ENDOSCOPIC ULTRASOUND WITH FINE NEEDLE BIOPSY VERSUS FINE NEEDLE ASPIRATION WITH ON-SITE CYTOPATHOLOGY IN THE EVALUATION OF SOLID PANCREATIC MASSES: RANDOMIZED SINGLE BLINDED CLINICAL TRIAL

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Study Products: None
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Protocol Revision Record

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1. OBJECTIVES

The objective of this single center paired cohort study is to evaluate the diagnostic accuracy of EUS-FNA with ROSE compared to EUS-FNB without ROSE. If EUS-FNB without ROSE is shown to be non-inferior to the current standard of care of EUS-FNA with ROSE in pancreatic lesions, this study has the potential to make EUS-guided tissue acquisition more economical (with elimination for the need for cytopathology staff onsite) as well as provide core histological specimen without sacrificing the overall diagnostic yield.

1.1 STUDY DESIGN

Multicenter, Prospective, Single Blind, Randomized clinical trial.
Patients will be randomly allocated (Using computerized software) with a 1:1 ratio either to the EUS-FNA with ROSE or FNB first group.

1.2 Primary Objectives

To compare the diagnostic accuracy of fine-needle biopsy (FNB) sampling without rapid onsite evaluation (ROSE) with the fine needle aspiration (FNA) with ROSE in pancreatic mass lesions

1.3 Secondary Objectives

To compare:

- Specimen adequacy
- Percentage of histology cores obtained
- Number of passes
- Rate of technical failures
- Adverse events

2. BACKGROUND AND RATIONALE

2.1 Background

Endoscopic ultrasound (EUS) guided fine needle aspiration (EUS-FNA) is the primary technique for tissue acquisition for pancreatic lesions. Despite widespread adoption of the techniques, the diagnostic yield of EUS-FNA for pancreatic lesion is highly variable, with sensitivities ranging from 64-95%, specificities ranging from 75-100% and overall diagnostic accuracy ranging from 78-95%.

Despite its mainstay as the primary technique for tissue acquisition, EUS-FNA has several limitations. The standard EUS-FNA does not routinely provide core biopsy specimen with preserved tissue architecture, which is required for immunohistochemical staining and for definitive diagnosis of conditions, such as lymphoma, gastrointestinal stromal tumors, IgG-4-associated lymphoplasmacytic sclerosing pancreatitis. Furthermore, the diagnostic yield of EUS-FNA is highly dependent on the availability of bedside cytotechnologist or cytopathologist for rapid onsite evaluation (ROSE), which increases the overall cost required to perform EUS-FNA.

Recently, multiple dedicated EUS fine needle biopsy (FNB) needles have been developed to obtain core specimens. Early small studies have shown promising results with these EUS-FNB needles (1-6).

The objective of this single center paired cohort study is to evaluate the diagnostic accuracy of EUS-FNA with ROSE compared to EUS-FNA with ROSE. If EUS-FNB

without ROSE is shown to be non-inferior to the current standard of care of EUS-FNA with ROSE in pancreatic lesions, this study has the potential to make EUS-guided tissue acquisition more economical (with elimination for the need for cytopathology staff onsite) as well as provide core histological specimen without sacrificing the overall diagnostic yield.

2.2 RATIONALE

The rationale for this study is as follows:
The objective of this single center paired cohort study is to evaluate the diagnostic accuracy of EUS-FNA with ROSE compared to EUS-FNA with ROSE. If EUS-FNB without ROSE is shown to be non-inferior to the current standard of care of EUS-FNA with ROSE in pancreatic lesions, this study has the potential to make EUS-guided tissue acquisition more economical (with elimination for the need for cytopathology staff onsite) as well as provide core histological specimen without sacrificing the overall diagnostic yield.

2.3 PARTICIPANT SELECTION

Eligibility Criteria

Inclusion Criteria for Participants

Patient ≥ 18 years of age referred for EUS-guided biopsy for pancreatic mass lesions

Exclusion Criteria

Refusal to consent form
Uncorrectable coagulopathy (INR > 1.5)
Uncorrectable thrombocytopenia (platelet < 50,000)
Uncooperative patients
Pregnant women (women of childbearing age will undergo urine pregnancy testing, which is routine for all endoscopic procedures)
Medically unstable for sedation
Entirely cystic lesions
Lesions inaccessible to EUS

Inclusion of Women, Minorities and Other Underrepresented Populations
This protocol is open to males and females of all races.

