Protocol Title

The RAVI Registry: A Prospective, Multi-Center, Observational Study of Radial Access Embolization Procedures using HydroPearl Microspheres

SPONSOR

Terumo Medical Corporation
265 Davidson Avenue
Somerset, NJ 08873
USA

Study Number: TIS2019-02

Version Number: 2.0

Version Date: 15-Jan-2021

Confidentiality Statement:

Table of Contents

A. Summary Of Revisions

Version	Date	Description of change and rationale
1.0	13-Sep-2019	Initial Release
2.0	15-Jan-2021	Addition of BPH indication Statistical updates and clarifications Remove potential AEs for consistency with standard of care registry study Extended expected enrollment time due to COVID-19 delays Minor typo and grammar corrections Addition of 365-day visit Minor changes to comply with EU (Europe) regulations

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B. Protocol Approval Page

Study Title: The RAVI Registry: A Prospective, Multi-Center, Observational Study of Radial Access Embolization Procedures using HydroPearl Microspheres

Study Number: TIS2019-02

PROTOCOL APPROVAL SIGNATURES AND DATES:

Hinna Shahid

01/29/2021

Hinna Shahid, MD, Clinical Project Manager — Date

Terumo Medical Corporation

Gash Robert

Digitally signed by Gash Robert
Date: 2021.02.02 09:41:06 -05'00'

Robert Gash, Director of Clinical Research & Operations — Date

Terumo Medical Corporation

C. Study Roles and Responsibilities

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Ethics Statement: The study will be completed in accordance with applicable regulations and standards to provide public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their

origin in the Declaration of Helsinki. This clinical investigation will be conducted in compliance with Good Clinical Practice (GCP), ISO 14155 and MDR (EU) 2017/745.

D. Investigator Approval and Agreement

PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt, review and understanding of the protocol entitled, "The RAVI Registry: A Prospective, Multi-Center, Observational Study of Radial Access Embolization Procedures Using HydroPearl Microspheres" and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the signed Clinical Trial Research Agreement (CTRA), protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal and European regulations (MDR (EU) 2017/745).

_____ _____

Investigator Signature Date

_____

Investigator Name (please print)

_____

Investigator Institution (please print)

E. Study Synopsis

Study Title	The RAVI Registry: A Prospective, Multi-center, Observational Study of Radial Access Embolization Procedures Using HydroPearl Microspheres.
Study Number	TIS2019-02
Study Sponsor	Terumo Medical Corporation 265 Davidson Somerset, NJ 08873 USA
Study Objective	The objective of this registry study is to assess the procedural success and complication rates in real-world patients undergoing HydroPearl embolization procedures via radial access.
Study Design	Multicenter, prospective, non-randomized post-market registry
Procedure(s):	Embolization of hypervascular tumors and arteriovenous malformations, including uterine fibroids and prostate artery embolizationfor symptomatic benign prostatic hyperplasia, via radial access.
Subject Population	Up to 100 subjects with procedures planned using radial artery access
Study Duration	Study enrollment is expected to take up to 18 months. Primary endpoint data will be collected at 30 days post-procedure, 180 days post-procedure, and 365 days post-procedure.
Primary Study Evaluations	1. Procedural success defined as completing the planned procedure without femoral access bailout 2. Technical success defined as delivery of HydroPearl to the target vessel and slowing the blood flow with microsphere embolization. 3. Freedom from Major Adverse Events within 30 days of procedure, defined as: a. Death b. MI c. Stroke 4. Freedom from radial access related complications at 30 days, defined as: a. Radial artery occlusion (reverse Barbeau and/or Ultrasound, per site standard of care) b. Hand ischemia c. Arteriovenous fistula d. Pseudoaneurysm e. Any complication requiring surgical and/or endovascular intervention within 30 days of index procedure
Additional Evaluations	1. Incidence of Radial Artery Occlusion Complications at any time a. Arteritis

	b. Cellulitis c. Ecchymosis d. Pain at puncture site e. Hematoma 2. Quality of Life and Health Economics 3. Procedural endpoints: a. Blood loss b. Patient radiation exposure c. Contrast volume d. Time to hemostasis e. Total procedural time f. Time to discharge g. Operative time h. Radial cocktail components and frequency of administration 4. Access endpoints: a. Radial artery spasm b. Time to discharge c. Radial access pain VAS 5. Closure endpoints a. Time to hemostasis b. Time to ambulation
Procedure Evaluations	1. Tumor type 2. Number and size of tumors / fibroids 3. Post embolization syndrome 4. UFE: a. If post-op MRI is obtained per standard of care: Effectiveness of HydroPearl measured by MRI. i. Infarction is characterized by complete (100%), 90-99%, 50-89%, or less than 50%. ii. Uterine Volume iii. Dominant Fibroid Volume b. EQ-5D c. UFS-QoL d. Return to normal activities e. Pain VAS f. Symptoms including bleeding and bulk g. Pregnancy intention and occurrence 5. Prostate Artery Embolization: a. IPSS with Quality of Life b. EQ-5D c. Return to normal activities d. Pain VAS

