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JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Title: Evaluation of a novel absorbable radiopaque hydrogel in patients undergoing image-guided radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma

Pancreatic ductal adenocarcinoma is now the third leading cause of cancer-related death, with a devastating 5-year overall survival (OS) rate of nearly 8%, despite having the 12th most common incidence of all malignancies in the United States [1]. One-third of patients will present with borderline resectable or unresectable, locally advanced pancreatic cancer (BR/LAPC) [2-5]. In the cases of LAPC, chemotherapy with or without radiation may be recommended to improve the quality of life by relieving symptoms and extending survival [6-11]. Despite aggressive combined modality therapy, the median survival remains between 9 and 15 months [12,13].

Current guidelines for the management of BR/LAPC patients include single- or multi-agent chemotherapy or chemoradiation (CRT) in sequence with chemotherapy [14]. Results of studies comparing chemotherapy alone to CRT for patients with BR/LAPC are mixed [6,9,12,15]. The importance of local control or delaying local progression on improving morbidity and possibly mortality in patients with pancreatic cancer is supported by autopsy data demonstrating that 30% of patients die of locally destructive disease [16]. It follows that in the cases of LAPC, advanced radiation therapy techniques using dose-escalation with intensity modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) are potential strategies to improve local control.

A consistent challenge to dose-escalation with IMRT or SBRT is the sensitivity of the surrounding gastrointestinal organs, particularly the small bowel which is directly adjacent to the head of the pancreas (HOP). For BR/LAPC patients treated with CRT, advances in image guidance have provided the opportunity to safely deliver higher biologically effective doses of radiation therapy using IMRT of >70 Gy (57.25 Gy in 25 fractions, BED 70.36 Gy) compared

to standard fractionation regimens (50.40 Gy in 28 fractions or 50 Gy in 25 fractions, BED 59.47 Gy and 60 Gy, respectively) [17]. Those patients who underwent dose-escalated CRT with BED>70 Gy, did have a superior OS compared to those receiving BED<70 Gy, supporting the utility of dose-escalation in improving long-term outcomes. SBRT involves a short course of radiation therapy, five fractions or less, and has demonstrated higher rates of local control compared to CRT in other disease sites [18]. Early studies evaluating SBRT for pancreatic cancer utilized single fractions of 25 Gy, resulting in local control rates of 100% at 1 year but unacceptably high rates of gastrointestinal toxicity [19-22]. More recently, hypofractionated SBRT (33 Gy total, 6.6 Gy daily fractions) has been evaluated and utilized by our group in an effort to reduce the toxicity of therapy, with results demonstrating nearly 80% rate of freedom from local progression at one year and an acceptable 11% long-term gastrointestinal toxicity [23]. Outcomes with SBRT are thus promising; however, higher local control rates with dose-escalation may be achievable, but current practice is limited due to risks of toxicity.

The goal of this pilot study is to evaluate the success of an endoscopic ultrasound (EUS) guided injection of TraceIT to mark the interface between the pancreas and duodenum in patients with a pathologically confirmed diagnosis of BR/LAPC pancreatic adenocarcinoma for whom a course of SBRT is indicated. TraceIT is already an FDA approved absorbable tissue marker, however, it has not yet been injected into the region between the pancreas and duodenum in humans. As this is the first in-human experience to attempt to use the hydrogel tissue marker to localize this important boundary, a clinical trial is warranted to investigate the success of this procedure. This study will thus set the stage for a planned future investigation using the TraceIT Tissue Marker as an organ spacing material (AGX-17-001-US) by injecting a larger volume of the hydrogel to displace the duodenum away from the pancreas to reduce risk of duodenum toxicity give the increased distance between the target and the duodenum and with the use of imaging localization..

2. **Objectives** (include all primary and secondary objectives)

Primary Objective:
To evaluate the success of marking the interface between the pancreas and duodenum with TraceIT Tissue Marker via EUS in patients undergoing image-guided radiotherapy for BR/LAPC pancreatic adenocarcinoma.

Secondary Objectives:

1) To assess the visibility of TraceIT on daily cone beam CT acquired as standard of care for image-guided radiation therapy.

