be calculated relative to the date of initial study treatment (i.e., Day 0 is the date of receipt of study treatment).

Differences in techniques and tumor location may impact outcomes of this investigation. Therefore randomization is stratified by investigational site and tumor location (hepatic vs. non-hepatic). Further, a test of homogeneity across sites and countries (US vs. OUS) will be done to determine if the study sites within a location have reasonably homogeneous responses. Another known foreseeable factor is missing data which could confound interpretation of primary effectiveness endpoint results. A tipping point sensitivity analysis will be used to assess the effect of missing data on the primary effectiveness endpoint results.

10.2 ANALYSIS POPULATIONS

10.2.1 Safety Population

The safety analysis population includes all randomized, treated subjects. Subjects will be analyzed for safety based on the treatment received.

10.2.2 Intent-To-Treat (ITT) Population

The ITT population will consist of all enrolled subjects who are randomized.

10.2.3 Modified Intent-To-Treat (mITT) Population

The mITT population will consist of all enrolled subjects who are randomized and have a target vessel treated (i.e. embolic agent/chemoembolic agent delivered to target tumor) with data analyzed according to randomized treatment assignment. This population will be utilized as a secondary analysis population for the primary and secondary effectiveness endpoints.

10.2.4 Per Protocol (PP) Population

Per Protocol (PP) Population: The PP population will consist of mITT subjects who do not have major protocol deviations with data analyzed according to treatment received. This population will be the basis for the Effectiveness Evaluable (EE) and Safety Evaluable (SE) populations, which will be utilized as the primary analysis population for the primary effectiveness and safety endpoints respectively.

The following are considered major protocol deviations and will exclude a subject from the PP population:

- Inclusionary/exclusionary deviations that may confound technical success
- If subject receives a treatment in the target vessel that is different from what (s)he was randomized to

- Other significant protocol non-compliance that may confound evaluation of the primary effectiveness and safety endpoints (i.e., significant procedural deviations or for the primary effectiveness endpoint uninterpretable images or for the primary safety endpoint withdrawal prior to the Day 30 visit-unless subject experiences a safety endpoint event prior to withdrawal).

Subjects with such non-compliance will be determined prior to database lock.

Note: Given the different timing of the effectiveness and safety endpoints (during procedure for effectiveness and through 30 days for safety), the Per Protocol population has been further separated into the Effectiveness Evaluable (EE) population and the Safety Evaluable (SE) population, as described in Sections 10.2.4.1 and 10.2.4.2, respectively.

10.2.4.1 Effectiveness Evaluable Population (EE)

The EE population will consist of mITT subjects who do not have major protocol deviations that would impact the primary effectiveness endpoint with data analyzed according to randomized treatment assignment. This population will be utilized as the primary analysis population for the primary effectiveness endpoint.

10.2.4.2 Safety Evaluable Population (SE)

The SE population will consist of mITT subjects who do not have major protocol deviations that would impact the primary safety endpoint with data analyzed according to randomized treatment assignment. This population will be utilized as the primary analysis population for the primary safety endpoint.

10.3 ENDPOINTS

10.3.1 Safety Endpoint and Statistical Hypothesis

The primary safety endpoint will be freedom from specific MAE through 30 days post-index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG). Specific events to be included as MAE are described in **Section 3.1**:

The safety hypotheses to be evaluated in this study are as follows:

$$H_0\ \delta \leq \mathrm{PG}$$

$$H_1\colon \delta > \mathrm{PG}$$

Where δ is the proportion of subjects who are free from CEC adjudicated MAE for Instylla HES and PG represents the literature-derived performance goal which has been set to 75.0%. A one-sided p-value will be derived based on an exact binomial test and the study device will be considered to have achieved the safety objective if the one-sided p-value is less than 0.05 (or equivalently, the lower limit of the one-sided 95% confidence limit based on the exact method is greater than the pre-specified performance goal.)

The literature-derived performance goal is based on a review of the literatures which has established that the cumulative threshold values for incidence of the safety endpoint events identified is 25%. Thus, the PG for Freedom from MAE has been set to 75%.

10.3.2 Primary Effectiveness Endpoint and Statistical hypothesis

The primary effectiveness endpoint for this study is the proportion of target vessels in which Technical Success is achieved defined as delivery of the embolic agent to the index tumor feeding vessel with stasis of flow defined as absence of contrast flow within the targeted tumor feeding vessel as determined by a central independent radiologist (Core Laboratory) via comparison of the pre and final post procedure angiograms.

Note: Subjects may contribute more than one endpoint evaluation, i.e., it is anticipated that on average the number of target vessel embolizations per subject will be 1.5.

The primary study hypothesis is that Instylla HES is non-inferior to standard of care TAE/cTACE (Control) for successfully embolizing hypervascular tumors. Therefore, the statistical hypotheses are as follows:

$$H_0: \pi_2 - \pi_1 \geq 0.1$$

$$H_1: \pi_2 - \pi_1 < 0.1$$

where π_1 and $\pi_2$is the true incidence for tumors achieving primary effectiveness endpoint success for Instylla HES and standard of care TAE/cTACE (Control) respectively. The non-inferiority margin of 10% was developed based upon consensus from Instylla's interventional radiologist advisors. This value takes into account that some vascular territories may be more difficult to embolize and therefore there may be some variability in achieving primary endpoint success.