3. MULTICENTER GUIDELINES

Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

4. QUALITY ASSURANCE

Authorized representatives of the Coordinating Center may visit participating sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

5. DATA SUBMISSION

Data and/or completed case report forms must be transmitted by fax or e-mail to the Coordinating Center following the completion of each cycle as detailed in Section 16.1.1. Case report forms will be provided to participating sites by the Coordinating Center.

6. ADVERSE EVENT REPORTING

Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a procedure done, whether or not considered causally related to the procedure. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during the procedure or any time after the procedure, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Protocol Chair
The Protocol Chair is ultimately responsible for the required reporting of all adverse events.

Coordinating Center
The Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

Participating Sites
Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within three (3) working days of the participating site Principal Investigator's learning of the event.

Adverse Events which result in no change to protocol, informed consent, or risk to subjects must be reported to the Coordinating Center on a monthly basis.

All SAEs must be collected whether or not they are considered causally related to the investigational procedure. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

7. PROCEDURE PLAN

All EUS/FNB and EUS/FNA will be performed using a linear array echoendoscope by one of seven experienced EUS physicians at JHH. All patients will undergo both EUS/FNB and EUS/FNA. Patients will be randomized to either FNB or FNA first by

means of computer-generated numbers. The endoscopist will not be blinded to the randomization; however, the study pathologist will be blinded to randomization.

EUS/FNB will be performed using similar techniques for tissue acquisition as FNA using 22-g FNB needle (Medtronic SharkCore or Boston Scientific Acquire). Lesions will be identified using EUS and punctured with the 22-g FNB needle (10-15 back and forth movements per needle pass, fanning as appropriate). After the lesion is punctured, the stylet will be removed and 10cc suction will be applied. FNB samples will be placed directly into formalin containers and sent to be processed by surgical pathology.

EUS/FNA with ROSE will be performed using standard techniques via 22-g FNA needle (Cook Medical EchoTip Ultra or Boston Scientific Expect or Medtronic Beacon). Lesions will be identified using EUS and punctured with the FNA needle (10-15 back and forth movements per needle pass, fanning as appropriate). After the lesion is punctured, the stylet will be removed and 10cc suction will be applied. FNA specimens will be processed for ROSE using standard techniques with bedside smear slide evaluation and liquid-based cytology and cell-block preparation.

The first randomization assigned EUS sampling technique will be used until adequate specimen is achieved (up to 3 passes total). After 3 passes, the patient will undergo the other EUS sampling technique until adequate specimen is achieved (up to 3 passes total). If inadequate biopsies are obtained after a total of 6 passes (3 with initial tissue acquisition techniques, 3 with the other technique), the endosonographer will be permitted to utilize any EUS sampling technique preferred to obtain a diagnosis during the same procedure or at a later date.

8. PATIENT FOLLOW-UP

All patients will recover from their procedures according to standard practice. They will remain NPO the night after the procedure. After finishing the procedure, all patients will be carefully monitored per standard protocol in the recovery room and be discharged when fully awake and pain-free. Patients will be contacted by telephone at 24-48 hours to ascertain and document any early adverse events that may have arisen. Long-term clinical follow up will be based on clinical indications.

To determine the safety of procedure, all pre, intra- and immediate post-procedure adverse events will be recorded and rated according to ASGE lexicon (7) for adverse events. Inpatients will be evaluated by study coordinator/PI on a daily basis during their hospitalization. Potential complications will be explained for patients at their discharge time and will be advised to refer whenever they have problems.

a. Study duration and number of study visits required of research participants.
   Study duration: 2 years
   Number of subjects: 132
   Follow-up visits: 0

b. Blinding, including justification for blinding or not blinding the trial, if applicable.
   Due to the nature of study, treatment team will be aware of patient's group and it is not possible to make it double blinded. However, the study pathologist will be blinded to randomization.

c. Justification of why participants will not receive routine care or will have current therapy stopped.
Routine care will be followed

d. Justification for inclusion of a placebo or non-treatment group.
N/A

e. Definition of treatment failure or participant removal criteria.
The first randomization assigned EUS sampling technique will be used until adequate specimen is achieved (up to 3 passes total). After 3 passes, the patient will undergo the other EUS sampling technique until adequate specimen is achieved (up to 3 passes total). If inadequate biopsies are obtained after a total of 6 passes (3 with initial tissue acquisition techniques, 3 with the other technique), the endosongrapher will be permitted to utilize any EUS sampling technique preferred to obtain a diagnosis during the same procedure or at a later date.

f. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
No change in medical care will be expected.