	e. Qmax f. Prostate volume 6. Liver Tumor Embolization: a. Tumor response (CR, PR, SD, PD) b. EQ-5D c. Return to normal activities d. Pain VAS e. Disease stage 7. Other Hypervascular tumors a. Infarction b. Return to normal activities c. Pain VAS 8. Arteriovenous malformations: a. EQ-5D b. Return to normal activities c. Pain VAS
Inclusion Criteria	1. Subject is ≥ 18 years old 2. Subject is scheduled for an embolization procedure for treatment with HydroPearl microspheres via radial access. 3. Subject is willing and able to complete follow-up requirements 4. Subject is willing and able to sign a written Informed Consent form prior participating in the registry.
Exclusion Criteria	1. Unable to have a procedure with radial access for any reason. 2. Participating in another clinical study which, in the opinion of the investigator, could impact the results of this registry. 3. Pregnant or planning to become pregnant during the study.
Statistical Analysis	Endpoints will be reported with descriptive statistics as well Kaplan-Meier survival curves where appropriate. Sub-group analyses include, but are not limited to: • UFE procedure • PAE procedure • Liver embolization procedure • Other hypervascular tumors procedure • AVM embolization procedures
Imaging Assessments	Imaging datasets will be conducted for baseline, procedure, and follow-ups per site standard of care and results entered into eCRF. Images will not be collected or archived by the Sponsor.
Safety	The Principal Investigator at each site will be responsible for reviewing and following any adverse events per site standard of care.
Data Quality	Electronic case report forms will be used to collect data evaluations in this registry.

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F. List of Abbreviations and Definition of Terms

AE:	Adverse Event
AV:	Arteriovenous
BMI:	Body Mass Index
BPH:	Benign Prostatic Hyperplasia
CEC:	Clinical Events Committee
CFR:	Code of Federal Regulations
CIP:	Clinical Investigational Plan, also referred to as (study) protocol
CRO:	Clinical Research Organization
CTRA:	Clinical Trial Research Agreement
eCRF:	Electronic Case Report Form
EQ-5D:	EuroQol Group standardized measure with 5 dimensions
HIPAA:	Health Care Portability and Accountability Act
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IFU:	Instructions for Use
IRB/EC:	Institutional Review Board/Ethics Committee
IPSS:	International Prostate Symptom Score
MI:	Myocardial Infarction
mRECIST:	Modified Response Evaluation Criteria in Solid Tumors
PAE:	Prostate Artery Embolization
PG:	Performance Goal
QoL:	Quality of Life
SAE:	Serious Adverse Event
SDV :	Source Document Verification
UADE:	Unanticipated Adverse Device Effect
UFE	Uterine Fibroid Embolization
UFS-QOL:	Uterine Fibroid Symptom Quality of Life Questionnaire
VAS	Visual Analog Scale

1 Background

The transradial approach to percutaneous interventions has generated intense interest over the past decades. Initially researched in the context of percutaneous coronary interventions (PCI), early reports of successful transradial access (TRA) included coronary angiography in 1989 (Campeau, 1989) and the first successful TRA coronary angioplasty and stent implantation in the years 1992 and 1993, respectively. (Kiemeneji & Laarman, 1993). Further studies of TRA for PCI have consistently demonstrated its benefits as compared to femoral access, including decreased bleeding, access site complications and post-procedure recovery time, and increased patient satisfaction and cost effectiveness. (Rao, Cohen, Kandzari, Bertrand, & Gilchrist, 2010) . Limitations to the transradial approach have been recognized, such as a learning curve which must be overcome by new operators, limitations of available equipment suitable for radial use, and relatively rare complications such as localized access site hematoma. Radial artery occlusion is reportedly rare and upon occurrence is often asymptomatic due to collateral perfusion supplied by the ulnar artery. (Fischman, Swinburne, & Patel, 2015).

