COMIRB PROPOSAL FOR:

Comparison of traditional back-loaded fiducial needles with preloaded fiducial needles in EUS-guided fiducial marker placement for image-guided radiation therapy in patients with pancreatic cancer: A multicenter randomized controlled trial.

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PROTOCOL SUMMARY:

Title	Comparison of traditional back-loaded fiducial needles with preloaded fiducial needles in EUS-guided fiducial marker placement for image-guided radiation therapy in patients with pancreatic cancer: A multicenter randomized controlled trial.
Design	Multi-center randomized controlled trial
Hypothesis	*1) Use of a 22 G preloaded needle for EUS guided fiducial marker placement in patients with pancreatic cancer will be delivered in at least 60% of the procedure time that it takes for traditional back-loaded 22G needles, improving overall procedure efficiency.* *2) Use of a 22 G preloaded needle for EUS guided fiducial marker placement in patients with pancreatic cancer will maintain comparable technical success and adverse event rates when compared to traditional back-loaded 22G needles.*
Aims	1) To compare procedure time of fiducial marker placement using the 22G preloaded fiducial needle vs back-loading 3 Visicoil fiducial markers using a 22G needle. 2) To compare endpoints of technical success defined as proper placement of three fiducial markers in a pancreatic neoplasm with 22G needle placement of Visicoil fiducial markers and 22G needle preloaded fiducial markers. 3) To compare adverse event rates in 22G needle placement of Visicoil fiducial markers and 22G needle preloaded fiducial markers.
Primary Endpoints	To compare the procedure time for placement of 3 fiducial markers using the 22G preloaded fiducial needle to the traditional back-loaded technique using a 22G needle. To

Secondary Endpoints	1. Ease of fiducial deployment 2. EUS visualization of the delivery system needle 3. EUS visual appearance of fiducials *4.* Visualization as assessed by radiation oncology 5. Rate of fiducial migration 6. Ease of passage of delivery system 7. Inadvertent deployment of fiducial marker 8. Adverse event rates recorded throughout the study period 9. Descriptive comparison of outcomes across sites
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1. INTRODUCTION

1.1. Background and Significance

Pancreatic cancer is the twelfth most common cancer worldwide, with about 45,220 new cases diagnosed in the US in 2013 [1,2]. Given its nonspecific subtle presentation, close to 50% of patients with pancreatic cancer unfortunately have metastatic disease by the time of their presentation, with average 5-year survival of approximately 6% [2].

Neoadjuvant chemoradiation therapy in patients with borderline resectable pancreatic adenocarcinoma has become standard of care and is associated with higher rates of complete resection without microscopic evidence of residual tumor (R0 resection), lower rates of lymph node positivity, and improvement of overall survival in this patient population [3,4]. Radiation therapy to a soft tissue organ such as the pancreas can be difficult, as it is not readily visualized radiographically. In the past, bony structures have been used as surrogate markers for approximation of the pancreas. However, respiratory variation can lead to large differences in tumor location leading to suboptimal radiation delivery and radiation of healthy tissue. Thus, image guided radiation therapy (IGRT) is a commonly implemented modality for delivering high doses of radiation directed at cancer tissue, while reducing collateral damage to adjacent healthy tissue [5,6]. Fiducials, which are inert radiographic markers typically made from gold or carbon, can be placed in and around the tumor to delineate tumor margins to allow for IGRT.

Endoscopic ultrasound (EUS) has been pivotal in accomplishing IGRT by allowing precise contouring and identification of target lesions in the pancreas via placement of fiducials. This has traditionally been accomplished with the use of 19-guage or 22-guage fine needle aspiration (FNA) needles [7-14]. To prepare the needle for fiducial placement, one to two fiducials are manually back-loaded into the tip of the needle after the stylet has been removed. Different size fiducials are used for different gauge needles. In order to hold the fiducials within the needle, sterile lubrication or bone wax can be applied [21]. Once the pancreatic mass has been targeted, fiducial injection can be accomplished via stylet reinsertion or sterile water injection [15,16].

Currently, back-loading the fiducials is the only option for preparing delivery of fiducials via the EUS approach. Difficulties associated with fiducial loading and deployment can increase procedure duration due to cumbersome fiducial back-loading, fiducial misplacement & migration, as well as inability to pass the fidicual marker through the needle due to endoscope angulation.

Multiple observational studies ranging from 7 to 57 patients have sited a technical success rate of 86-100% using 19 and/or 22 gauge needles [8,10-14, 17-19], with average procedure time between 7-12 minutes [12] using the fiducial back-loading technique.