Non-inferiority will be assessed using a generalized estimating equation (GEE) model with robust estimation where (a) the dependent variable is the binomial primary effectiveness endpoint of success, the independent variable is treatment group (Instylla HES and control); (b) the exchangeable correlation structure will be the assumed within-patient correlation structure; (c) the identity link will be used for the GEE model in order to obtain an estimate of the risk difference between treatments and its two-sided 95% confidence interval.

10.4 ADDITIONAL SAFETY ANALYSES

An additional safety analysis will be to compare the incidence of device (i.e., embolic agent) and procedure-related events between the Instylla HES and SOC treatment groups. 95% exact (Clopper-Pearson) confidence intervals for the true proportions and a 95% confidence interval based on the normal approximation for the difference in proportions between treatments will be presented. The true proportions will be compared using a two-sided Fisher's Exact Test at the 0.05 significance level.

Further, all adverse events experienced by subjects occurring from the time of the Index Procedure and up through and including the Day 90 visit will be reported and listed. The incidence of adverse events will be summarized by term, by term and primary attribution, and by term and severity. The true proportions of adverse events by body category and SOC term using MEDDRA will be compared using a two-sided Fisher's Exact Test at the 0.05 significance level.

The analyses of adverse events will be conducted on the Safety Population.

There will be no adjustment for multiple comparisons due to the exploratory nature of these analyses.

The results from the additional safety analyses are informative only and are not intended for product labeling.

10.5 DETERMINATION OF SAMPLE SIZE

It is anticipated that a sample size of 150 randomized and treated subjects with an allocation ratio of 2:1, resulting in approximately 100 subjects in the Investigational Group and approximately 50 subjects in the Control Group. Since both the safety and effectiveness hypotheses must be satisfied for the study to be considered successful, each endpoint is powered at 90% to assure that the overall probability that both null hypotheses are rejected will be at least 80.0%. The overall sample size of 150 randomized and treated subjects also accounts for an approximately 10% attrition and/or missing data rate for effectiveness (anticipated to be primarily due to inadequate or incomplete data) and for an approximately 10% attrition and/or missing data rate for safety (anticipated to be primarily due to subject dropout).

This sample size determination was made based on the following specifications:

Safety Endpoint Assumptions:

The following assumptions were made for estimating sample size for the safety endpoint:

1. Analyzed based on Investigation Group (HES) only with comparison to Performance Goal criterion for Freedom from specific MAE's set to 75.0%
2. True Freedom from Specific MAE's for the Investigational Group is 88.0%
3. Alpha of 0.05 (one-sided)

4. Use of the exact binomial test
5. 90% power

Based on the above assumptions, the minimum sample required for the Investigational Group (HES) for evaluation of safety (unadjusted) is 79 subjects. As is discussed below, 100 subjects will be randomized to the HES group; it is anticipated that this will yield the (up to) 90 required evaluable subjects for the primary safety analysis after accounting for premature dropout before 30 days and after accounting for missing data.

Primary Effectiveness Endpoint Assumptions:

The following assumptions were made for estimating sample size for the primary effectiveness endpoint:

1. The underlying technical success rate is 96% for both treatment groups,
2. 10% non-inferiority delta,
3. Each subject contributes on average 1.5 endpoints and assuming low correlation of 0.01,
4. One-sided alpha of 0.025
5. 90% power.
6. Use of the Farrington-Manning test statistic for non-inferiority

The weak correlation (0.01) is justified as follows. Each vascular territory to be embolized will present with its own angioarchitecture and challenges to embolization, and therefore, it is not believed that outcomes will be correlated. This observation is consistent with the opinion of our advising interventional radiologist. Thus, the correlation factor that was selected (0.01 representing a weak correlation) is believed to be conservative. Further, the mechanism of operation of the Instylla HES is not dependent on subject factors such as coagulation status, thus further reducing the potential for any inherent correlation parameter between tumors in a single subject. This provides additional confidence that there will not be a correlation in outcomes for embolization of multiple vascular territories within the same subject. That being said, power is maintained at the desired level if the correlation is as high as 0.10 and power decreases by only approximately 3% if the correlation is as high as 0.25. Thus, power is generally robust even if the correlation assumption of 0.01 is incorrect and the correlation is as high as 0.25. To support this statement, below is a table containing relevant results from PASS 2020 output, formatted and labeled for ease of interpretation, where PASS 2020 is the software used to determine sample size in this scenario. As can be seen from the first 2 columns in this table, power ranges from 90% to 87% and the within-patient correlation ranges from 0.01 to 0.25.