The benefits of transradial access are considered by many physicians to outweigh these drawbacks, leading to the steady uptake of TRA for PCI; an estimated 16% of PCI procedures in the US were conducted transradially in the year 2012, up from 1.2% in 2007. Within the previous decade, additional support for TR-PCI has been generated by multiple prospective, randomized trials, including the RIFLE, RIVAL and MATRIX trials which have consistently demonstrated decreased access site bleeding and net adverse events. (Fischman, Swinburne, & Patel, 2015). The expanding body of evidence favoring transradial access for PCI prompted physicians to branch beyond the coronary space to transradial access for visceral and peripheral arterial interventions, (Rao, Cohen, Kandzari, Bertrand, & Gilchrist, 2010) and more recently, for interventional radiology procedures, such as embolization of hypervascular tumors, including uterine fibroids and liver tumors ((Yamada, et al., 2018)).

Uterine fibroid embolization, traditionally achieved via femoral access, is considered by the American College of Obstetrics and Gynecology as a safe, minimally invasive primary treatment for symptomatic uterine fibroids. (Keung, Spies, & Caridi, 2018) . The first reported series of UFE achieved via radial access dates to 2014, where Resnick, et al. (2014) conducted UFE on 29 patients at a single institution with a 100% success rate. No immediate major or minor complications were observed in any patients, and radial artery patency was evident in all patients at one month follow up. (Resnick, et al., 2014). Recently,

Gjoreski, et al. (2019) directly compared the safety and feasibility of UFE when achieved through radial as opposed to femoral access. In this retrospective study, 13 femoral procedures and 11 transradial procedures all yielded a 100% success rate with no significant difference in access site related and overall adverse events noted between cohorts. Procedure and fluoroscopy times were reportedly shorter in the radial group; a mean procedure time of 60.3 minutes was associated with the radial group as compared to 72.4 minutes in the femoral cohort, and mean fluoroscopy time was 21.1 minutes and 25.3 minutes in the radial and femoral cohorts, respectively. (Gjoreski, Gjoreski, & Nancheva, 2019).

The development of transradial access for embolization of hepatic tumors can be traced back to a 2003 report by Shiozawa et al. (2003) which described transcatheter arterial chemoembolization (TACE) in 327 patients, 177 of which were accessed radially and 150 via femoral access. Therapeutic efficiency was observed in both cohorts, with a lower complication rate in the radial cohort (4.6%) compared to the femoral (12.7%). (Shiozawa, et al., 2003). In addition to chemoembolization, radial access has also been utilized for radioembolization of hepatic tumors. A study by Fischman, et al. published in 2016 described 30 procedures conducted in 26 patients which supported the safety and tolerability of TRA for hepatic artery embolization. In this study, 14 TACE procedures, 14 Y90 procedures and 2 bland embolization procedures yielded a 100% technical success rate with no major AEs reported at one month follow up. (Fischman, et al., 2013) . In a 318 patient study, a total of 329 planning angiograms and 245 Y90 embolization procedures resulted in technical success in 97.7% of cases, superficial bruising observed in 2.3% of cases, and a radial artery occlusion rate of 1.6%. (Bishay, et al., 2016) .

A study by Kis and colleagues, comparing the feasibility of transradial vs transfemoral access for hepatic radioembolization, demonstrated 100% technical success in both radial and femoral cohorts, totaling 64 procedures in 50 patients. Direct savings in cost and time were noted in the radial group; approximately $100 and 1-hour decrease post procedure stay was observed on a per procedure basis. Despite a caveat noted in this study surrounded the technical challenges associated with radial access which led to longer fluoroscopy time and greater radiation doses, the authors recommended radial access as the primary choice in selected patients, such as those with low platelet count and/or morbid obesity. (Kis, Mills, & Hoffe, 2016) The association between increased radiation exposure and fluoroscopy time with radial access was challenged in a later study, in which 124 intraarterial procedures were performed on 55 liver cancer patients, which demonstrated

significantly less radiation exposure to operators using radial artery access, and similar contrast agent volume and patient radiation exposure between groups. This randomized, prospective study was primarily conducted in order to assess patient access preference for intraarterial liver cancer therapies; of 36 patients who experienced at least one radial and one femoral access procedure, 81% preferred TRA compared to 19% who preferred TFA. (Yamada, et al., 2018)

A recent paper from an Italian University hospital from a study of 60 pts treated with TACE for HCC reported 0% of cross-over rate from trans-femoral access (TFA) to trans-radial access (TRA). A positive association between operator experience and time spent for fluoroscopy, puncture, procedure and total examination was noted. A negative relationship between TRA and contrast volumes and radiation exposure were also reported. A higher percentage of pts treated with TFA reported post-procedural complains at the puncture site and limitations in performing basic activities. The operator learning curve was estimated to be low, with an estimated threshold of 20 procedures. (Iezzi, et al., 2019)

