



**YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE**

**Application to Involve Human Subjects in Biomedical Research
100 FR1 (2013-1)**

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at <http://www.yale.edu/hrpp/forms-templates/biomedical.html>

Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.

HIC OFFICE USE ONLY

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Percutaneous ethanol ablation for treatment of primary papillary thyroid microcarcinoma			
Principal Investigator: Glenda Callender, MD		Yale Academic Appointment: Assistant Professor, Department of Surgery, Endocrine Surgery	
Department: Surgery, Section of Endocrine Surgery			
Campus Address: 330 Cedar Street FMB 130C New Haven, CT, 06510			
Campus Phone: 203-737-2036	Fax: 203-785-2498	Pager:	E-mail: glenda.callender@yale.edu
Protocol Correspondent Name & Address (if different than PI): Glenda Callender, MD 330 Cedar Street FMB 120 New Haven, CT 06510			
Campus Phone: 203-737-2170	Fax:	E-mail: glenda.callender@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (if applicable): n/a			
Campus Phone:	Fax:	E-mail:	
Business Manager:			
Campus Phone :	Fax :	E-mail	

Faculty Advisor: (required if PI is a student, resident, fellow or other trainee) <input checked="" type="checkbox"/> NA	Yale Academic Appointment:
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Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research

<http://www.yale.edu/hrpp/policies/index.html#COI>

☐ Yes ☒ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☒ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: <http://www.yale.edu/coi/>

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- | | |
|--|---|
| <input type="checkbox"/> Magnetic Resonance Research Center (MR-TAC)
<input type="checkbox"/> Yale Cancer Center/Clinical Trials Office (CTO)
<input checked="" type="checkbox"/> Yale Cancer Center/Smilow
<input checked="" type="checkbox"/> Yale-New Haven Hospital
<input type="checkbox"/> Cancer Data Repository/Tumor Registry
<input checked="" type="checkbox"/> Specify Other Yale Location: | <input type="checkbox"/> Yale University PET Center
<input type="checkbox"/> YCCI/Church Street Research Unit (CSRU)
<input type="checkbox"/> YCCI/Hospital Research Unit (HRU)
<input type="checkbox"/> YCCI/Keck Laboratories
<input type="checkbox"/> Yale-New Haven Hospital—Saint Raphael Campus
Department of Radiology, Section of Interventional Radiology |
|--|---|

b. External Location[s]:

- | | |
|---|---|
| <input type="checkbox"/> APT Foundation, Inc.
<input type="checkbox"/> Connecticut Mental Health Center
<input type="checkbox"/> Clinical Neuroscience Research Unit (CNRU)
<input type="checkbox"/> Other Locations, Specify: | <input type="checkbox"/> Haskins Laboratories
<input type="checkbox"/> John B. Pierce Laboratory, Inc.
<input type="checkbox"/> Veterans Affairs Hospital, West Haven
<input type="checkbox"/> International Research Site
(Specify location(s)): |
|---|---|

c. Additional Required Documents (check all that apply):

- | | |
|---|--|
| <input type="checkbox"/> *YCCI-Scientific and Safety Committee (YCCI-SSC)
<input type="checkbox"/> *Pediatric Protocol Review Committee (PPRC)
<input type="checkbox"/> *YCC Protocol Review Committee (YRC-PRC)
<input type="checkbox"/> *Dept. of Veterans Affairs, West Haven VA HSS
<input type="checkbox"/> *Radioactive Drug Research Committee (RDRC)
<input type="checkbox"/> YNHH-Radiation Safety Committee (YNHH-RSC)
<input type="checkbox"/> Magnetic Resonance Research Center PRC (MRRC-PRC)
<input type="checkbox"/> YSM/YNHH Cancer Data Repository (CaDR)
<input type="checkbox"/> Dept. of Lab Medicine request for services or specimens form
<input type="checkbox"/> Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx | <input type="checkbox"/> N/A
Approval Date:
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***Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.**

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

We plan to recruit patients over 3 years and follow patients for 5 years after their procedures. After initial treatment, patients will be followed every 6 months for the first two years, and then annually for the next 3 years. Interim data analysis will be performed every 6 months.

3. **Research Type/Phase: (Check all that apply)**a. **Study Type**☒ Single Center Study☐ Multi-Center StudyDoes the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐☐ Coordinating Center/Data Management☐ Other:b. **Study Phase** ☐ N/A☒ Pilot☐ Phase I☐ Phase II☐ Phase III☐ Phase IV☐ Other (*Specify*)4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:☒ Clinical Research: Patient-Oriented☒ Clinical Research: Outcomes and Health Services☐ Clinical Research: Epidemiologic and Behavioral☐ Translational Research #1 ("Bench-to-Bedside")☒ Interdisciplinary Research☐ Translational Research #2 ("Bedside-to-Community")☐ Community-Based Research5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒Other (*Specify*)

Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, <http://ycci.yale.edu/researchers/ors/registerstudy.aspx> or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?

Yes ☐ No ☒

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☒ No ☐

If you answered "yes", this study will need to be set up in OnCore Support

<http://medicine.yale.edu/ymg/systems/ppm/index.aspx>

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☒ No ☐ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

- a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes. Dr. Arici, from Interventional Radiology, will perform the interventional radiology procedures. Percutaneous ethanol ablation of a variety of targets is within the scope of interventional radiology practice. Drs. Udelsman, Carling, Callender and Quinn will perform the surgical procedures. Total thyroidectomy with central neck dissection is a routine procedure in an endocrine surgery practice.
- b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? No.
- c. Will a novel approach using existing equipment be applied?
No. Percutaneous ethanol ablation is a well-established method for management of recurrent thyroid cancer nodal metastasis in patients that are not amenable to surgery. It is also a recognized treatment modality in patients with certain benign thyroid nodules.

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. Funding Source: Indicate all of the funding source(s) for this study. Check all boxes that apply.

Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is “pending” at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note “Pending” in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Glenda Callender, MD	Investigator	Department of Surgery	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Robert Udelsman, MD, MBA	Investigator	Department of Surgery Chair of Surgery	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

Tobias Carling, MD, PhD	Investigator	Department of Surgery	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Courtney Quinn, MD, MS	Investigator	Department of Surgery	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Melih Arici, MD	Investigator	Department of Radiology	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Jonathan Kirsch, MD	Investigator	Department of Radiology	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

Elizabeth Holt, MD, PhD	Investigator	Department of Internal Medicine	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Adebowale J. Adeniran, MD	Investigator	Department of Pathology	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input checked="" type="checkbox"/> Other Internal Department Funding	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input checked="" type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

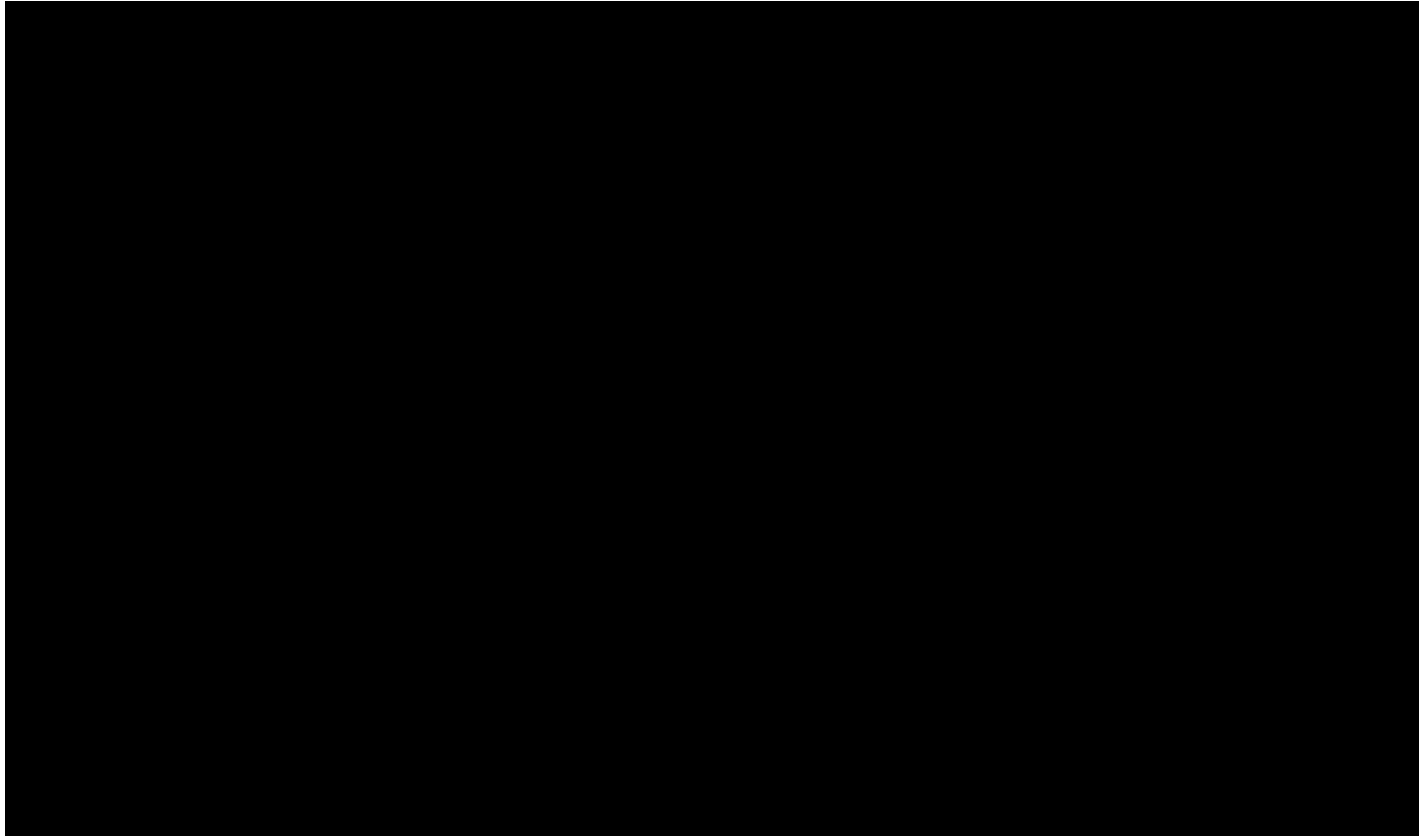
IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Not applicable

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training.



A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR
AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Glenda Callender, MD
PI Name (PRINT) and Signature

Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

Advisor Name (PRINT) and Signature

Date

Signature of PI

Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)

☒ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)

☒ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

Robert Udelsman, MD, MBA

Chair Name (PRINT) and Signature

Date

Department: Department of Surgery

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

YNHH HSPA Name (PRINT) and Signature

Date

For HIC Use Only

Date Approved

Human Investigation Committee Signature

This protocol is valid through _____

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Primary Objectives

The primary objective of the study is to determine the effect of percutaneous ethanol ablation on:

- a) Quality of life, through the SF-36 form
- b) Thyroid-related symptoms, through the Thyroid Symptom Questionnaire (TSQ)
- c) Pain (BPI), voice (VHI) and cosmesis (POSAS)
- d) Reduction and/or elimination of size of primary thyroid microcarcinoma

Secondary Objectives

A secondary objective of the study is to confirm the safety, feasibility, and cost of treating primary papillary thyroid microcarcinoma with percutaneous ethanol ablation.

Another secondary objective of the study is the assessment of oncologic outcomes, including disease-free survival and overall survival (exploratory endpoints).

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Papillary thyroid cancer (PTC) is the most common endocrine malignancy. It is estimated that approximately 60,220 people in the United States will be diagnosed with thyroid cancer in 2013 [1]. The incidence of PTC has risen more rapidly over the past decades than that of any other malignancy (annual incidence rate in 1990: 5.50 per 100,000; in 2010: 13.83 per 100,000) [2, 3]. One reason for the increasing incidence of PTC is the widespread availability and use of high-resolution neck ultrasonography; more PTCs are being diagnosed than previously because patients are undergoing diagnostic studies. However, an actual increase of incidence of PTC has also been documented [3]. The largest contributing factor to the rising incidence of PTC is the diagnosis of papillary thyroid microcarcinomas (PTMC) [4, 5]. The World Health Organization (WHO) defines PTMC as a papillary thyroid cancer measuring 10 mm or less in greatest dimension [6]. Because the prognosis of patients with PTC is generally very favorable, even when the tumor is diagnosed at a larger size, there is considerable debate regarding the optimal management of PTMCs that are often incidentally discovered. Clinicians must balance the overall very low morbidity of PTMCs with the potential morbidity of treatment.

PTMCs are actually very common: autopsy studies have demonstrated that up to 35.6% of people who have died from other causes are found to have occult thyroid cancer at autopsy [7-9]. The vast majority of these cancers remain silent throughout a patient's lifetime. Since PTMCs are indolent tumors that may never progress to a clinically significant degree, clinicians have begun to question whether they can be treated with less than the currently accepted standard of care for localized PTC per American Thyroid Association guidelines: total thyroidectomy (with or without central neck lymph node dissection) or thyroid lobectomy in select situations.