Power	Within-Patient Correlation	Experimental: Number of Subjects/ Number of Territories Per Patient	Control: Number of Subjects/ Number of Territories Per Patient	Control Success Rate	Experimental Success Rate	Non-Inferiority Margin	One-sided Alpha
90%	0.01	90/1.5	45/1.5	96%	96%	-10%	0.025
90%	0.02	90/1.5	45/1.5	96%	96%	-10%	0.025
90%	0.05	90/1.5	45/1.5	96%	96%	-10%	0.025
89%	0.1	90/1.5	45/1.5	96%	96%	-10%	0.025
87%	0.2	90/1.5	45/1.5	96%	96%	-10%	0.025
87%	0.25	90/1.5	45/1.5	96%	96%	-10%	0.025

Based on the above assumptions, the minimum evaluable (PP) sample size required for evaluation of effectiveness (unadjusted) is 135 subjects (90 Investigational Group: 45 Control Group).

As noted above, to account for both the safety and effectiveness hypotheses, and to allow for 10% attrition/missing data for effectiveness and 10% attrition/missing data for safety, the overall randomized sample size has been increased to 150 patients (100 Investigational Group: 50 Control Group).

Note that power/sample size for the effectiveness endpoint was calculated using the PASS 2020 software as follows: (a) once PASS was opened, the "Proportions" category was clicked; (b) the "Two Proportions (Cluster-Randomized)" option was then clicked; (c) the "Non-Inferiority" option was then clicked; and finally (d) the module "Non-Inferiority Tests for the Difference of Two Proportions in a Cluster-Randomized Design" was chosen. Note that this module assesses power/sample size for non-inferiority using the Farrington-Manning test, accounting for an assumption of the value of the intra-cluster (i.e., within-patient) correlation. However, the application of the Farrington-Manning test to actual study data in the presence of clustering is not well developed. Thus, the GEE approach to assessing non-inferiority will be used to assess non-inferiority for the primary effectiveness endpoint in the presence of clustering, as discussed in Section 10.3.2.

10.6 SAMPLE SIZE RE-ESTIMATION

An unblinded conditional power calculation and sample size re-estimation will be conducted once approximately 142 total effectiveness evaluable (EE) territories (~70% of the expected 202 [=135*1.5] planned number of evaluable territories) have been evaluated for the primary effectiveness endpoint and approximately 63 HES investigational group subjects (~70% of the 90 expected planned number of SE subjects) have been evaluated for the primary safety endpoint (i.e. experienced the event of interest or completed 30 days of follow-up post-index procedure)

(whichever occurs later). The sample size re-estimation will be performed by an independent statistician who is unrelated to the day-to-day conduct of the study and results will be presented to the independent DMC.

The sample size re-estimation will be performed on the basis of the number of subjects and territories (observations), as follows:

1. First, in a blinded manner (i.e., for both treatment groups combined), if the observed attrition rate at the interim effectiveness analysis exceeds the currently expected value of 10%, then the planned final number of randomized subjects for the final effectiveness analysis, prior to performing any sample size-recalculations below, will increase from 150 in order to maintain 135 evaluable subjects for the effectiveness analysis
2. Similarly, in a blinded manner (i.e., for both treatment groups combined), if the observed attrition rate at the interim safety analysis indicates that less than 90 safety-evaluable patients will be available for the primary safety analysis, then the planned final number of randomized subjects, prior to performing any sample size-recalculations below, will increase from 150 in order to maintain 90 evaluable HES subjects for the safety analysis.
3. The number of subjects to be randomized (prior to performing any unblinded sample size recalculations below) will be the maximum of the numbers found in items 1 and 2 above.

After this point, the following unblinded analysis, for the purposes of sample size recalculation, will proceed for effectiveness:

1. The conditional power to achieve non-inferiority of Instylla HES to standard of care TAE/cTACE (Control) at the final analysis will be calculated, assuming (a) 202 total territories for the final analysis (202 is the protocol-planned expected-evaluable number of territories; note that this expected number of evaluable territories for the final analysis may change from 202 based on the blinded analysis in items 1-3 directly above; if so, the final expected number of evaluable territories will be used in the conditional power calculation in place of 202); (b) the average number of territories per subject in the final analysis is equal to the average observed at the interim; (c) the interim observed effect size (TAE/cTACE primary endpoint rate minus Instylla HES primary endpoint rate) is the true effect size; and (d) non-inferiority margin of 10%.

2. If this conditional power is in the Mehta-Pocock promising zone, then the final number of evaluable territories required to achieve 90% conditional power will be calculated under assumptions (b) through (d) in item 2 directly above.
3. Enrollment will continue until the total number of evaluable territories required to achieve 90% conditional power is reached (regardless of the number of PP subjects it took to reach this total).

As referenced in item 2 above, the sample size re-estimation analysis will be performed according to the Mehta & Pocock Promising Zone approach and the DMC may recommend adjusting the

sample size upwards (to a maximum of twice the protocol-specified number of evaluable territories and with consideration of the interim observed average number of observations per EE subject) as indicated by the sample size re-estimation analysis, as long as the conditional power for success using the protocol-specified final number of evaluable territories is in the promising zone (38% - 90%). This analysis will be performed on the Per Protocol Effectiveness Evaluable (EE) analysis population.