8.1 ANTICIPATED RISKS

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
We do not anticipate major risk or discomfort beyond that associated with the conventional procedure.
1) Perforation: Only physicians specially trained in EUS will be performing these procedures. The exact risk is minimal (<1%).
2) Infection: It is not standard practice to give antibiotics to all patients prophylactically for either percutaneous liver biopsy or EUS-FNA of non-cystic lesions. Therefore, no subjects will receive antibiotics prophylactically for EUS sampling except those patients at risk for infective endocarditis according to American Heart Association guidelines.
3) Bleeding: The exact risk is minimal (1 in 5,000 chance). Doppler examination will be performed under EUS guidance prior to biopsy to ensure that the needle does not traverse a blood vessel. As a precautionary measure, furthermore, all patients will have PTT, PT/INR, hemoglobin, and platelet count checked prior to the procedure. Those below acceptable standards will not be offered inclusion into the study. Frequent vital signs will be measured and recorded. If vital signs are abnormal and prolonged, a repeat CBC and possibly CT scan will be performed after procedure to ensure the absence of internal or external hemorrhage. These measures should ensure any clinically significant hemorrhage is detected and treated in a timely manner.
4) Pancreatitis: Will be detected by the presence of pain with or without nausea and vomiting after pancreatic biopsy. If present, the patient will be hospitalized, kept NPO, and receive IV hydration.

b. Steps taken to minimize the risks.
Adherence to the standard of practice of the Johns Hopkins Hospital Division of Gastroenterology will be kept (as described in part a).

c. Legal risks such as the risks that would be associated with breach of confidentiality. There are no legal risks associated with participation in this study. All measures to protect confidentiality will be taken.

d. Financial risks to the participants.
None.

9. ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after the procedure, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

9.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Prolongs inpatient hospitalization (prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission

9.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.
The description and the grading for the adverse events will be done according to ASGE severity scale.

9.3 Reporting Requirements

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

9.4 Reporting to the Study Team

9.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the procedure, during the procedure, or within 30 days of the procedure must be reported to the Principle Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.
- Progressive disease will be reported within 7 days

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the overall Principal Investigator within one business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within one business day of learning of it and document the time of his or her first awareness of the adverse event.

Report serious adverse events by telephone, email or facsimile to:

Mouen Khashab, MD
Telephone Number: 443-287-1960
Email: mkhasha1@jhmi.edu
Fax: 443-683-8335
Emergency Contact #: 443-509-3388 (mobile)

Within the subsequent 1-2 business day from initial report, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

9.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be not be reported Reporting to the Institutional Review Board (IRB)

Investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Mouen Khashab, MD
Telephone Number: 443-287-1960
Email: mkhasha1@jhmi.edu
Fax: 443-683-8335
Emergency Contact #: 443-509-3388 (mobile)

9.5 Reporting to the Food and Drug Administration (FDA)
N/A

9.6 Reporting to the NIH Office of Biotechnology Activities (OBA)
N/A

9.7 Reporting to the Institutional Biosafety Committee (IBC)
N/A

9.8 Reporting to Hospital Risk Management
Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

9.9 Monitoring of Adverse Events and Period of Observation
All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Overall Investigator or respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

10. DATA AND SAFETY MONITORING

10.1 Data Reporting

Case report forms will be provided for all study mandated data points and should be submitted based on the deadlines detailed in Section 10.1.2

10.1.1 Data Submission

Case report forms should be submitted to the JHBox account

10.2 Auditing/Monitoring

A data safety and monitoring board (DSMB) will be appointed (TBD). The DSMB will be responsible for reviewing all major complications (perforation, hospitalization for > 48 hours, bleeding requiring transfusion, deaths etc). If any serious adverse event is noted during the study then the DSMB will be required to meet.

11. REGULATORY CONSIDERATIONS

11.1 Protocol Review and Amendments

This protocol, the proposed informed consents, all forms of participant information related to the study and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location. This will occur following approval by the Coordinating Center IRB.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The overall Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

11.2 Informed Consent

All participants must be provided a consent form describing each portion of this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

11.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

11.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

11.6 Multi-center Guidelines

- Overall Principal Investigator/Coordinating Center is responsible for distributing all Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

12. STATISTICAL CONSIDERATIONS

Overview: This study is designed as a non-inferiority trial.