A new mode of fiducial delivery has recently been developed that hopes to circumvent some of the technical issues inherent to traditional fiducial marker loading and deployment. In a feasibility study by Draganov et al, a prototype 22-Gauge EUS needle preloaded with four fiducials were used in a porcine model to test ease of deployment, technical success, accuracy, EUS visualization of the needle, fiducial visualization on EUS as well as fluoroscopy and CT, as well as time for placement and adverse events. Fiducial deployment was successful 95.6% of the time with all 172 fiducial markers deployed on predetermined targets. Using a 5 point Likert scale, needles were deemed easy to pass, relatively easy to

deploy, and easily visualized on EUS, with excellent fluoroscopic and CT visualization. In addition, time for deployment was on average less than 60 seconds.

To date, there is no randomized controlled trials comparing total duration of time needed for placement of fiducials using the traditional back-loading technique of fiducial markers to the new preloaded needles in regards to EUS based fiducial marker placement for IGRT in pancreatic cancer.

1.2 Hypotheses and Endpoints

Hypotheses

1) Use of a 22 G preloaded needle for EUS guided fiducial marker placement in patients with pancreatic cancer will be delivered in at least 60% of the procedure time that it takes for traditional back-loaded 22G needles, improving overall procedure efficiency.

2) Use of a 22 G preloaded needle for EUS guided fiducial marker placement in patients with pancreatic cancer will maintain comparable technical success and adverse event rates when compared to traditional back-loaded 22G needles.

Primary Aims

1) To compare the procedure time of 22G needle placement of three Visicoil fiducial markers and 22G needle preloaded fiducial markers.

Secondary Aims

1) To compare endpoints of technical success defined as proper placement of three fiducial markers in a pancreatic neoplasm in 22G needle placement of Visicoil fiducial markers and 22G needle preloaded fiducial markers.

2) To compare adverse event rates in 22G needle placement of Visicoil fiducial markers and 22G needle preloaded fiducial markers

1.3. Preliminary Studies/Progress Report: To date, there are no preliminary studies of the above proposed study.

2. RESEARCH DESIGN AND METHODOLOGY

A. Description of Population to be Enrolled. (Appendix AP1)

Inclusion Criteria:

- Patients with pathologically confirmed pancreatic cancer referred for IGRT.

Exclusion Criteria:

- Age <18
- Inability to consent
- Known coagulopathy/thrombocytopenia (INR >1.5, platelets <75)
- Patients on antiplatelet/anticoagulant medication that cannot safely be discontinued 5-7 days prior to the procedure
- Gold allergy
- Current infection
- EUS evidence of vessel interfering with path of fiducial marker
- Pregnancy

B. Study Design and Research Methods: Patients with pancreatic cancer referred for fiducial marker placement for IGRT will be eligible for enrollment in the study. Eligibility of study enrollment will be determined prior to the endoscopic evaluation. Subjects will be contacted via telephone before their scheduled visit to inform the subject about the study with a copy of the consent form sent to the subject prior to the EUS procedure (please see Appendix AP2 for copy of phone script). The consent form will then be reviewed in person either in the pre-operative endoscopy unit or in the gastrointestinal clinic if pre-procedure consultation was obtained. Prior to the patients undergoing EUS evaluation, patients will be excluded from the study if they meet any of the exclusion criteria as listed above. All patients who are not excluded from the study as outlined above will be eligible for the study.

Patients without a previous diagnosis of pancreatic cancer but are referred for EUS guided FNA of a suspicious for pancreatic malignancy may also be eligible if a diagnosis of pancreatic cancer can be made by an on-site by a cytopathologist, and the stage dictates that they will need IGRT based on clear discussion with the radiation oncologist, oncologist and surgeon. In this situation fiducial markers may be placed in the same setting.

DESCRIPTION OF THE PROCEDURE (Fig. 1)

Once the patient is consented for the study, randomization will then be performed using stratified (based on location of the tumor – head/neck vs. body/tail) block randomization. The patients will undergo Linear EUS, as previously described by Devila Fejardo et al. and have fiducial marker placement via a traditional 22G back-loaded needle (Visicoil) [22] or the new 22G preloaded needle (PreLoad4). Multiple endpoints will be recorded, including total length of procedure, how many markers are successfully deployed, and technical success (Ease of passage of delivery system, ease of deployment of fiducials, EUS visualization of delivery system needle, EUS visual appearance of fiducials, and time for fiducial placement defined as starting time of removing the needle from its packaging and ending time as removal of needle after final marker deployment). Procedure time will be recorded by a research assistant at each site. Fiducial marker location will be confirmed via fluoroscopy at time of placement and on 4D treatment planning CT ordered by the radiation oncologist for simulation.