For safety, the conditional power to meet the safety performance goal criterion for freedom from specific MAEs at the final analysis will be calculated, assuming (i) 90 Investigation Group (HES) evaluable subjects for the final analysis (90 is the protocol-planned expected evaluable number of HES patients for the safety analysis; note that this expected number of evaluable patients for the final analysis may change from 90 based on the blinded analysis discussed above; if so, the final expected number of safety-evaluable patients will be used in the conditional power calculation in place of 90); and (ii) the interim observed rate of freedom from specific MAE for investigation group is the true rate. If this conditional power is in the Mehta-Pocock promising zone, then the number of evaluable subjects required to achieve 90% conditional power will be calculated under assumption (ii). The evaluable sample size can be increased (up to double the planned sample size) in order to maintain 90% conditional power to meet the safety performance goal criterion for freedom from specific MAEs at the final analysis. This analysis will be performed on the Safety Evaluable (SE) population.

If an increase in sample size is needed for both the primary effectiveness and safety endpoints according to Mehta & Pocock Promising Zone approach, then the sample size will increase so that at least 90% conditional power for each primary endpoint will be achieved using the evaluable population for that endpoint.

If the primary safety endpoint requires a sample size increase, but the primary effectiveness endpoint does not, then the sample size will be increased to maintain 90% conditional power for the primary safety endpoint. The final analysis for the primary safety endpoint will be done on the SE population. The primary analysis for the primary effectiveness endpoint will be done on the subset of subjects in the evaluable population at the time the initial planned evaluable sample size is achieved (i.e., the first 135 evaluable (EE) subjects enrolled). A sensitivity analysis will be conducted on the entire evaluable (EE) population.

Similarly, if the primary effectiveness endpoint requires a sample size increase, but the primary safety endpoint does not, then the sample size will be increased to maintain 90% conditional power for the primary effectiveness endpoint. The final analysis for the primary effectiveness endpoint will be done on the full EE population. The primary analysis for the primary safety endpoint will be done on the subset of subjects in the SE population at the time the initial planned sample size is achieved (i.e., the first 90 evaluable subjects enrolled). A sensitivity analysis will be conducted on the entire safety evaluable (SE) population.

In general, for each endpoint, the primary analysis will be on the initial sample size or, if a sample size increase is required, only on the increased sample size required for that endpoint.

As discussed in Mehta and Pocock (2011) such a sample size increase will not require a penalty to the final significance level. The results of the sample size re-estimation, regardless of outcome, will be summarized and reported to the FDA.

10.7 INTERIM SAFETY REVIEW/STOPPING RULES

An interim review of safety data by an independent Data Monitoring Committee will be performed following accrual of 20 Instylla HES-treated subjects (at that time there will be approximately 10 Control subjects).

In consultation with medical experts, a formal stopping rule for safety has been established. The formal stopping rule will be considered reached if 4 Instylla HES subjects experience the following specific definitely or probably device or procedure-related events meeting criteria for a Grade ≥3 event per the 2017 SIR adverse event severity classification (as determined by the CEC):

- Non-target injury,
- Target organ ischemia or
- Serious and severe unanticipated adverse device effect.

Non-target injury and target organ ischemia have been targeted as stopping rule events as they represent events which are of significant concern to interventional radiologists and are those that are most likely to be attributed to the embolic agent and its mode of delivery. Since not all possible adverse events associated with the investigational device may be known at this time, severe and serious (Grade ≥ 3) UADE's will also be considered a stopping rule event. Per the SIR guidelines, the combined acceptable threshold for non-target injury and target organ ischemia for percutaneous transcatheter embolization is approximately 6.5%; however, the combined reported rates reported in the literature for such events approaches 13.5% (26).

The probability for stopping the trial if 4 subjects experience a stopping rule event once 20 subjects are accrued is dependent on the true (population) event rate as follows:

Accrual (Investigational Group: HES)	**Events Needed to Halt**	**True Event Rate**	**Probability of Halting**
20	**4**	**6.5%**	**3.7%**
		10.0%	**13.3%**

Therefore, for example, if the true underlying event rate is 6.5%, then it is unlikely (3.7% probability) that 4 subjects will experience an event; so if 4 subjects do experience an event, the

true event rate is likely > 6.5% and the study should stop. If the true event rate is 10%, the probability of stopping the trial is greater at 13.3%.

10.8 STRATIFICATION OF RANDOMIZATION

Subjects will be randomly assigned to undergo treatment with the HES System or standard of care Control using a 2:1 randomization stratified by institution and tumor type (i.e., hepatic or non-hepatic tumor). Randomization will be performed via envelope-based randomization following a satisfactory pre-embolization angiogram.

10.9 IMPUTATION METHODS

The primary effectiveness and safety analyses will be performed on observed (available) data. Every attempt will be made to contact subjects who are non-compliant or lost to follow-up, and such attempts will be documented in the subject's study record. All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Since effectiveness endpoints are assessed acutely (during the index procedure), it is anticipated that there will be minimal missing data and therefore no imputation methods are planned for the primary analysis.