The morbidity of thyroidectomy is largely related to the surgical procedure. Total thyroidectomy is associated with a recurrent laryngeal nerve injury in 1.1-2.1% and permanent hypoparathyroidism with lifelong dependence on calcium in 1.5-2.9% of patients [10-13]. The cognitive and psychological consequences after thyroidectomy can also be a challenge in the post-operative period, despite adequate thyroid hormone replacement [14-19]. Although thyroid hormone replacement is effective in the majority of patients, a substantial proportion remain symptomatic and fail to regain a normal sense of well-being [17]. A case-control study in the United Kingdom showed that post-surgical patients on levothyroxine (T4) replacement displayed significant impairment in their psychological well-being, even with a normal TSH [20]. Furthermore, 34.4% of the patients who underwent a total thyroidectomy and had a recent normal TSH stated that they were dissatisfied with their overall health status [20]. Additional studies have shown that combination replacement with levothyroxine (T4) and liothyronine (T3) therapy did not improve mood and cognitive performance compared to standard T4 monotherapy [21-23].

Some centers currently recommend thyroid lobectomy alone, instead of total thyroidectomy, for patients with small, well-differentiated PTCs. In a retrospective analysis of 889 patients, Nixon and colleagues from Memorial Sloan-Kettering Cancer Center compared the outcomes of patients undergoing thyroid lobectomy versus total thyroidectomy for small, well-differentiated PTCs and found no significant differences between both groups. The extent of surgery had no effect on overall survival or locoregional recurrence rates. Notably, those patients who underwent thyroid lobectomy were not followed with serum thyroglobulin levels or annual ultrasonography, which is routinely done for patients who have undergone total thyroidectomy; therefore, it is possible that some locoregional recurrences were

not detected in the thyroid lobectomy group. The authors concluded that patients with small, well-differentiated PTCs could be safely managed with thyroid lobectomy alone [24].

A center in Japan has gone one step further by managing select patients with PTMC using observation alone. Ito and colleagues hypothesized that most PTMCs do not require immediate surgery, and therefore, they began an observational trial in 1993 [25]. Patients who were diagnosed with PTC measuring less than 1 cm were offered two options: observation without surgery or standard surgical treatment. The observation group was followed to determine whether the tumor size had changed or whether lymph node metastasis had developed. Patients with progressive disease subsequently underwent standard surgical therapy. The authors compared the outcomes of 340 patients who underwent observation and 1055 patients who underwent immediate surgery. In the observation group, 109 patients eventually underwent surgical treatment, but 231 patients (68%) continue to be observed after more than 20 years of follow-up. The authors concluded that observation is safe in select patients with PTMCs in the absence of unfavorable tumor features, and in the event of disease progression, patients can undergo surgery without a clinically significant difference in outcome.

Although thyroid lobectomy and observation are less invasive than total thyroidectomy, thyroid lobectomy is still associated with risks, and many patients and healthcare providers are uncomfortable with simple observation when cancer is involved. Therefore, neither thyroid lobectomy nor observation seems to strike the ideal balance in the treatment of PTMC. Percutaneous ablative therapy may accomplish this goal.

Percutaneous ethanol ablation has not previously been used as a treatment for primary PTC, but has been shown to be an effective treatment for recurrent PTC in patients who are not candidates for surgery for various reasons (medical comorbidity, unacceptably high risk of complications due to extensive prior surgery or radiation) [26-29]. Percutaneous ethanol ablation has successfully treated known metastatic lymphadenopathy from PTC as measured by decreased tumor volume and blood flow to the nodal metastases [27].

Heilo and colleagues from the Mayo Clinic evaluated the efficacy of percutaneous ethanol ablation in the treatment of patients with PTC metastatic to a limited number of cervical lymph nodes. Their retrospective review included 63 patients with PTC and 109

cervical lymph nodes with metastasis. Mean observation time was 38.4 months (range 3 to 72 months). A total of 101 of the 109 (93%) metastatic lymph nodes responded to percutaneous ethanol ablation, 92 with a complete response and 9 with a partial response. Two lymph nodes did not respond, and four lymph nodes demonstrated progressive disease. Two lymph nodes previously considered successfully treated showed evidence of recurrent malignancy during follow-up [28].

Percutaneous ethanol ablation has also been performed for benign thyroid disease, such as focal and diffuse autonomy of the thyroid, benign nodules, and cystic lesions. This procedure has not gained widespread acceptance, although there is accumulating evidence of the efficacy and safety of this therapeutic tool. [30-32]. Livraghi and colleagues first proposed percutaneous ethanol ablation in 1990 as an alternative novel therapeutic tool for the treatment of autonomously functioning thyroid nodules (AFTN) [31]. Other centers subsequently published small series and case reports describing successful percutaneous ethanol ablation of amiodarone-induced thyrotoxicosis, AFTN in pregnancy, and large AFTNs (nodule volume > 40 mL) [33] [34] [35-37]. Importantly, when surgery is subsequently necessary in patients who have undergone percutaneous ethanol ablation of benign thyroid nodules, surgical resection remains feasible and does not appear to carry increased risk due to scarring [38].

Percutaneous ethanol ablation of benign thyroid disease is generally well tolerated. A very common adverse effect is transient pain at the injection site. Additional transient adverse effects include dysphonia in 3.9%, worsening of thyrotoxicosis in 1.1%, self-limited fever in 5% and hematoma in 1.8% [37, 39]. There exists a single case report from Germany describing severe ethyl toxic necrosis of the larynx and overlying skin in a patient who previously underwent ethanol instillation as a treatment for an AFTN. The patient almost immediately developed aphonia and severe odynophagia, and was admitted to the hospital for eleven days. Topical ointment, intravenous and inhaled steroids, and intravenous antibiotics were administered. The patient did not require invasive therapy in the acute setting, and the voice returned to near normal within 2 weeks. Follow-up ultrasound several months after the procedure demonstrated that the target nodule was essentially unchanged, suggesting that the majority of the instilled ethanol was actually injected into the subcutaneous tissue and larynx instead of into the thyroid. Six months after the initial procedure, follow-up

laryngoscopy demonstrated that a right false vocal fold cyst had developed; this was successfully resected endoscopically ten months after the initial procedure [30].