The largest study involving safety and feasibility of transradial access for non-coronary interventions includes both UFE and hepatic artery embolization among other visceral interventions. In this single center study, 936 patients undergoing 1,512 consecutive TRA procedures were retrospectively analyzed. Of these procedures, UFE accounted for 116, and TACE, Y90 mapping and Y90 infusion accounted for 485, 391 and 293 procedures, respectively. Combined analysis indicated a technical success rate of 98.2%. Major complications, including one pseudoaneurysm and one seizure, were reported at 0.13%, and minor complications, including hematomas, RAO, RAS and arm pain, were observed in 2.38% of cases. Twenty-seven cases, representing 1.8%, required crossover to transfemoral access. The favorability of these results towards radial access led authors to pronounce TRA as a promising alternate primary access site in a variety of peripheral vascular interventions. (Posham, et al., 2016)

1.1 HydroPearl microspheres and Indications For Use

HydroPearl microspheres are indicated for use in arteriovenous malformations and hypervascular tumors, including uterine fibroids, and for prostate artery embolization for symptomatic benign prostatic hyperplasia (BPH).

1.2 Summary of Clinical Studies

No clinical studies using HydroPearl have been published, although a small retrospective study of 17 PAE patients treated with HydroPearl for BPH was presented at the Spectrum, an annual conference for IR (interventional radiology) oncological diseases.

2 Study Design, Sample Size and Duration

2.1 Study Design

This is a prospective, multi-center, non-randomized registry to record the real-world safety and efficacy of the HydroPearl microspheres for arteriovenous malformations and hypervascular tumors including uterine fibroids, and for embolization prostatic arteries for symptomatic benign prostatic hyperplasia (BPH).

2.2 Sample Size

Up to 10 sites in the US and EU are expected to participate in the study with 100 subjects enrolled. Each study site will be limited to 30% of total patient population.

The target population is comprised of subjects scheduled for embolization procedures with HydroPearl microspheres used on-label via radial access.

2.3 Study Duration

Study enrollment is expected to occur over an 18-month period. Follow-up will continue for each subject through 365-days post-procedure.

3 Study Objective and Evaluations

3.1 Study Objective

The objective of this registry study is to assess the technical and procedural success and complication rates in real-world patients undergoing embolization procedures with HydroPearl microspheres via radial access.

3.2 Evaluations

This clinical study will assess the primary and secondary evaluations as described below.

3.2.1 Primary Evaluations

Primary Safety Evaluation:

The primary safety evaluation is freedom from major adverse events and radial access complications within 30 days post-procedure.

Major Adverse Events are defined as:

1. Death
2. MI
3. Stroke

Radial Access related complications are defined as:

1. Radial artery occlusion
2. Hand ischemia
3. Arteriovenous fistula
4. Pseudoaneurysm
5. Any complication requiring surgical and/or endovascular intervention within 30 days of index procedure.

Primary Efficacy Evaluation:

The primary efficacy evaluations are procedural success and technical success.

1. Procedural success is defined as completing the planned procedure without femoral access bailout.
2. Technical success is defined as delivery of HydroPearl to the target vessel and slowing the blood flow with microsphere embolization. Embolization may be confirmed clinically or radiologically at the discretion of the site investigator.

3.2.2 Additional Evaluations

Additional evaluations include:

1. Incidence of Radial Artery Occlusion Complications at any time
    a. Arteritis
    b. Cellulitis
    c. Ecchymosis
    d. Pain at puncture site
    e. Hematoma

2. Quality of Life and health economics
3. Post embolization syndrome
4. Procedural endpoints:
    a. Blood loss
    b. Patient radiation exposure
    c. Contrast volume
    d. Time to hemostasis
    e. Total procedural time
    f. Time to discharge
    g. Operative time
5. Access endpoints:
    a. Radial artery spasm,
    b. Time to discharge
6. Closure endpoints
    a. Time to hemostasis
    b. Time to ambulation
7. Tumor type
8. Number and size of tumors / fibroids
9. Post embolization syndrome
10. UFE:
    a. If post-op MRI is obtained per standard of care: Effectiveness of HydroPearl measured by MRI.
        i. Infarction is characterized by complete (100%), 90-99%, 50-89%, or less than 50%.
        ii. Uterine Volume
        iii. Dominant Fibroid Volume
    b. EQ-5D
    c. UFS-QoL
    d. Return to normal activities
    e. Pain VAS
    f. Symptoms including bleeding and bulk
    g. Pregnancy intention and occurrence
11. PAE:
    a. IPSS with Quality of Life

b. EQ-5D
c. Return to normal activities
d. Pain VAS
e. Qmax
f. Prostate volume

12. Liver Tumor Embolization:
    a. Tumor response (mRECIST - CR, PR, SD, PD)
    b. EQ-5D
    c. Return to normal activities
    d. Pain VAS
    e. Disease stage
13. Other Hypervascular Tumors
    a. Infarction
    b. Tumor Response (mRECIST – CR, PR, SD, PD)
    c. Return to normal activities
    d. Pain VAS
14. Arteriovenous malformations:
    a. EQ-5D
    b. Return to normal activities
    c. Pain VAS