For the primary effectiveness endpoint, a tipping point sensitivity analysis will be used to assess the effect of missing data on the primary effectiveness endpoint results. i.e., if the null hypothesis is rejected on the EE population, then the EE population with missing data (e.g., uninterpretable imaging for core lab review) will be imputed as a technical failure, one at a time cumulatively, and the null hypothesis will be tested after each cumulative imputation until the "tipping point" is reached (i.e., until the null hypothesis is no longer rejected). There will be no imputation of missing data for any other endpoints.

10.10 ASSESSMENT OF HOMOGENEITY

A test of homogeneity across sites will be done to determine if the study sites within a location have reasonably homogeneous responses. This analysis will be done by assessing treatment-by-site interaction assessment in the appropriate model (i.e., GEE regression with identity link for the primary effectiveness dichotomous outcome), using a 0.15 level of significance. If the responses are not homogenous, the appropriate regression analysis will be done to determine if the lack of homogeneity is due to the site or due to a possible imbalance in baseline characteristics of the subjects [or tumor type] across study sites. If the site effect is no longer significant at $P<0.15$ after adding the potentially unbalanced baseline covariates, then site will not be considered a source of lack of homogeneity. A similar analysis will be conducted to assess homogeneity between US and OUS sites.

10.11 SUBGROUP ANALYSES

For informational purposes, the primary safety and effectiveness endpoints will be presented by strata (i.e., hepatic and non-hepatic) and by gender. While the study is not powered to detect a difference between subgroups, an analysis to check homogeneity across subgroups will be conducted as outlined in Section 10.10.

11 QUALITY CONTROL AND ASSURANCE (STUDY MONITORING)

11.1 QUALITY CONTROL

In accordance with applicable regulations, ISO 14155, 21 CFR 812, and Instylla procedures, Instylla's monitors (or their designees) will contact the site prior to the start of the study to review with the site staff the study requirements, and their responsibilities to satisfy regulatory, ethical, and Instylla's requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the subject chart or eCRF will serve as the source document.

Instylla, or their designees, will monitor the study to ensure that the:

- data are authentic, accurate, and complete.
- the safety and rights of subjects are being protected.
- the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

11.2 MONITORING

Monitoring will be performed by Instylla or its designees, to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, Declaration of Helsinki, the current version of ISO 14155, 21 CFR 812, and applicable regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

Site monitoring will be conducted by a monitor (CRA) on behalf of Instylla. This will include conducting study initiation visits, interim monitoring visits, and study closure visits, as well as device reconciliation procedures for each participating clinical site. The study site should ensure COVID-19 restrictions specific to country and institution are reviewed prior to each monitoring visit as guidelines may change frequently. Site monitoring may be done in-person or remotely.

The monitor will ensure that the applicable data points on the eCRFs match the source documents and resolve any discrepancies. Records of each visit will be documented in the appropriate

monitoring report format and will include a statement of findings, conclusions, and any actions taken to correct any deficiencies noted during the visit.

The monitor will report to Instylla any non-compliance with the signed Investigator Statement, the study protocol, applicable GCP requirements, or any conditions imposed by the IRB/EC or local regulatory authority. Instylla will evaluate the non-compliance and issue corrective actions. If compliance cannot be secured, device shipments to the Investigator may be discontinued and the Investigator's participation in the investigation terminated.

The frequency of monitoring visits will be determined by Instylla but should not be less than two site visits annually.

A representative from the sponsor company, Instylla Inc. or a designee, may be present to observe and answer any questions related to the Instylla HES during the index procedure. They will be observing only and will not participate in any procedures.

Investigators and site coordinators are expected to make source files, investigator site files, and other records and reports available to the Monitors as required.

11.3 ACCESS TO SOURCE DOCUMENTATION

Instylla or its designee may perform periodic site and study file audits to evaluate compliance with its own clinical standard operating procedures (SOP) and Good Clinical Practice (GCP) standards. Investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection by providing direct access to all study records. In the event of an audit, the investigator agrees to allow Instylla, representatives of Instylla, Competent Authority, the United States Food and Drug Administration (FDA), or other regulatory authorities access to all study records.

The investigator should promptly notify Instylla of any audits scheduled by the regulatory authorities and promptly forward copies of any audit reports received to Instylla.

12 ADMINISTRATIVE AND DATA MANAGEMENT

12.1 CONFIDENTIALITY

All data used in the analysis and reporting of the study will be without identifiable reference to the subject. Only the unique subject number will be used to identify subject data submitted to Instylla, and only the investigating site will be able to link the unique subject ID to the subject's name.

All information and data sent to Instylla concerning study subjects or their participation in this trial will be considered confidential. Only authorized personnel will have access to these confidential files. All records will be kept in secure storage areas and on password-protected computers.