In summary, the rising incidence of PTMC in asymptomatic patients is real, and there is no indication that this trend is beginning to plateau. Standard surgical therapy, even if limited to thyroid lobectomy, may be considered over-treatment of patients with PTMCs. Although observation alone may be sufficient for some patients, it may be preferable to treat the cancer in lieu of observation. A minimally-invasive technique such as percutaneous ethanol ablation may strike a balance between the low overall risk of PTMC and the minimal morbidity of this treatment. Percutaneous ethanol ablation has not been reported to have been used for primary thyroid cancers, but has been used to successfully treat benign thyroid disease as well as PTC recurrences and metastatic lymph nodes. Percutaneous ethanol ablation may prove to be a safe alternative to either surgical intervention or observation for patients with PTMC.

References:

1. Howlader, N.N., AM, SEER cancer Statistics Review. 2013.
2. Pacini, F., Management of papillary thyroid microcarcinoma: primum non nocere! J Clin Endocrinol Metab, 2013. 98(4): p. 1391-3.
3. Ito, Y. and A. Miyauchi, A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. Nat Clin Pract Endocrinol Metab, 2007. 3(3): p. 240-8.
4. Enewold, L., et al., Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev, 2009. 18(3): p. 784-91.
5. Chen, A.Y., A. Jemal, and E.M. Ward, Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer, 2009. 115(16): p. 3801-7.
6. Lloyd R, D.L.R., Heitz P et al World Health Organization Classification of Tumours: pathology and genetics of tumours of the endocrine organs. International Agency for Research on Cancer (IARC) Press, Lyon. 2004.
7. Fukunaga, F.H. and R. Yatani, Geographic pathology of occult thyroid carcinomas. Cancer, 1975. 36(3): p. 1095-9.
8. Harach, H.R., K.O. Franssila, and V.M. Wasenius, Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. Cancer, 1985. 56(3): p. 531-8.
9. Thorvaldsson, S.E., et al., Latent thyroid carcinoma in Iceland at autopsy. Pathol Res Pract, 1992. 188(6): p. 747-50.
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3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

The purpose of this study is to evaluate a new treatment option for the management of primary papillary thyroid microcarcinoma (PTMC). Patients referred to Yale Endocrine Surgery for management of cytology-proven PTMC (PTC measuring 1 cm or less in diameter) will be offered inclusion into the study. (See page 24 for specific exclusion criteria.) After enrollment, patients will be assigned to percutaneous ethanol ablation (PEA) of the primary PTMC. Importantly, PEA will not be offered to patients outside of inclusion in the study.

After informed consent is obtained, baseline evaluation includes the following tests:

- a) Baseline ultrasound assessment to confirm size and location of PTMC
- b) Baseline laryngoscopy before initiation of treatment
- c) Baseline quality of life assessment ("SF-36"; Appendix 1)
- d) Baseline pain assessment ("Brief Pain Inventory", BPI; Appendix 2)
- e) Baseline voice assessment ("Voice Handicap Index", VHI; Appendix 3)
- f) Baseline symptom assessment ("Thyroid Symptom Questionnaire", TSQ; Appendix 4)

The SF-36 is a set of easily-administered quality-of-life measures and is a validated tool to evaluate patient quality of life [40-42]. The VHI is an established tool used to assess voice after an intervention [43-45]. The BPI is a simple, well-accepted instrument for the objective assessment of pain [46-48]. The TSQ is a 12-item based questionnaire assessing specific thyroid related symptoms.

Therapy

a. Percutaneous ethanol ablation

Patients in the PEA group will constitute the sole treatment group of the study. These patients will be scheduled for an outpatient procedure with Dr. Melih Arici from Interventional Radiology. The volume of 99% ethanol to be injected is calculated using a standardized formula ($\text{Ethanol Volume} = \text{length} \times \text{width} \times \text{height} \times \pi / 6$) and instilled with a 3-4 cm long 22-25-gauge needle under ultrasound-guidance after administration of local anesthesia. If the patient cannot tolerate the procedure despite adequate local anesthesia, they will be offered conscious sedation. Conscious sedation is a combination of medicines to help you relax (a sedative) and to block pain (an anesthetic) during a medical. You will probably stay awake but may not be able to speak.

It is usually safe, however, overmedication could result in respiratory depression. The patient will be monitored carefully during the entire procedure and the appropriate equipment will be employed if needed.

The procedure itself usually takes only about 60-90 minutes and the patient will be observed for 2-3 hours in the hospital before discharge home.

All patients will receive a phone call to their home 48 hours after the PEA procedure and will be assessed for pain level and voice quality (BPI and VHI).

Every patient will be scheduled for a post-procedure visit in the endocrine surgery clinic approximately 7 – 14 days after their procedure. The post-procedure clinic visit will include the following assessments:

- a) Evaluation of the wound after the intervention
- b) Follow-up ultrasound assessment
- c) Follow-up laryngoscopy after treatment
- d) Follow-up quality of life assessment (SF-36)
- e) Follow-up pain assessment (BPI)
- f) Follow-up voice assessment (VHI)
- g) Follow-up symptom assessment (TSQ)
- h) Cosmesis assessment ("Patient and Observer Scar Assessment Scale", POSAS; Appendix 5)

During this clinic visit, a thorough evaluation will be performed of the patient's injection site. An endocrine surgeon will evaluate the injection site during this visit using POSAS, a validated tool for the evaluation of surgical scars [49-52].

Formal cancer restaging for patients will take place every 6 months for the first two years and then annually for the following 3 years. These clinic visits will include a thorough clinical examination, surveillance ultrasonography of the neck (thyroid bed, central and bilateral lateral neck lymph nodes), laboratory tests (TSH, free T4, Tg, TgAb), quality of life assessment, pain assessment, voice assessment, symptom assessment, and cosmesis assessment.

Disease progression based on radiographic images utilizing the RECIST (Response Evaluation Criteria in Solid Tumors) criteria will result in recommendation to patient for total thyroidectomy. Disease progression is defined by $\geq 20\%$ increase of diameter of any residual visible tumor, a $\geq 5\text{mm}$ absolute increase in size of any residual visible tumor, appearance of new metastasis to central or lateral neck lymph nodes by ultrasound and FNA biopsy, or appearance of new distant metastases [53].

Duration of Project and Follow Up

Patients will be recruited over 3 years and followed for 5 years after the procedure. After initial treatment, patients will be followed every 6 months for the first two years, and then annually for the next 3 years. The data will be analyzed on an annual basis.

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4. Genetic Testing N/A ☒

A. Describe

- i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
- ii. the plan for the collection of material or the conditions under which material will be received
- iii. the types of information about the donor/individual contributors that will be entered into a database
- iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?