4 Study Design

This is a prospective, multi-center, registry study to assess the procedural success, technical success, and complication rate of radial access procedures using HydroPearl microspheres.

A subject is considered enrolled into the study once the guidewire is inserted into the radial artery.

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Subject must meet all the following inclusion criteria to be enrolled in the study:

1. Subject is ≥ 18 years old

2. Subject is scheduled for a procedure for treatment with HydroPearl microspheres using radial access.
3. Subject is willing and able to complete follow-up requirements
4. Subject is willing and able to sign a written Informed Consent form prior to participating in the registry.

4.1.2 Exclusion Criteria

Subjects will not be permitted to participate in the study if they meet any of the following exclusion criteria:

1. Unable to have a procedure with radial access for any reason.
2. Participating in another clinical study which, in the opinion of the investigator, could impact the results of this registry.
3. Pregnant or planning to become pregnant during the study.

4.2 Subject Enrollment

Up to 10 sites in the US and EU are expected to participate in the study with up to 100 subjects enrolled.

5 Ethics

5.1 Role of the Sponsor

The Sponsor has the overall responsibility for the conduct of the study, including assurance that the study meets all regulatory requirements. In this study, the Sponsor will have certain direct responsibilities and will delegate other responsibilities to the Clinical Research Organization (CRO). The Sponsor will conduct all its responsibilities in compliance with GCP and any applicable regulations.

5.2 Role of Clinical Research Organization

The Clinical Research Organization (CRO) will support the data management which includes, but is not limited to, informing the Sponsor of any unanticipated adverse device effects (UADEs) and serious adverse events (SAEs) as appropriate. The CRO will conduct all its responsibilities in compliance with the Code of Federal Regulations (CFR).

5.3 Ethics Review

The final study protocol and written Informed Consent Form must be approved in writing by an Institutional Review Board (IRB) and/or Ethics Committee (EC). The principal investigator is responsible for informing the IRB/EC of any amendments to the protocol in accordance with local requirements. In addition, if any advertising is used to recruit subjects to the study, the IRB/EC must approve prior to use. The protocol must be re-approved by the IRB/ EC annually, as local regulations require and where applicable.

Progress reports and notification of serious, unexpected adverse events will be provided to the IRB/EC according to local regulations and guidelines.

5.4 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH/GCP, ISO 14155 and MDR (EU) 2017/745. and applicable regulatory requirements.

5.5 Written Informed Consent

Written Informed Consent must be obtained prior to any study-related procedures*. The site principal investigator will ensure that proper informed consent is provided, including ensuring the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified that they are free to withdraw from the study at any time. The subject must be given the opportunity to ask questions and adequate time to consider the information provided. The site principal investigator will ensure that the subject has met all eligibility criteria prior to enrollment in the study.

The site principal investigator must store the original, signed written ICF per site specific procedures. A copy of the written ICF (paper or electronic) must be given to the subject. Any modifications made to the ICF must first be approved by the Sponsor and IRB/EC.

**Pre-procedure assessments considered standard of care completed prior to obtaining informed consent do not need to be repeated if performed within 90 days of the procedure unless the investigator feels it is medically necessary.*

5.6 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to the study Sponsor and/or allow the Sponsor or their designate, any regulatory authority, and IRB access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

In accordance with General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), the written Informed Consent form must include a subject authorization to release medical information to the study Sponsor and or allow the Sponsor or their designate, a regulatory authority, or EC access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

To protect the patient's identity, a unique patient identification code will be assigned by the investigator to each trial patient and used instead of patient's name when the investigator reports adverse event and/or other trial related data. Thus, this number, rather than the patient's name, will appear on all documents and will be cross-referenced by the patient's date of birth. Personal information will be treated as confidential, but may need to be reviewed by the PIs, the ethics committee and regulatory authorities.