This includes, but is not limited to the following:

- Study subjects will be identified on all eCRFs by a unique subject ID
- eCRFs are confidential documents and will only be available to Instylla (including delegates, such as contract monitors), the investigator, the biostatistician, and if requested, to regulatory authorities. The investigator will maintain, as part of the investigation file, a list identifying all subjects entered into the trial (by their unique subject ID).

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality.

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. The investigator and all site staff involved in this study may not disclose (or use for any purpose other than performance of the study), any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Instylla or its designee must be obtained for the disclosure of any said confidential information to other parties.

The subject's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. Instylla will take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

12.2 DATA MANAGEMENT

A study-specific Data Management Plan will be created to address data review, database cleaning and database queries.

12.2.1 Data Protection

Subjects will be assigned unique identifiers by the site. Any subject records or datasets that are transferred to Instylla will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by Instylla in accordance with local data protection law(s). The level of disclosure must also be explained to the subject as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical auditors or other authorized personnel appointed by Instylla, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

12.3 FINANCIAL DISCLOSURE

Before the start of the study, the Investigator will disclose to the Sponsor any proprietary or financial interests he/she might hold in the investigational product or the Sponsor companies as outlined in the financial disclosure form provided by the Sponsor. Investigators and Sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to collect complete and accurate financial disclosure statements. Investigators must update this information in case of significant changes during the study and within 1 year of its completion.

12.4 MODIFICATIONS TO THE PROTOCOL

If any significant changes to the protocol are made during the course of the study, the Sponsor will create a protocol amendment which must be approved by the regulatory body (if applicable) and/or local EC/IRB prior to implementation of the changes by the Investigator. A significant change is one that affects the safety of the subjects, the scope of the investigation, or the scientific quality of the study. Changes to the protocol that do not affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study will also be made by the Sponsor in the form of a protocol amendment. Implementation of these changes cannot be made until the amendment is reviewed and approved by the local EC/IRB.

12.5 SUBJECT INSURANCE AND STUDY COSTS

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. Instylla has issued clinical trial liability insurance with appropriate coverage for the continuation of the entire study.

Any travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's procedure.

12.6 CASE REPORT FORMS AND CLINICAL INVESTIGATION RECORDS

12.6.1 Electronic Case Report Forms (eCRFs)

Electronic CRFs will be used for this study. The electronic database will be verified, validated and secured as appropriate.

The investigator is responsible for the accuracy and completeness of data reported on the eCRFs. Each set of subject eCRFs must be reviewed and signed by the investigator. The investigator also agrees to maintain accurate source documentation as part of the subject's medical records. Data entered in the eCRF that are transcribed from source documents must be consistent with the source

documents or the discrepancies must be explained. Guidance on completion of CRFs will be provided in CRF Completion Guidelines (CCGs).

12.6.2 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

These source documents may include chart notes, laboratory reports, images, video footage from cases, etc. A copy of these source documents or any pathological reports (de-identified and with the subject's study ID number) shall be provided to Instylla upon request.

The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

12.6.3 Retention of Data

Investigators shall maintain all study-related documentation (including correspondence related to this clinical study, subject records, source documents, eCRFs, device accountability records, etc.) 5 years or longer (as per the local institutional and/or country specific regulatory guidelines) from completion of the clinical study.

12.7 REPORT OF THE CLINICAL INVESTIGATION

A final report of the clinical investigation (a "Clinical Investigation Report") will be completed, even if the clinical investigation is prematurely terminated. The report will be prepared by the Sponsor according to ISO 14155 and 21 CFR 812.

The report will be finalized and distributed as appropriate.

13 SUSPENSION OR PREMATURE STUDY/SITE TERMINATION

Instylla Inc., reserves the right to discontinue the study at any stage, with suitable written notice to the Investigators and regulatory authorities as appropriate. Similarly, Investigators may withdraw from the study subject to providing written notification to Instylla, within 30 days prior to intent to withdraw. However, Instylla and Investigators will be bound by their obligation to complete the follow-up of subjects already enrolled in the trial. The subjects must be followed according to the

clinical protocol and information obtained during subject follow-up shall be reported to Instylla, on follow-up CRFs.

The study may be terminated for any of the following reasons:

- It appears that there is no potential for benefit associated with the Instylla HES;
- If a reasonable case can be made for terminating the research in the interest of the subject's health;
- If it is determined that study continuation cannot serve any scientific purpose;
- If the regulatory authority reviewing the program has made an irrevocable objection;
- If one of the two parties (sponsor or institution) has been declared insolvent, or if a petition has been filed for liquidation of one of the two parties;
- If one of the two parties persistently fails to comply with the obligations of the trial agreement.

When terminating the study, the sponsor and investigator will assure that adequate consideration is given to the protection of the subjects' interests.

14 PUBLICATION POLICY

The clinical investigation will be registered in a publicly accessible database in compliance with local requirements.