Patients will be discharged home after post procedure recovery. Patients will be contacted at home by a research coordinator or endoscopy staff 24-48 hours and 7-10 days after the procedure to document any

immediate and delayed complications. Patients will return for their IGRT visit, and any evidence of fiducial marker migration will be recorded by the radiation oncologist.

For patients who have preceding diagnostic FNA, this will be recorded, with number of passes/aspiration attempts recorded as well.

Endpoints

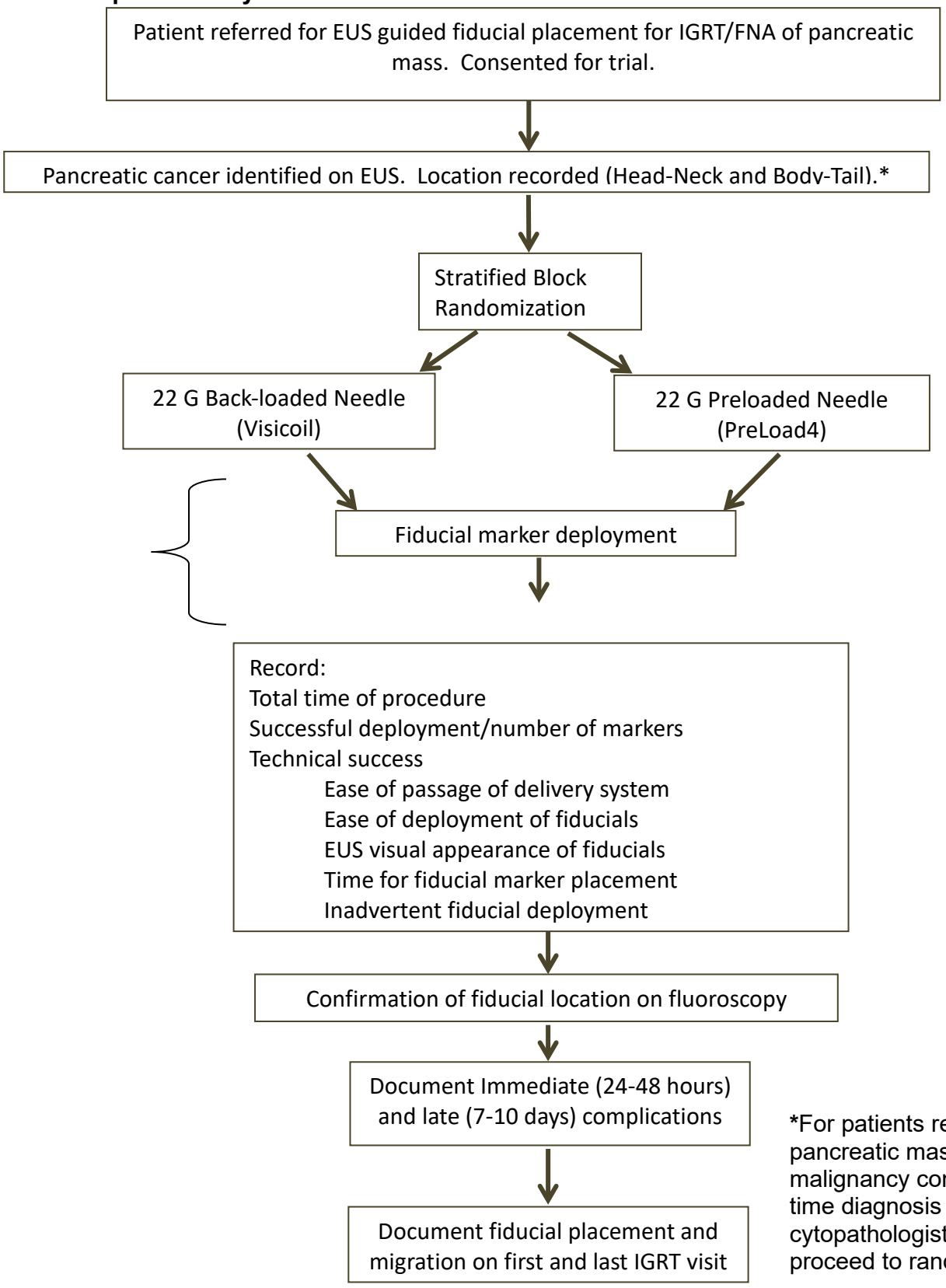
Primary endpoints utilized in this study will be:

- To compare procedure time of 22G needle placement of three Visicoil fiducial markers and 22G needle preloaded fiducial markers.