In order to be compliant with any country-specific laws, all relevant submissions, to the respective authorities will be done and the corresponding approval will be obtained before collection of any data considered to be sensitive, such as: ethnic origin, race, full date of birth etc

5.7 Subject Withdrawal

Subject participation in the study is voluntary. Subjects may withdraw their consent from participation in the study at any time. A subject may withdraw completely or may withdraw but leave the authorization to access their medical records in compliance with local regulations. Should a subject leave the study for any reason, the investigator will document the reason if known, and report in the study database.

5.8 Discontinuing Subject Participation

A subject's participation in the study may be terminated for the following reasons:

1. Serious or severe adverse event or unanticipated adverse device effect.
2. Termination of study by the Sponsor.
3. Investigator determination that continued participation is not in the best interest of the subject.
4. Subject withdrawal of consent at any time.

6 Device Supply Information

6.1 Documentation

This is a registry study observing on-label use of HydroPearl microspheres; therefore, all product will be obtained from the commercial stock at each study site for clinical use. All product information should be recorded in source documents and the study eCRF.

6.2 Malfunctioning / Failed Device

If a Terumo device has malfunctioned and/or failed, the investigator must follow the standard institutional policies for reporting complaints. In addition, the device failure should be reported in the eCRF.

7 General Procedures

7.1 Screening/ Baseline Visit

Prior to the procedure, subjects must sign the informed consent form, meet all the inclusion and none of the exclusion criteria. The screening visit will follow each study site's standard of care and typically consists of a review of medical history and demographics, blood tests, imaging, review of concomitant medications, and pregnancy test if appropriate.

7.2 Procedure

Subjects that meet the eligibility criteria and have signed the informed consent will have their scheduled procedure performed in accordance with investigator/site standard practices.
Any on-label use of HydroPearl microspheres are permitted this study; that is, treatment of arteriovenous malformations and hypervascular tumors including uterine fibroids.

Table 2: Schedule of Events

Assessment	Screening / Baseline	Procedure	Discharge	30 Day Follow-up ±14 days	180 Day Follow-up ±30 days	365 Day Follow-up ±30 days
Informed Consent	X					
Eligibility Criteria	X					
Medical History/Demographics	X					
Pregnancy Test ¶	X					
Blood Tests, including platelets and INR (if available) *	X	X	X	X	X	X
Embolized target organ Imaging (if available)	X	X	X	X	X	X
Physical Exam	X		X	X	X	X
Procedure, Access, Closure Evaluations		X				
Quality of Life questionnaires and return to normal activities	X		X	X	X	X
Concomitant Medications (Intra-op and Anticoagulation / Antiplatelets Only)	X	X	X	X		
Device Related Adverse Events ⌘		X	X	X	X	X

¶ Pregnancy test if female of child-bearing potential (collected prior to procedure according to site standard of care)

* Blood Tests include Complete Blood Count (CBC), Platelet Count, Serum Creatinine, Hemoglobin (HGB), Blood Urea Nitrogen (BUN), Hematocrit (HCT) and Prothrombin time/INR, only as collected per standard of care

⌘ Device related adverse events should be recorded during the entire course of the study from time of enrollment through end of 180 Day Follow-up visit.

7.3 Device Set-up and Preparation

Please refer to the IFU for guidance.

7.4 Blood Tests

Blood samples will be collected and analyzed per each site standard of care. Specific blood tests are not required per protocol; examples of typical tests are listed, but only need to be reported if collected per standard of care.

7.5 Concomitant Medical Therapy

Subjects enrolled in this study should be medicated according to investigator's standard of care prior to, during, and after the procedure.

Intraoperative medications and any anticoagulant / antiplatelet medications should be recorded on the appropriate eCRF. Other concomitant medications will not be collected for this study.

7.6 Follow-up Procedures

Subjects will be evaluated prior to discharge, 30 days post-procedure,180 days post-procedure, and 365 days post-procedure. All follow-up visit dates will be calculated based on a 30-day calendar.

7.6.1 Discharge Visit

The subject may be discharged when clinically stable, at the discretion of the investigator.

7.6.2 30 Day Visit (± 14 days)

All study sites will be asked to collect follow-up data per each subject at 30 days post-procedure. Study reported evaluations are not required except for the quality of life questionnaire; otherwise all data collected will be per standard of care. A typical follow-up visit may include blood tests, imaging, physical exam, review of concomitant medications and any device related adverse events.

7.6.3 180 Day Visit (± 30 days)

All study sites will be asked to collect follow-up data for each subject at 180 days post-procedure, per site standard of care. Study reported evaluations are not required except for the quality of life questionnaire; otherwise all data collected will be per standard of care. A typical follow-up visit may include blood tests, imaging, physical exam, review of concomitant medications and any device related adverse events.