Instylla will comply with the requirements for publication of study results. The conduct and results of this clinical investigation will be documented in the final report. Because this investigation is a multicenter investigation, it is intended that the combined clinical data from all participating sites will be presented and/or published. In accordance with standard editorial and ethical practice, Instylla intends to support the publication of this multicenter study, and may support the publication of individual site data. Individual investigators will not publish or present results prior to publication of the combined multicenter results and without prior written consent from the Sponsor. All publications must include the name of the Sponsor (Instylla Inc.). All data, results, and all intellectual property rights derived from the study will be the property of Instylla Inc. The investigator must discuss any publication or presentation with Instylla Inc. prior to release and obtain written consent on the intended publication.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The Investigator should make every effort to avoid deviating from the Clinical Investigation Plan. Periodic monitoring of protocol compliance will be performed. Instylla has the right to suspend enrollment if there are excessive compliance issues.

All deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment must be appropriately documented and reported. Other deviations to be considered include non-adherence to the protocol that results in a significant additional risk to the subject, or non-adherence to IRB/EC requirements and/or ISO 14155 and 21 CFR 812.

The investigator must document and explain any protocol deviation in the subject's source documentation and eCRF. Protocol deviations should be reported to the IRB/EC according to their requirements. Deviations will also be documented by the monitor during site visits and those observations will be reviewed with the investigator. Corrective and preventative actions will be identified and managed per the Monitoring Plan.

If the investigator believes that any exception to the protocol is justified for an individual subject or if the investigator has a question concerning a subject who may not meet an eligibility criterion, they should contact Instylla.

Instylla will evaluate circumstances where the investigator deviates from the study protocol and will retain the right to remove either the investigator or the investigational site from the study in the event that there are recurring major protocol deviations (i.e., deviations that affect the rights, safety and welfare of study subjects or jeopardize the scientific soundness of the study).

16 COMPLIANCE STATEMENT

This clinical investigation is designed to be performed in accordance with the ethical principles outlined in the Declaration of Helsinki, ISO 14155, 21 CFR 812, and Local and National regulations. Any corrections to the CIP that might become necessary to be in conformity with new standards and regulations will be issued as amendments to this CIP. This clinical investigation shall not begin until the required favorable opinion and approvals from the IRB/ECs and the applicable regulatory authorities have been obtained. Any specific requirement imposed by the IRB/ECs or the regulatory authority shall be followed.

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APPENDIX 1: CRITERIA FOR TUMOR RESPONSE

Excerpted from Gaba RC et al. Transcatheter Therapy for Hepatic Malignancy: Standardization of Terminology and Reporting Criteria. J Vasc Interv Radiol 2016;27:457-473. (27)

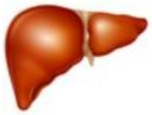
Table 1. Response Outcome Definitions for Radiologic Response Assessment Schemes

Response Outcome	WHO	RECIST	EASL	mRECIST
CR	No measurable disease	No measurable disease	Disappearance of intratumoral arterial enhancement in all arterially enhancing tumors	Disappearance of intratumoral arterial enhancement in all target tumors
PR	≥ 50% decrease in sum of cross-products	≥ 30% decrease in sum of longest diameters	≥ 50% decrease in sum of cross-products of viable tumor tissue	≥ 30% decrease in sum of longest diameters of arterially enhancing viable tissue in target tumors
PD	≥ 25% increase in cross-product of any tumor or appearance of new tumor	≥ 20% increase in sum of longest diameter measured on any previous study (must be ≥ 5 mm increase)	≥ 25% increase in cross-product of any viable tumor tissue or appearance of new tumor	≥ 20% increase in sum of longest diameter of viable target tumor measured on any previous study (must be > 5 mm increase)
SD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD

CR = complete response; EASL = European Association for the Study of the Liver; mRECIST = modified Response Evaluation Criteria In Solid Tumors; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease; WHO = World Health Organization.

APPENDIX 2: CHILD-PUGH CLASSIFICATION OF CIRRHOSIS

Excerpted From http://medicineaddicts.blogspot.com/2013/03/child-pugh-classification-of-cirrhosis.html.



Child-Pugh Classification of Cirrhosis

©Medical Addicts

Factor	Units	1	2	3
Serum bilirubin	mol/L mg/dL	<34 <2.0	34-51 2.0-3.0	>51 >3.0
Serum albumin	g/L g/dL	>35 >3.5	30-35 3.0-3.5	<30 <3.0
Prothrombin time	seconds prolonged INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5 to 15. Child-Pugh class can be A (a score of 5-6), B (7-9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of >7 (class B). This level has been the accepted criterion for listing liver transplantation.

APPENDIX 3: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF HEART FAILURE

Excerpted From http://reliantheart.com/wp-content/uploads/2013/04/nyha-classes1-4.jpg.

New York Heart Association (NYHA) Classification of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.

APPENDIX 4: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCORE (ECOG PS)

Excerpted From http://thumbnail.egloos.net/600x0/http://pds26.egloos.com/pds/201310/06/19/c0024719_5251527245578.png.