2) To examine the hydrogel injection sites for implant location and presence of local inflammatory reactions as a result of TraceIT placement in patients who proceed to surgical resection.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Pre-clinical: Our preclinical study on human cadavers was done in September 2016. Using three human cadaveric specimens, TraceIT Tissue Marker was injected between the HOP and duodenum via open laparotomy in one case and endoscopic-ultrasound (EUS) guidance in two cases. Cadavers were subsequently imaged using CT and dissected for histologic confirmation of hydrogel placement. Compared to pre-injection scans, post-injection axial CT demonstrated successful injection of the radiopaque hydrogel as a contrast-enhancing region between the HOP and duodenum. After injection, a pancreatic surgeon dissected each cadaveric specimen by performing an en-bloc resection of the pancreas and the duodenum, preserving the injection site for histologic examination. The tissue was serially sectioned to grossly visualize the injection cavity and sections were then formalin-fixed, paraffin embedded (FFPE) and stained with hematoxylin and eosin (H&E) for microscopic examination of gel placement. Microscopic examination of the FFPE sections following H&E staining revealed a complete separation of the full duodenal mucosa from the pancreatic tissue in most regions without injection into the muscularis propia (Rao et al., IJROBP, 2017).

We have also conducted two distinct preclinical studies on swine animals. The first study assessed for toxicities of direct injection of TraceIT into the pancreas or wall of the duodenum. These studies did not reveal any incidence of pancreatitis or evidence of necrosis of the duodenum by these injections simulating "worse-case" mis-injections of TraceIT when targeting this interface between the HOP and duodenum. In a second porcine study, we were able to demonstrate successful placement of TraceIT via EUS in 6 of the 8 swines. Subsequent imaging on diagnostic CT and cone beam CT (CBCT) demonstrated adequate visibility of the injected TraceIT highlighting the potential utility of TraceIT injection to facilitate visualizing this HOP-duodenum interface on daily image guidance with CBCT.

Clinical: TraceIT Tissue Marker has several publications for marking purposes demonstrating its stability in the esophagus [24], bladder [25], and cervix [26]. Given the unique enzymatic and mobile environment in the peripancreatic region, distinct investigation of the injection in the pancreas-duodenum space is necessary.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This is a prospective, single institution, single arm pilot study to evaluate the feasibility of injecting TraceIT Tissue Marker to mark the interface between the pancreas and duodenum. Six patients with pathologically confirmed BR/LAPC pancreatic adenocarcinoma for whom a course of SBRT is indicated will be enrolled.

Enrolled subjects will be scheduled for TraceIT placement at the time of standard of care fiducial placement using an endoscopic transduodenal approach with material delivered using an EUS-fine needle in accordance with the manufacturer's instructions. Prophylactic antibiotics will be administered prior to fiducial placement in accordance with institutional practices. At the same time that the fiducials are being placed, TraceIT will also be placed by loading the hydrogel into a syringe and injecting it in the space between the pancreas and the duodenum using a similar needle and procedure as is done during the placement of the fiducial. TraceIT injections will be limited to 0.3 mL to 1.0 mL of material per injection site. The fiducial placement and antibiotics administration are as part of the standard of care. The TraceIT placement is a part of the research. There will be no additional radiation exposure to the patient to place TraceIT.

Standard of care CT planning simulation scans will be performed within 10 days post TraceIT hydrogel placement. These scans will be used to generate the RT treatment plan following Johns Hopkins standard of care to deliver up to 33 Gy in 5 fractions using SBRT within 28 days following TraceIT placement.

The procedure will be determined successful if injected TraceIT is identified between the region of the pancreatic tumor and the duodenum on axial cross-sectional planning CT scan.

Per standard of care, subjects will receive SBRT treatments (up to 33 Gy in 5 fractions) with image-guidance using cone beam CT technology for alignment and will be monitored for radiation toxicity. There will be no additional radiation exposure to the patient to evaluate TraceIT. Following completion of SBRT, patients will proceed with routine standard of care follow-up.

If a patient on study undergoes successful surgical resection, the hydrogel injection sites between pancreas and duodenum will be examined for implant location and to identify any local inflammatory reactions.

b. Study duration and number of study visits required of research participants.

The TraceIT injection will be performed during the endoscopic fiducial placement which is the standard of care. Therefore, there will be no additional study visits needed by patients participating in this study.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

There is no blinding on this trial.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Patients will receive the standard of care treatment and will not have routine therapy stopped.

e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo group in this trial.

f. Definition of treatment failure or participant removal criteria.

Patients will not be enrolled if the routine standard-of-care procedure of fiducial placement cannot be performed.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Patients will continue to receive the standard-of-care for their radiation therapy treatment.