C. Is widespread sharing of materials planned?

D. When and under what conditions will materials be stripped of all identifiers?

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?

- i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy

G. Describe the methods for the security of storage and sharing of materials

5. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

The Yale Endocrine Surgery program is the largest provider of surgical care for patients with endocrine disorders in the State of Connecticut. Yale Endocrine Surgery serves as both a

primary treatment site and a tertiary referral center for patients from surrounding counties and neighboring states. Statistics describing the demographic distribution of the population seeking care by endocrine surgeons are incomplete at this time, but as we begin enrollment into our studies, we anticipate that we will be able to compile and update descriptive statistics on the demographics of our population. In this capacity, we will be able to compare the demographic distribution of patients enrolled to the county-level statistics.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

None. All patients referred to Yale Endocrine Surgery who meet inclusion criteria and do not meet exclusion criteria will be offered enrollment into the study. It is possible that the study will eventually include patients who also incidentally belong to one of the following classifications, but no attempt will be made to specifically enroll patients from a particular vulnerable population.

- | | | |
|--|--|--|
| <input type="checkbox"/> Children | <input type="checkbox"/> Healthy | <input type="checkbox"/> Fetal material, placenta, or dead fetus |
| <input type="checkbox"/> Non-English Speaking | <input type="checkbox"/> Prisoners | <input type="checkbox"/> Economically disadvantaged persons |
| <input type="checkbox"/> Decisionally Impaired | <input type="checkbox"/> Employees | <input type="checkbox"/> Pregnant women and/or fetuses |
| <input type="checkbox"/> Yale Students | <input type="checkbox"/> Females of childbearing potential | |

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

1. Age 18 years and older
2. Diagnosis: single, cytology-proven papillary thyroid carcinoma measuring 1 cm or less in diameter (microcarcinoma, T1a), without visible extrathyroidal extension, and with negative central and lateral neck lymph nodes by ultrasound

Exclusion criteria:

1. Patient refusal to participate
2. History of prior thyroid or parathyroid surgery
3. History of prior recurrent laryngeal nerve injury
4. Inability to make decisions or comply with follow up
5. Co-existing indication for thyroidectomy
6. Aggressive cytologic or molecular features
7. Multifocal papillary thyroid carcinoma
8. Pregnant or breast-feeding
9. Anatomically unfavorable location of the tumor (proximity to recurrent laryngeal nerve or trachea)

10. Documented or suspected distant metastasis
11. History of prior radiation to neck or face
12. Family history of pathological thyroid cancer

Points of Clarification

1. Presence of BRAF V600E mutation is not automatic exclusion
2. Co-existing benign thyroid condition is not automatic exclusion
3. Family history of incidentally identified, asymptomatic, papillary microcarcinoma is not automatic exclusion

8. How will **eligibility** be determined, and by whom?

All patients referred to Yale Endocrine Surgery who meet eligibility criteria and do not meet exclusion criteria will be offered enrollment in the study. The attending endocrine surgeon (Drs. Udelsman, Carling, Callender or Quinn) will determine eligibility at the time of the initial clinic visit.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

According to the literature, percutaneous ethanol ablation of a thyroid lesion is generally well tolerated. A common adverse effect is transient pain at the injection site. Additional transient adverse effects include dysphonia in 3.9%, worsening of thyrotoxicosis in 1.1%, self-limited fever in 5% and hematoma in 1.8% [37, 39]. There exists a single case report from Germany describing severe ethyl toxic necrosis of the larynx and overlying skin in a patient who previously underwent ethanol instillation as a treatment for an autonomously functioning thyroid nodule (AFTN). The patient almost immediately developed aphonia and severe odynophagia, and was admitted to the hospital for eleven days. Topical ointment, intravenous and inhaled steroids, and intravenous antibiotics were administered. The patient did not require invasive therapy in the acute setting, and the voice returned to near normal within 2 weeks. Follow-up ultrasound several months after the procedure demonstrated that the target nodule was essentially unchanged, suggesting that the majority of the instilled ethanol was actually injected into the subcutaneous tissue and larynx instead of into the thyroid. Six months after the initial procedure, follow-up laryngoscopy demonstrated that a right false vocal fold cyst had developed; this was successfully resected endoscopically ten months after the initial procedure [30]. Finally, there is a risk of recurrence or progression of the PTMC. If follow-up ultrasound examinations demonstrate recurrence or progression, patients will be offered thyroidectomy as standard-of-care treatment.

There exist non-physical risks with this type of study. One of these is the potential loss of privacy. In order to ensure confidentiality within the study, patients are assigned unique identifiers. All electronic data files for this study will either be stored as password-protected files on the secure Yale ITS server or in the Yale Clinical Trials Management System

(OnCore). OnCore is accessed through Yale-networked computers and access is granted only to appropriate study personnel. Any files that contain protected health information will be maintained separately from the rest of other data files and only on the secure server or in OnCore. Ability to access the files is restricted to study investigators.

References:

1. Christou, N. and M. Mathonnet, Complications after total thyroidectomy. J Visc Surg, 2013.
2. Thomusch, O., et al., Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. World J Surg, 2000. 24(11): p. 1335-41.
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4. Bellantone, R., et al., Total thyroidectomy for management of benign thyroid disease: review of 526 cases. World J Surg, 2002. 26(12): p. 1468-71.
5. Ferrari, C., E. Reschini, and A. Paracchi, Treatment of the autonomous thyroid nodule: a review. Eur J Endocrinol, 1996. 135(4): p. 383-90.
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7. Mauz, P.S., et al., Complications of ultrasound guided percutaneous ethanol injection therapy of the thyroid and parathyroid glands. Ultraschall Med, 2005. 26(2): p. 142-5.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

In order to minimize risk in the treatment group, i.e. the percutaneous ethanol ablation group, all procedures will be performed by a single interventional radiologist, Dr. Melih Arici, who has prior experience with ethanol ablation and extensive experience with percutaneous procedures.

In order to minimize risk of surgery in patients with disease progression after percutaneous ethanol ablation, a high-volume surgeon from Yale Endocrine Surgery will perform all surgical procedures. Thyroidectomy performed by a high-volume surgeon is associated with better outcomes.

In order to maintain confidentiality, data will be coded and only authorized personnel will have access to this information.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

- a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
Greater than minimal risk
- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
N/A. No children will be participating in this study.