Considering a success rate of 85% in the FNA with ROSE group, based published studies, we selected a non-inferiority margin (*∂*) of 10%, in accordance with the USFDA recommendations (8). Based on the following formula (9):

$$n = f(\alpha, \beta) \times [\pi s \times (100 - \pi s) + \pi e \times (100 - \pi e)] / (\pi s - \pi e - d)2$$

where πs and πe are the true percent 'success' in the standard and experimental treatment group respectively, and

$f(\alpha, \beta) = [\Phi\text{-}1(\alpha) + \Phi\text{-}1(\beta)]2$

Φ-1 is the cumulative distribution function of a standardized normal deviate

We calculated that our trial will require enrolling 120 patients for power of 80% and two sided α of 0.05.

Taking into consideration a 10% dropout rate, the total patients to be enrolled=132

Baseline demographics, pre-, intra- and post-intervention data will be prospectively collected on data collection forms which will be maintained in an electronic database system. Results will be reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups will be compared using the Student's t- test or Wilcoxon rank sum test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. To compare

diagnostic accuracy between two EUS sampling techniques, we will use McNemar's test. Statistical significance will be based on two-sided design-based tests evaluated at $\alpha = 0.05$. All statistical analyses will be performed using STATA.

a. Endpoints:
Primary:

Diagnostic accuracy will be defined as (true positive + true negative)/all samples. The final diagnosis will be based on one of the following criteria: (i) surgical pathology specimen from patients who underwent surgical resection; (ii) cytological or histopathological diagnosis of malignancy in patients with unresectable disease with appropriate imaging and clinical course of disease; (iii) cytological and histopathological diagnosis of benign disease with an appropriate clinical course of disease for minimum of 6 months.

Secondary:

1. Specimen adequacy
   This will be defined as the proportion of samples in which a final histopathological diagnosis could be made.

2. Percentage of histology cores obtained
   This will be defined as the proportion of samples in which a visible histology core biopsy was obtained

3. Number of passes
   Number of passes required for diagnosis

4. Rate of technical failures
   Technical failure was defined as the inability to perform the procedure, including the need to change the needle

5. Adverse events
   All pre, intra- and immediate post-procedure adverse events will be recorded and rated according to ASGE lexicon for adverse events.

13. SAFETY MONITORINGN AND STOPPING RULE

The DSMB will perform a blinded analysis after enrolment and initial outpatient follow-up of 50% of the study cohort.

Interim analysis will be performed at 50% recruitment. If a > 20% difference in sensitivity is found between both methods then the study will be terminated early

14. PUBLICATION PLAN

The study team will aim to publish the study results within 24 months of the end of data collection in a peer reviewed journal.

15. References

1.Hucl T, Wee E, Anuradha S et al. Feasibility and efficiency of a new 22G core needle: a prospective comparison study. Endoscopy 2013;45: 792 – 798

2.Vanbiervliet G, Napoleon B, Saint Paul MC et al. Core needle versus standard needle for endoscopic ultrasound-guided biopsy of solid pancreatic masses: a randomized crossover study. Endoscopy 2014; 46: 1063 – 1070

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4.Lin M, Hair CD, Green LK et al. Endoscopic ultrasound-guided fine needle aspiration with on-site cytopathology versus core biopsy: a comparison of both techniques performed at the same endoscopic session. Endosc Int Open 2014; 2: E220 – E223

5.Mavrogenis G, Weynand B, Sibille A et al. 25-gauge histology needle versus 22-gauge cytology needle in endoscopic ultrasonographyguided sampling of pancreatic lesions and lymphadenopathy. Endosc Int Open 2015; 3: E63 – E68

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7.Cotton, Peter B., Glenn M. Eisen, Lars Aabakken, Todd H. Baron, Matt M. Hutter, Brian C. Jacobson, Klaus Mergener et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointestinal endoscopy. 2010; 71.3: 446-454.

8.Blackwelder WC. "Proving the Null Hypothesis" in Clinical Trials.Control. Clin. Trials 1982; 3:345-353.

9.Powers JH, Ross DB, Brittain E, Albrecht R, Goldberger MJ, The United States Food and Drug Administration and Noninferiority Margins in Clinical Trials of Antimicrobial Agents. Clin Infect Dis. 2002; 34: (6):879-881.owers JH, Ross DB, Brittain E, Albrecht R, Goldberger MJ, The United States Food and Drug Administration and Noninferiority Margins in Clinical Trials of Antimicrobial Agents. Clin Infect Dis. 2002; 34: (6):879-881.