1. Inclusion/Exclusion Criteria

Inclusion criteria:
Subjects must meet all of the following criteria to be eligible for participation in the study:

1. Age ≥18 years old
2. BR/LAPC disease as defined by the NCCN guidelines (Figure 1) as follows confirmed via CT, EUS or other imaging modality (e.g., PET):

Figure 1: NCCN guidelines version 2.2017 for pancreatic adenocarcinoma

CRITERIA DEFINING RESECTABILITY STATUS[1]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

3. SBRT for local therapy of BL/LAPC is indicated and patient has confirmed intent to undergo SBRT at Johns Hopkins.
4. Subjects Screening/Baseline laboratory testing must meet the following laboratory value criteria:
    a. White blood cell count: ≥ 3.0 x 10^9/L

b. Absolute neutrophil count (ANC): ≥ 1.5 x 10^9/L
c. Platelets: ≥ 100 x 10^9/L
d. Total bilirubin: ≤ 2.0 times upper limit of normal (ULN)
e. AST and ALT: ≤ 3.0 times institutional upper normal limit
f. estimated GFR >50
g. INR: < 1.5
Hemoglobin: ≥ 8.0 g/dl

5. Zubrod Performance Status 0-2
6. Subject or authorized representative, has been informed of the nature of the study and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site.

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

1. Previous thoracic radiotherapy
2. Any GI abnormality that would interfere with the ability to access the injection site
3. Duodenal invasion detected on endoscopic ultrasound which would exclude candidacy for SBRT
4. Active gastroduodenal ulcer or watery diarrhea
5. Active bleeding disorder or a clinically significant coagulopathy defined as a PTT>35s or INR>1.4 or platelet count less than 100,000 per mm^3.
6. Active inflammatory or infectious process involving the gastrointestinal tract based on positive diagnosis or suspected diagnosis in the presence of fever>38°C or WBC>12,000/uL.
7. Compromised immune system: WBC<4000/uL or >12,000/uL.
8. History of Chronic Renal Failure.
9. Documented history of uncontrolled diabetes (i.e., symptomatic hyperglycemia that cannot be medically managed, fasting blood glucose level above 300 mg/dL, and/or frequent swings between hyperglycemia and hypoglycemia)
10. Currently enrolled in another investigational drug or device trial that clinically interferes with this study.
11. Unable to comply with the study requirements or follow-up schedule.
12. Any condition or comorbidity that the Investigator believes would interfere with the intent of the study or would make participation not in the best interest of the subject.
13. Women of child bearing potential or sexually active fertile men with partners who are women of child bearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study

2. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

TraceIT Tissue Marker consists of an absorbable polyethylene glycol (PEG) hydrogel with covalently bound iodine (~1%). TraceIT Tissue Marker is indicated for use to radiographically mark soft tissue during a surgical procedure or for future surgical

procedures. TraceIT hydrogel is intended to mark tissue for at least 3 months after injection. TraceIT Tissue Marker is FDA approved for marking anywhere in the body, including the interface between duodenum and pancreas however this has not yet been attempted in clinical practice.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/a

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/a

3. Study Statistics

a. Primary outcome variable:
The success of injecting TraceIT using EUS for guidance will be assessed on post-injection simulation CT scan and determined as successful if TraceIT hydrogel is visible between the pancreatic tumor and duodenum on axial CT.

b. Secondary outcome variables:
   1) Visibility of TraceIT on daily cone beam CT acquired as standard of care for image-guided radiation therapy, defined as no visibility, poor visibility, or acceptable visibility by radiation oncologist.
   2) For patients proceeding to surgical resection, the pathologic specimen will be analyzed grossly and on histopathologic specimen sections for TraceIT placement location and inflammation surrounding placement site.

c. Statistical plan including sample size justification and interim data analysis.

No formal hypothesis or sample size estimation has been established since this is an early feasibility study with an intent to collect information concerning the procedural characteristics and safety for TraceIT administration within the peri-duodenal space. Six (6) subjects should provide sufficient experience to assess the success of the procedure to result in injecting of the hydrogel marker in the desired location.

No interim data analysis is planned

d. Early stopping rules.

If TraceIT placement is unsuccessful as defined by the primary variable outcome in all of the first 3 patients, then the study will be terminated early as this would be an indication that revisions to the procedure would be necessary to facilitate success of the procedure.

4. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
b. Steps taken to minimize the risks.
c. Plan for reporting unanticipated problems or study deviations.
d. Legal risks such as the risks that would be associated with breach of confidentiality.
e. Financial risks to the participants.

a. Medical risks associated with the study procedures can be divided into those associated with the EUS procedure for fiducial/TraceIT hydrogel administration and potential risks associated with the hydrogel.