7.6.4 365 Day Visit (± 60 days)

All study sites will be asked to collect follow-up data via telephone or visit for each subject at 365 days post-procedure. If a clinic visit is standard of care at 365 days, data from the visit will be collected. If a clinic visit is not standard of care, follow-up information for this visit will be collected via telephone. This 365-day visit will conclude the subject's participation in the study.

7.7 Clinical Data Collection

Information about subject demographics, eligibility requirements, procedure, specific concomitant mediations as well as complications and/or device related adverse events will be collected on the eCRFs provided by the Sponsor. The eCRFs should accurately reflect data contained in the subject's medical records (i.e. source documents).

8 Adverse Events

Subject complications will be monitored via the reporting of device related adverse events occurring from the time of enrollment (insertion of guidewire into radial artery) through study completion (withdrawal for any reason or completion of 365-day follow-up visit). For this registry, adverse events collected will be limited to any events possibly, probably or definitely related to a Terumo device, as described below in Section 8.2.

Where an adverse event has, by its nature, a prolonged course, the event will be considered a single event and not multiple events.

The investigator is not required to actively seek adverse events from a subject once a subject has exited the study. If the investigator learns of any device related adverse event at

any time after a subject's exit from the study, the investigator should promptly report it to the Sponsor.

8.1 Definitions

An *adverse event* (AE) is defined as an unwanted medical occurrence in a subject. This definition does not imply that there is a relationship between the AE and the device under investigation. This can include, but is not limited to, a change in the subject's health status from baseline that is related to the disease process, interventional procedures, investigational device, and/or side effects to medications.

An *adverse device effect* is defined as those adverse events that are caused by, or related to, the device.

A *serious adverse event* (SAE) is an adverse event that led to a death or led to a serious deterioration in the health of a subject that:

1. Resulted in a life-threatening illness or injury,
2. Resulted in a permanent impairment of a body structure or body function,
3. Required in-subject hospitalization or prolongation of existing hospitalization,
4. Resulted in medical or surgical intervention to prevent impairment to body structure or a body function, or
5. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Each AE will be assessed by the site investigator to determine whether it is serious or non-serious. (Note: Seriousness is different from severity; severity is used to describe the intensity of an event experienced by the subject).

A *serious adverse device effect* is an adverse event that is both serious and device related.

8.2 Anticipated Adverse Events (AEs)

All expected adverse events are listed in each device's IFU. Potential complications associated with interventional procedures, access, and device are described per each site's

standard of care pre-procedure consenting. Since this observational registry does not include any investigational devices or procedures, anticipated AEs are only specified in the IFUs, not in the protocol.

There may be additional unforeseen adverse events.

8.3 Follow-up of Adverse Events

All device related adverse events observed from the time of enrollment throughout the duration of the study must be reported on the eCRF. All device related adverse events will be followed until resolution or stabilization of symptoms through study completion and/or the subject withdraws consent. Resolution means that the subject has returned to a baseline state of health. Stabilization means that the investigator does not expect any further improvement or worsening of the adverse event.

8.4 Causality Rating

The causal relationship of an adverse event to the device will be rated as follows:
Possible: An event that is unlikely caused by using the device. An alternative explanation - e.g., concomitant drug(s), concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable: An event that might be due to the use of the device. An alternative explanation is less likely - e.g., concomitant drug(s), concomitant disease(s). The relationship in time is suggestive of a direct relationship to the device.

Definitely: An event that is attributed to the use of the device. The event cannot be reasonably explained by an alternative explanation - e.g., concomitant drug(s), concomitant disease(s).

8.5 Severity of Adverse Events

The severity of adverse events will be rated as follows:

Mild	An adverse event that is tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities, does not need medical treatment or intervention.
Moderate	An adverse event that is sufficiently discomforting to interfere with normal everyday activities; intervention may or may not be needed.
Severe	An adverse `event that prevents normal everyday activities; treatment or other intervention usually needed.

8.6 Adverse Event Monitoring

Adverse events will be reviewed and assessed by the principal investigator at each site. Treatment for adverse events will be per standard of care as determined by the site investigator. Device related adverse events reported in the eCRF will be processed in the standard compliant fashion for the manufacturer.

9 Risk Assessment

9.1 Risk Management Procedure

Subjects will be monitored for the duration of the study. Risks will be mitigated through selection of qualified physicians, appropriate training, and study monitoring ensured by the following:

- Investigators who participate in the study will be experienced and skilled in radial access for visceral interventions. Additionally, investigators, in conjunction with the investigational site, will have adequate resources for participation in a registry study.
- Each investigator will ensure oversight and approval of the study by their IRB/EC prior to initiation of the study at their site.
- The investigator and study personnel will be trained on the study protocol.
- Subjects will be carefully evaluated against the eligibility criteria prior to entering the study to ensure that their diagnosis and medical status are appropriate for participation.