The principal investigator or the Human Investigation Committee (HIC) have the authority to stop or suspend the study or require modifications. This protocol presents greater than minimal risks to the subjects. The offered treatment modalities are considered routine in the course of standard clinical care. Although highly unexpected, serious unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 5 days to the HIC (using the appropriate forms on the website) and the Department of Surgery. The principal investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of the research project during regular study meetings and e-mails when urgent, as these events are reviewed by the principal investigator.

The principal investigator will assess study data on a continuing basis. All individuals will be recruited without bias for ethnicity, race, gender or age. Any identifying information will remain confidential. All electronic data files for this study will either be stored as password-protected files on an encrypted, password-protected computer, in the Yale Clinical Trials Management System (OnCore), or on the secure Yale ITS server. OnCore is accessed through Yale-networked computers and access is granted only to appropriate study personnel. Any files that contain protected health information will be maintained separately from the rest of other data files and only on the secure server or in OnCore. The research team will only give this coded information to others to carry out this research study. We do not anticipate any adverse events with regard to safety. Should anything unexpected occur, we will comply with current HIC reporting requirements. We will complete annual reports to the HIC about study progress.

There is a theoretical risk that percutaneous ethanol ablation may not work and the microcarcinoma may progress.

Since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods, we provide a plan for monitoring the data and safety of the proposed study as follows:

The principal investigator will report the following types of events to the IRB:

- a) Adverse events that are serious or life-threatening
 - a. Unanticipated (or anticipated but occurring with a greater frequency than expected)
 - b. Possibly, probably, or definitely related to the drug/device/intervention; and
- b) Other unanticipated problems involving risks to subjects or others.

Moderate Risk DSMP**1. Personnel responsible for the safety review and its frequency:**

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons:

(choose those that apply)

1. We do not view the risks associated with the percutaneous ethanol injection for PTMC as minimal.
2. Given the now established safety and validity of percutaneous ethanol ablation in the current literature for benign thyroid lesions, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Dr. Glenda Callender according to the following categories:

- a.) Definite: Adverse event is clearly related to investigational procedure(s)/agent(s).
- b.) Probably: Adverse event is likely related to investigational procedure(s)/agent(s).
- c.) Possible: Adverse event may be related to investigational procedure(s)/agent(s).
- d.) Unlikely: Adverse event is likely not to be related to the investigational procedure(s)/agent(s).
- e.) Unrelated: Adverse event is clearly not related to investigational procedure(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:**Serious Adverse Events:**

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. Is life-threatening OR
2. results in in-patient hospitalization or prolongation of existing hospitalization OR

3. Results in persistent or significant disability or incapacity OR
4. results in a congenital anomaly or birth defect OR
5. Results in death OR
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
7. Adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

All Co-Investigators listed on the protocol.
Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
National Institutes of Health
Food and Drug Administration (Physician-Sponsored IND # _____)
Medical Research Foundation (Grant _____)

The principal investigator Dr. Glenda Callender will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

12. Statistical Considerations: Describe the statistical analyses that support the study design.

The Yale Center for Analytical Science was consulted to assist with statistics and will contribute to this study (Fangyong Li, MPH).

The primary aim of this study is to evaluate the effect of PEA on patient-related outcomes. The primary endpoint will be symptom assessment using the Thyroid Symptom Questionnaire (TSQ)

at the patient's 12-month visit. In addition, quality of life assessment (QOL) using SF36, pain assessment using BPI and voice assessment using VHI will be performed.

A secondary aim of this study is to evaluate the safety and feasibility of using PEA to treat primary PTMC. Consequently, we will monitor potential adverse events at the first clinic visit, including dysphonia, thyrotoxicosis, fever, hematoma, and skin necrosis. By analyzing these variables, the study team hopes to evaluate the safety and feasibility of this treatment modality.

Given the excellent prognosis of patients with PTMC (100% 5-yr survival), we do not expect any death events, progression, and recurrence related to the procedure in a feasible follow-up period. Therefore, the oncologic outcomes, including disease-free interval and overall survival (up to 5-yr follow-up), will be collected but will only serve as exploratory endpoints, evaluated at 5-year follow-up.

Descriptive statistics, including mean and standard deviation for continuous variables and frequency and percentage for categorical variables, will be used to summarize patient characteristics. The adverse events will be investigated in order to assess the safety of the new procedure. The primary analysis will be comparing the pre-operative TSQ score to the post-operative TSQ score. Using standard deviation of 6.38 as reported in the DEPTH (DEPressure and THyroid) study [54], the sample size of 16 achieves 90% power to detect a difference of 5.65 between pre- and post-PEA with a type I error of 0.05 using a paired t-test. This effect size is equivalent to one-level difference in responses for 6 items (such as from "Much worse" to "Little worse"), or three-level differences in responses for 2 items (such as from "Much worse" to "Much better"), etc.

Similarly, a power analysis was performed for QOL. The Physical Component and Mental Component of SF-36 will be used. The standard deviations, 9.7 and 11.0 for patients with thyroid disease, respectively, were used to estimate statistical power. The sample size of 16 in each group achieves 90% power to detect a difference of 8.6 in SF-36 Physical Component summary score and 9.8 in Mental Component summary score between the PEA and thyroidectomy groups with a type I error of 0.05.

Time and motion studies and a cost analysis will also be conducted.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. Identification of Drug, Biologic or Radiotracer: What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Percutaneous ethanol injection is approved by the FDA and is a well-accepted treatment modality for the management of metastatic thyroid carcinoma to the neck, as well as benign thyroid cysts or autonomic nodules [27, 28, 30-32, 36, 55]. The injection of ethanol has been also used successfully in the cure of liver tumors [56-61].