Potential Risk Associated with the EUS Procedure and Fiducial Placement (STANDARD OF CARE)

Likely	• N/A
Less Likely	• Minor bleeding • Pain • Melena (blood in the stool)
Unlikely	• Fever/Infection • Major bleeding due to damage to blood vessels • Nerve damage • Inflammation of the pancreas • Temporary issues with breathing or infection to the lung as a result of improper swallowing • Side-effects or complications related to anesthesia (temporary low blood pressure and worsening of pre-existing heart or lung problems) • Improper placement or migration of the fiducial implant • Foreign body reaction to fiducial
Rare but serious	• Difficulty breathing or death due to anesthesia • Unintentional perforation of organs not intentionally involved in the procedure • Spread of the cancer to nearby tissues as a result of spillage caused by the procedure • Infection of the blood or other organs • Death

Potential Risk Associated with the TraceIT Hydrogel Material (RESEARCH)

Likely	• N/A
Less Likely	• Minor bleeding • Pain
Unlikely	• Infection of the blood or other organs Clogging nearby blood vessels by the hydrogel material • Inflammation of the pancreas or surrounding organs causing pain or discomfort • Dislodgement of the TraceIT resulting in tracking to another site • Improper placement of TraceIT into neighboring structures (e.g., duodenal wall) • Foreign body reaction to TraceIT • Delay in starting radiation therapy or surgery
Rare but serious	• Potential to worsen local progression of the cancer due to undiagnosed/microscopic invasion into the duodenum

There may be side effects and discomforts that are not yet known.

b. Steps taken to minimize the risks:

The risks associated with EUS procedures and fiducial marker/TraceIT administration will be minimized via selection of experienced investigators who are skilled in EUS/transduodenal fiducial placement procedures. Additionally, participating gastroenterologist has prior experience with placement of the TraceIT hydrogel in human cadavers. Subjects will be selected and enrolled using clearly defined inclusion and exclusion criteria to ensure the best possible treatment outcome. Additionally, subjects will receive full and careful follow-up.

The TraceIT hydrogel, is FDA cleared for use as a Tissue Marker and is specifically indicated for use to radiographically mark soft tissue during a surgical procedure or for future surgical procedures. The risks associated with the TraceIT hydrogel have been minimized by formulating the hydrogel with constituents that have a long history of safe use in implantable medical devices. The study sponsor conducted Biocompatibility testing in compliance with FDA's Good Laboratory Practices regulation and in accordance with ISO 10993 – Biological Evaluation of Medical Devices. Tests were selected and performed according to the type of device, intended use, and degree and duration of tissue contact. The response to TraceIT hydrogel was evaluated in healthy tissues including subcutaneous and intramuscular implant locations. All biocompatibility testing results are consistent with a biocompatible material.

Preclinical studies were also done to evaluate the response to TraceIT hydrogel when placed in the pancreatic parenchyma and duodenal wall. No adverse histologic change or safety concerns were noted.

Appropriate therapeutic intervention following standard medical practices will be used in the event of medical complications.

c. Plan for reporting unanticipated problems or study deviations:

The principal investigator will notify the appropriate regulatory agencies of any serious adverse event due to any cause during the course of this investigation. These include the Johns Hopkins Cancer Center Data and Safety Monitoring Committee, and the Johns Hopkins Medical Institutional Review Board (JHM-IRB) of The Johns Hopkins Medical Institutions. The required reporting time period is 3 days for fatal events, and 10 days for all other events.

d. Legal risks such as the risks that would be associated with breach of confidentiality:

While data will be stored data in securely locked files (computer files will be password protected and any paper records will be stored in the research office at Johns Hopkins under lock and key) in which only the research team has access, there is always the risk that confidentiality will be lost.

e. Financial risks to the participants: None

5. Benefits

a. Description of the probable benefits for the participant and for society:

The tissue interface between pancreas and duodenum can be potentially marked using this radiopaque hydrogel. There is no benefit to the patient from participation in the study. Potential benefits to society include those to future patients undergoing SBRT treatments, who may receive improved treatment as a direct result of the research performed in this study. If this procedure is determined to be feasible in this study, future investigations will be planned to use the hydrogel to increase the distance between the pancreas and duodenum in the region of the pancreatic tumor to serve as a physical spacer so that the duodenum can be displaced away from the higher dose region.

6. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol:

There will be no compensation for participants.

7. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them:

Augmenix will provide the device (TraceIT Tissue Marker) and a separate FNA needle for injecting TraceIT.

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