Secondary endpoints will include:

- Technical success of fiducial marker placement in 22G back-loaded needles and 22G preloaded needles defined by proper placement of three fiducial markers in a pancreatic neoplasm.
- Rate of fiducial migration
- Ease of passage of delivery system
- Ease of fiducial deployment
- EUS visual appearance of fiducials
- Visualization as assessed by radiation oncology
- Inadvertent deployment of fiducials
- Adverse event rates recorded throughout the study period
- Descriptive comparison of outcomes across sites

Figure 1- Proposed Study Methods



*For patients receiving FNA of pancreatic mass, if pancreatic malignancy confirmed on real time diagnosis by cytopathologist, patient will proceed to randomization.

C. Description, Risks, and Justification of Procedures and Data Collection Tools.

Recording of Complications
Complications will be defined as any deviation from the clinical course after the procedure. All adverse event data will be collected during the study period and graded as:

Minor: nausea, vomiting, abdominal pain

Major: perforation, pancreatitis, major bleeding, infection, transfusion secondary to major bleeding, aspiration, arrhythmia, hypotension, death

The investigator at each site will assess each adverse event with respect to severity and relationship to the study interventions. Patients will be contacted at 24-48 hours post-procedure by an experienced GI nurse to assess for complications post procedure (See Appendix AP5/6). All adverse events (whether or not considered device-related) must be reported immediately (within 48 hours) to the study coordinator, confirmed in writing by the Investigator and recorded in the Adverse Events section of the case report form (CRF). Those adverse events that meet the criteria for a Serious Adverse Event will be reported additionally on a Serious Adverse Event CRF. The investigator at each site will make the determination regarding reportability of any AE or SAE to their respective IRB. The University of Colorado will be the central site for all SAE reporting at any site within 24 hours of the occurrence. They will also control randomization, and receive/manage AE/SAE reporting and DSMC. A group of PIs at the cancer center DSMC will review all reports every 6 months. SAE reporting will be reviewed within 24 hours, and all sites and IRBs (per IRB policy) will be informed within a 12-24 hour period of the event and review regarding whether the SAE was thought to be potentially related to the study/new device.

Monitoring and Oversight
The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all unanticipated adverse device effects, serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs, UAPs and reportable AEs including unanticipated adverse device effects are to be reported to the DSMC within 5 business days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, adverse device effects, treatment modifications and treatment responses will be discussed and documented in the meeting's minutes. The sponsor investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The sponsor investigator will also be responsible for including data from all of the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's six month DSM report.
The sponsor investigator will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of adverse device effects to include specific unanticipated adverse device effects, SAEs, UAPs and AEs; any treatment modifications; all protocol deviations; and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this six month report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

Quality Control and Quality Assurance
Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.
Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

Data Collection

- Demographic data collection (Appendix AP3)
  - Age
  - Sex
  - BMI
  - Tumor location and size

- Likert Scale for technical evaluation (Appendix AP4)
- Adverse event collection (immediate/delayed complications- Appendix AP5/6)

At UCD, eligible patients who consent to the study will have their data captured in a password protected database through Redcap. Protected Health Information will be de-identified after extraction, and each subject assigned a unique random number. This database will be stored in a password-protected database, in a password-protected folder on the secure server behind the UCD firewall. The information will, at all times, only be able to be accessed by the primary investigator and co-investigators. All study personnel have completed HIPAA and CITI training in human subjects' research. In order to de-identify patients from their health information a spreadsheet will be created that assigns a number to each patient. The legend will be stored separately in a password-protected folder for patient numbers. Once the data

collection is complete the spreadsheet containing the names and numbers will be destroyed. The de-identified information will be stored on a secure server behind the UCD firewall and will be password protected.

Regarding multicenter data, any institutional data will be shared via encrypted email to the primary site (UCD). At UCD, the Case Report Forms will be reviewed by UCD's investigators and study coordinators periodically throughout the conduct of the trial to review adverse events

D. Potential Scientific Problems.
Factors that could threaten our ability to obtain meaningful generalizable knowledge from this study would be lack of patient followup to reevaluate fiducial marker location. However, as patients are having this procedure performed for cancer therapy, it is unlikely that there will be a large proportion of patients who are lost to followup.