- Subjects will be monitored throughout the follow-up period as defined in the study protocol. Subjects will have visits with the investigator or designee to review the subjects' status.

9.2 Potential Benefits

Subjects enrolled in this clinical study will be monitored closely throughout the study and have regular assessments according to the investigator's standards of care. The data collected during the clinical study will provide further understanding of procedural and technical success of radial access for HydroPearl procedures.

10 Monitoring

Data will be collected using eCRFs for this study. Sites will enter data directly into the eCRFs via a web-based system. Sponsor representatives (study monitors) will schedule periodic, on-site visits to review source data and compare to eCRFs.

Study monitors will work in accordance with Sponsor standard operating procedures (SOPs) and the Study Monitoring Plan.

At the site, monitors will perform and verify the following:

- The adequacy and experience of the study center including Sponsor notification of any problems relating to facilities, technical equipment or medical staff
- Written Informed Consent has been obtained from all subjects prior to any study related procedures being performed and that data is recorded correctly and completely
- Source Document Verification (SDV): comparing data in the eCRFs to ensure they correspond with applicable source data, and to inform the Sponsor and investigator of any discrepancies, errors or omissions
- Ensure adherence to the protocol and applicable regulations at the site and notify the Sponsor promptly of any deviations
- Evaluate subject compliance and support subject retention efforts at the site

11 Image Analysis

Imaging, if completed, will be analyzed per standard of care at each site and results reported in eCRF; however, images will not be collected nor archived by the Sponsor.

12 Device Failure and Malfunction

A device failure has occurred when the device is used in accordance with the IFU, but does not perform as described in the IFU, and negatively impacts treatment of the study subject.

13 Statistical Methods

13.1 Sample Size Determination

. This observational study is not testing a hypothesis; therefore, no power calculations were completed. The stated sample size will provide a reasonable assimilation of safety of the device and will allow detection of rare major complication with a reasonable probability. That is, a sample size of 100 evaluable patients would provide greater than 80% probability of observing 1 or more major complications that may occur at a population rate of 1.6% or more.

13.2 General Considerations

Evaluations will be reported with descriptive statistics including 95% confidence intervals. Continuous endpoints will report the mean and standard error, median, min, and maximum values. Categorical endpoints will be summarized by proportion of each category. Time-to-event endpoints will be summarized via Kaplan-Meier survival analyses, along with median and associated 95% interval. The associated Kaplan-Meier curves will be displayed as appropriate.

Sub-group analyses include, but are not limited to:

- UFE treatment procedure
- Hypervascular benign and malignant liver treatment procedures
- AVM procedures
- PAE treatment procedure

13.2.1 Study Visit

The Study Visit Day 0 is the date of the index procedure. Day in study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = End Date – Start Date

13.2.2 Visit Windows

Unless otherwise specified, visit assessments will be analyzed for each analysis time point according to the visit entered in the eCRF.

13.3 Analysis Populations

Analyses for primary and secondary evaluations will be based on the Primary Analysis Set, defined as all enrolled subjects (i.e., those who signed the informed consent form and meet all protocol eligibility criteria) who are treated.

13.4 Poolability Analysis

All investigational sites will follow the requirements of the study protocol and standardized data collection procedures. The primary evaluations will be presented separately for each site using descriptive statistics. Poolability of the primary evaluations across investigational sites will be evaluated using a regression model with fixed effects for site. Sites enrolling less than 5 subjects will be combined to form one-quasi site. If the p-value for the site effect is < 0.15, additional exploratory analyses will be performed to understand any variations in outcomes by site.

13.5 Handling of Missing Data

All data will be collected when possible to limit the amount of missing data. Site study coordinators will work with the site principal investigator to collect accurate patient data. The number of missing data will be reported. Only observed cases will be considered.

13.6 Subject Disposition

Subjects who sign an informed consent form, but do not meet all protocol eligibility criteria (i.e., screening failure), will be excluded from the statistical analyses.

13.7 Analysis of Study Evaluations

Study success is defined as sample size enrolled with minimal missing data to allow for robust descriptive statistics. No formal hypothesis tests will be performed; endpoints will be summarized with descriptive statistics.

13.8 Protocol Deviations

Deviations from the procedures outlined in the study protocol will be reported by study sites on eCRFs. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

13.9 Changes to Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended protocol and approved prior to the analysis when possible.

Appendix 1 References

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