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

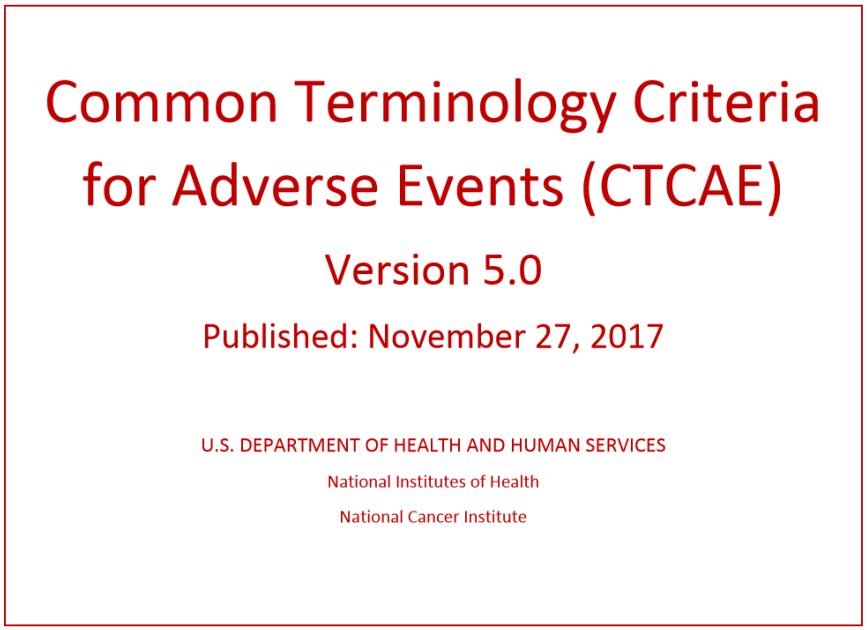
ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

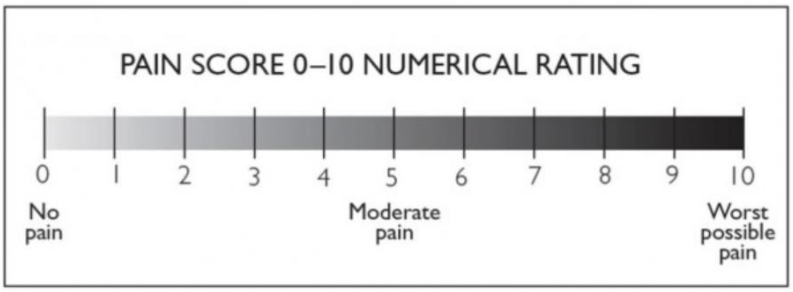
APPENDIX 5: NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE) VERSION 5.0

Excerpted From
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.



APPENDIX 6: NUMERIC RATED SCALE

Excerpted From https://www.physio-pedia.com/images/4/47/NRS_pain.jpg.



APPENDIX 7: QUALITY OF LIFE QUESTIONNAIRES

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

APPENDIX 8: RECOMMENDED ANGIOGRAPHY PROTOCOL

Imaging Modality:	DSA +/- CT or Conebeam CT angiography
Subject Positioning:	Supine on the table
Access:	Common femoral artery and/or left radial/brachial artery
Imaging View:	All vessels require a posteroanterior (PA) view. Supplemental oblique views may be taken as required.
Field of View (FOV):	Typical 22-32cm (a tighter FOV, such as 12-16cm may be required or larger for liver embolization).
Frame Rate:	Variable Frame Rate (VFR) protocols may be used. A typical VFR protocol may start with 2-3 frames per second (FPS) Increased frame rates may be used.
General Imaging:	High quality Digital Subtraction Angiography (DSA) before and after embolization is required, ideally with power injections at rates sufficient to fully opacify the target vessels.
SMA Imaging:	Example of Imaging Protocol: Select the Superior Mesenteric Artery (SMA) to evaluate any anomalous/accessory hepatic artery involvement and portal vein patency. Power inject iodinated contrast media (ICM) at a rate of 5mL/second for a minimum volume of 25mL using digital subtraction (DSA) as appropriate.
Celiac Artery Imaging:	Example of Imaging Protocol: If an adequate CT angiogram or a previous DSA is available, celiac artery imaging may not be required. Upon catheterization of the celiac artery, image the hepatic arterial supply to tumor by power injecting ICM at a rate of 3-5 mL/second for a minimum volume of 25mL using DSA as appropriate. Run until needed hepatic arterial tree and parenchymal phase are visualized.
Microcatheter Placement:	As required for desired microcatheter placement, power injections of ICM at ≤ 3mL/second for a volume of up to 15mL may be applied for a run duration adequate to image the desired sub-selected arterial tree and parenchymal phase.
Post-Embolization Imaging:	Remove the microcatheter system and perform a final DSA angiogram through the guide catheter within the parent vessels.
Image Collection:	Archive adequate images and runs to demonstrate baseline pathology, baseline vascular anatomy, key procedural steps, and final result.

APPENDIX 9: DETAILED SUMMARY OF PROTOCOL CHANGES

Details can be found in separate file titled INY-P-20-001 Appendix 9