E. Data Analysis Plan. This section should include:

For Quantitative analyses:
i) Statistical Analysis: Categorical variables will be summarized with counts and percentages whereas continuous covariates will be summarized with means and standard deviations (SD). For evaluation of the demographic data a Fisher's exact test or Mann-Whitney U test will be performed as applicable.

ii) Success rates for each of the two arms will be calculated as a proportion of number of successfully deployed fiducial markers over the total number of patients in whom this was attempted within the study population. This will be reported as a percentage. Comparison of successful deployment of fiducial markers by two comparative groups will be performed by Fisher's exact test. Similarly, comparison between the two arms will be performed for technical success, procedure time, adverse event rate, rate of migration, ease of fiducial deployment, and visualization of needle and fiducials via EUS and CT by using Fisher's exact test. When data is ordinal, comparisons will be made using Mann-Whitney U test.

Sample Size:

Sample size calculated for the primary aim showed that in order to detect that the PreLoad4 device can be delivered in at least 60% of the time it takes to deliver a fiducial marker by back-loading, for an 80% power and alpha of 0.05 (two-sided) a minimum of 20 patients will be required in each arm.

Randomization:
Patients will undergo central block randomization (5 blocks of 4 per stratified arm at each center) stratified based on tumor location (head/neck vs. body/tail). This will be performed by a computerized binary number generator at the University of Colorado, who will control randomization for all sites. The arm that the patient will be randomized to will be determined by the above process and with the use of opaque sealed envelopes.

F. Summarize Knowledge to be Gained.

This study offers the potential to illustrate a significant clinical difference in overall reduction in procedure duration between the current type of back-loaded fiducial deployment needle (Visicoil fiducials) and a novel preloaded fiducial deployment needle, thus offering potential for increased efficiency. This information would be useful to both endoscopists and patients to optimize procedure success rate and minimize procedure duration.

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Appendix:

AP 2

Phone Script
HELLO--I am [name] a [role (e.g. medical doctor/clinical investigator/study coordinator) at the University of Colorado Denver. You are currently scheduled to have an endoscopic ultrasound, also known as an "EUS", for fiducuial marker placement performed at the University of Colorado Denver on [date] for marking of your pancreatic cancer prior to undergoing chemoradiation therapy.

I wanted to tell you a little bit about a study to see if you would be interested in participating. Is now a good time? (if 'yes', proceed per below. If 'no', say "Is there a better time that I can call back?" If 'yes', thank the patient and call back repeating the above script. If 'no', thank the patient for their time, and say "That's OK. Thank you for your time. We look forward to seeing you at your scheduled EUS on [date]. Take care." Hang up phone.

Thank you. Before I get started, I want to inform you that agreeing or declining to participate in this study in no way affects the quality of care you will receive nor will it affect your future follow-up with this institution beyond the scope of the study.
We are currently conducting a research project to identify whether the use of one type of fiducial marker needle takes less time to use than the use of the current fiducial marker needle.

The name of the study is entitled "Comparison of traditional back-loaded fiducial needles with preloaded fiducial needles in EUS-guided fiducial marker placement for image-guided radiation therapy in patients with pancreatic cancer: A multicenter randomized controlled trial". Fiducial marker placement performed via EUS is traditionally performed at our institution with a 22G needle. This needle requires manual loading of the fiducial markers one at a time, and can lead to prolonged procedure times. A new type of fiducial marker needle has been designed, which has 4 fiducial markers already preloaded. This allows the endoscopist doing the procedure to place up to 4 fiducial markers without having to remove the endoscope or the fiducial marker placing needle. The hypothesized benefits of using this type of needle is shorter duration of endoscopic procedure. We will also be recording whether use of the preloaded needle is associated with less adverse events.

I would like to send you some more reading material about the study, and also a consent form for you to go over if you are interested in enrolling. On the day of your EUS, your doctor and the study coordinator will discuss the consent form again prior to the procedure if you are interested in participating, and answer any questions you may have. Would you prefer an email or a sent packet for further reading material and the consent form? (If email, ask for email address. If mail, ask for mailing address).

Thank you for your time. We look forward to seeing you at your procedure. Please make sure to bring all your forms and any questions you may have for your treatment team and the research team. Take care. (Hang up phone).
End Phone Script