1. Hay, I.D. and J.W. Charboneau, The coming of age of ultrasound-guided percutaneous ethanol ablation of selected neck nodal metastases in well-differentiated thyroid carcinoma. *J Clin Endocrinol Metab*, 2011. 96(9): p. 2717-20.
2. Heilo, A., et al., Efficacy of ultrasound-guided percutaneous ethanol injection treatment in patients with a limited number of metastatic cervical lymph nodes from papillary thyroid carcinoma. *J Clin Endocrinol Metab*, 2011. 96(9): p. 2750-5.
3. Mauz, P.S., et al., Complications of ultrasound guided percutaneous ethanol injection therapy of the thyroid and parathyroid glands. *Ultraschall Med*, 2005. 26(2): p. 142-5.
4. Livraghi, T., et al., Treatment of autonomous thyroid nodules with percutaneous ethanol injection: preliminary results. Work in progress. *Radiology*, 1990. 175(3): p. 827-9.
5. Lippi, F., et al., Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. *J Clin Endocrinol Metab*, 1996. 81(9): p. 3261-4.
6. Bennedbaek, F.N., S. Karstrup, and L. Hegedus, Percutaneous ethanol injection therapy in the treatment of thyroid and parathyroid diseases. *Eur J Endocrinol*, 1997. 136(3): p. 240-50.
7. Verde, G., et al., Ultrasound guided percutaneous ethanol injection in the treatment of cystic thyroid nodules. *Clin Endocrinol (Oxf)*, 1994. 41(6): p. 719-24.
8. Shiina, S., et al., Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR Am J Roentgenol*, 1987. 149(5): p. 949-52.
9. Ebara, M., et al., Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. *J Gastroenterol Hepatol*, 1990. 5(6): p. 616-26.
10. Shiina, S., et al., A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology*, 2005. 129(1): p. 122-30.
11. Livraghi, T., et al., Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology*, 1999. 210(3): p. 655-61.
12. Castells, A., et al., Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology*, 1993. 18(5): p. 1121-6.

13. Ohnishi, K., et al., Prospective randomized controlled trial comparing percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma. *Hepatology*, 1998. 27(1): p. 67-72.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information: NOT APPLICABLE

- a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
- b. Who holds the IND?
- c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____

Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate) _____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)

Go to <http://rsc.med.yale.edu/login.asp?url=myApps.asp>. When you have logged in, complete the application and attach a copy to this submission. NOT APPLICABLE

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories*): NOT APPLICABLE

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Percutaneous ethanol injection is approved by the FDA and is a well-accepted treatment modality for the management of metastatic thyroid cancer in the neck, as well as benign thyroid cysts or nodules. Ethanol (99%) is injected through the skin into the thyroid tissue under ultrasound guidance and it has been reported in the literature that 0.1 to 1.0 cc ethanol is sufficient for the successful ablation of a PTMC [27, 28, 30-32, 36, 55]. The actual volume of ethanol to be instilled into a particular tumor will be calculated through a standard formula (Ethanol Volume= length \times width \times height \times π / 6). Based on our experience and the existing literature, we believe that most PTMCs will be completely treated with a single procedure, given the small size of the tumors (≤ 1 cm). However, if follow-up ultrasound demonstrates residual tumor after initial treatment, re-treatment will be permitted.

1. Howlader, N.N., AM, *SEER cancer Statistics Review*. 2013.
2. Pacini, F., *Management of papillary thyroid microcarcinoma: primum non nocere!* J Clin Endocrinol Metab, 2013. **98**(4): p. 1391-3.
3. Ito, Y. and A. Miyauchi, *A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid*. Nat Clin Pract Endocrinol Metab, 2007. **3**(3): p. 240-8.
4. Enewold, L., et al., *Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005*. Cancer Epidemiol Biomarkers Prev, 2009. **18**(3): p. 784-91.

5. Chen, A.Y., A. Jemal, and E.M. Ward, *Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005*. Cancer, 2009. **115**(16): p. 3801-7.
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7. Fukunaga, F.H. and R. Yatani, *Geographic pathology of occult thyroid carcinomas*. Cancer, 1975. **36**(3): p. 1095-9.
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9. Thorvaldsson, S.E., et al., *Latent thyroid carcinoma in Iceland at autopsy*. Pathol Res Pract, 1992. **188**(6): p. 747-50.
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15. Bunevicius, R., et al., *Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism*. N Engl J Med, 1999. **340**(6): p. 424-9.
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19. Siegmund, W., et al., *Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism*. Clin Endocrinol (Oxf), 2004. **60**(6): p. 750-7.
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25. Ito, Y., et al., *An observational trial for papillary thyroid microcarcinoma in Japanese patients.* World J Surg, 2010. **34**(1): p. 28-35.
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27. Hay, I.D. and J.W. Charboneau, *The coming of age of ultrasound-guided percutaneous ethanol ablation of selected neck nodal metastases in well-differentiated thyroid carcinoma.* J Clin Endocrinol Metab, 2011. **96**(9): p. 2717-20.
28. Heilo, A., et al., *Efficacy of ultrasound-guided percutaneous ethanol injection treatment in patients with a limited number of metastatic cervical lymph nodes from papillary thyroid carcinoma.* J Clin Endocrinol Metab, 2011. **96**(9): p. 2750-5.
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30. Mauz, P.S., et al., *Complications of ultrasound guided percutaneous ethanol injection therapy of the thyroid and parathyroid glands.* Ultraschall Med, 2005. **26**(2): p. 142-5.
31. Livraghi, T., et al., *Treatment of autonomous thyroid nodules with percutaneous ethanol injection: preliminary results. Work in progress.* Radiology, 1990. **175**(3): p. 827-9.
32. Bennedbaek, F.N., S. Karstrup, and L. Hegedus, *Percutaneous ethanol injection therapy in the treatment of thyroid and parathyroid diseases.* Eur J Endocrinol, 1997. **136**(3): p. 240-50.
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36. Lippi, F., et al., *Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group.* J Clin Endocrinol Metab, 1996. **81**(9): p. 3261-4.
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56. Shiina, S., et al., *Percutaneous ethanol injection in the treatment of liver neoplasms*. AJR Am J Roentgenol, 1987. **149**(5): p. 949-52.
57. Ebara, M., et al., *Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients*. J Gastroenterol Hepatol, 1990. **5**(6): p. 616-26.
58. Shiina, S., et al., *A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma*. Gastroenterology, 2005. **129**(1): p. 122-30.
59. Livraghi, T., et al., *Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection*. Radiology, 1999. **210**(3): p. 655-61.
60. Castells, A., et al., *Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection*. Hepatology, 1993. **18**(5): p. 1121-6.

61. Ohnishi, K., et al., *Prospective randomized controlled trial comparing percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma*. Hepatology, 1998. **27**(1): p. 67-72.

3. **Source:** a) Identify the source of the drug or biologic to be used.
Percutaneous ethanol ablation is a standard procedure performed in the section of Interventional Radiology and the department has sufficient amounts of ethanol stocked in adequate storage.

b) Is the drug provided free of charge to subjects? ☐ Yes ☒ No
If yes, by whom?

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS**

☐ **CMHC Pharmacy**

☐ **PET Center**

☐ **Other:**

☐ **Yale Cancer Center**

☐ **West Haven VA**

☒ **None**

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☒ **Not applicable to this research project**

If use of a placebo is planned, provide a justification which addresses the following:

- Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
- State the maximum total length of time a participant may receive placebo while on the study.
- Address the greatest potential harm that may come to a participant as a result of receiving placebo.
- Describe the procedures that are in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?

☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings.*

If yes, is the use of the controlled substance considered:

☐ **Therapeutic:** The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.

☐ **Non-Therapeutic:** *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project**

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Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒

If Yes, please be aware of the following requirements:

- a. A YNHH New Product/Trial Request Form must be completed;
- b. Your request must be reviewed and approved by a Hospital Committee before patients may be scheduled; and
- c. The notice of approval from YNHH must be submitted to the HIC for the protocol file.

Please contact Gina D'Agostino, gina.d'agostino@ynhh.org or 203-688-5052, to initiate the process.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No

If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**

a) Identify the source of the device to be used.

b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents

impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions, Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability:**

State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES**1. Targeted Enrollment: Give the number of subjects:**

- a. Targeted for enrollment at Yale for this protocol: 40
- b. If this is a multi-site study, give the total number of subjects targeted across all sites
N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

- | | | |
|--|--|-------------------------------------|
| <input type="checkbox"/> Flyers | <input type="checkbox"/> Internet/Web Postings | <input type="checkbox"/> Radio |
| <input type="checkbox"/> Posters | <input type="checkbox"/> Mass E-mail Solicitation | <input type="checkbox"/> Telephone |
| <input checked="" type="checkbox"/> Letter | <input type="checkbox"/> Departmental/Center Website | <input type="checkbox"/> Television |
| <input type="checkbox"/> Medical Record Review | <input type="checkbox"/> Departmental/Center Research Boards | <input type="checkbox"/> Newspaper |
| <input type="checkbox"/> Departmental/Center Newsletters | <input type="checkbox"/> Web-Based Clinical Trial Registries | |
| <input type="checkbox"/> YCCI Recruitment database | <input checked="" type="checkbox"/> Clinicaltrials.gov Registry (do not send materials to HIC) | |
| <input checked="" type="checkbox"/> Other (describe): Patients who meet eligibility criteria will be approached by an attending surgeon at Yale Endocrine Surgery and will be asked about their interest in enrollment into the study. | | |

3. Recruitment Procedures:

- a. Describe how potential subjects will be identified.
A letter will be sent to referring endocrinologists to raise awareness for this clinical trial. This letter will inform the endocrinologists about the general study purpose, study design, and potential inclusion and exclusion criteria. All potential patients will be referred to Yale Endocrine Surgery for final assessment of eligibility. We include a copy of this letter with the amendment form.

All patients referred to Yale Endocrine Surgery who meet eligibility criteria and do not meet exclusion criteria will be offered enrollment in the study. The attending endocrine surgeon (Drs. Udelsman, Carling, Callender or Quinn) will determine eligibility at the time of the initial clinic visit.

- b. Describe how potential subjects are contacted.
Potential subjects will be approached during their regularly scheduled Yale Endocrine Surgery clinic appointment.
- c. Who is recruiting potential subjects?
Attending endocrine surgeons at Yale Endocrine Surgery will approach patients to discuss their interest in enrollment. Referring physicians who have heard about the study may also refer patients specifically for a discussion of enrollment into the study. Patients who have heard about the study may self-refer for a discussion of enrollment into the study.

4. Screening Procedures

- a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No

- b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process. N/A

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

- ☒ Yes, all subjects
☐ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.

All patients, who are enrolled in this study, will have clinical relationship with the principle investigator, as they will undergo surveillance for their procedure for 5 years. They will be scheduled for follow up clinic visits, initially by the surgical team (first clinic visit after procedure) and afterwards by Dr. Elizabeth Holt (also included in protocol; member of study team). For details of follow up clinic visits please see Appendix 6.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

N/A

Choose one: For entire study: _____ For recruitment purposes only: _____

- i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
- ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

- 7. Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

- ☐ Compound Consent and Authorization form
☐ HIPAA Research Authorization Form

N/A

- 8. Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

- a. Glenda Callender, MD
- b. Robert Udelsman, MD, MBA
- c. Tobias Carling, MD, PhD
- d. Courtney Quinn, MD
- e. Melih Arici, MD
- f. Jonathan Kirsch, MD
- g. Jennifer Malinowski, PhD, MS
- h. Elizabeth Holt, MD, PhD
- i. Patricia Donovan, RN, MBA

- 9. Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Patients will be consented in the Yale Endocrine Surgery clinic during their evaluation. This study does not involve children or patients without decision-making capacity.

- 10. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The patient will be assessed by a physician before obtaining informed consent/ assent. It is the duty of the physician to use his/her clinical judgment to determine if the patient has the ability and capacity to make his or her decision regarding medical treatment. In some circumstances, the patient may lack the mental capability to consent for the planned procedure. Circumstances such as being under the influence of drugs or alcohol may constitute grounds that the patient is temporarily incompetent to consent and the patient will not be consented for the planned procedure. Patients suffering from dementia are also considered incompetent to consent and the study team will exclude the patients from the study.

In the absence of any concerns about the patient's ability to consent, the patient will be asked to sign the consent for the procedure.

- 11. Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

We include our "Adult Informed Consent Form". We do not plan to enroll patients into the study who are decisionally impaired or minors that would require assent forms or child assent forms, respectively.

- 12. Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

We will not include non-English speaking subjects for this study.

- 13. Consent Waiver:** In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

- ☒ **Not requesting a consent waiver**
☐ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of signed consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6)**

- ☐ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note:

Recruitment/screening is generally a minimal risk research activity

☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

- ☐ **Requesting a waiver of signed consent for the Entire Study** (Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

- a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
- b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

- c. Does the research pose greater than minimal risk? ☐ Yes *If you answered yes, stop. A waiver cannot be granted.* ☐ No

AND

- d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. Full waiver of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

- a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes *If you answered yes, stop. A waiver cannot be granted.* Please note:
Recruitment/screening is generally a minimal risk research activity
☐ No
- b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
- c. Why would the research be impracticable to conduct without the waiver?
- d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

- a. Does the research pose greater than minimal risk to subjects?
☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
☐ No
- b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
- c. Why would the research be impracticable to conduct without the waiver?
- d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS
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Confidentiality & Security of Data:

- a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?
We will collect sufficient information about each enrollee such that should they move away from Yale-New Haven or they become otherwise "lost-to-follow-up", we can continue to track them using state and nationally-available resources such as the National Death Index,

Social Security Death Index and the Connecticut Tumor Registry. To ensure this, we will be collecting the following PHI on each enrollee:

- 1) Full given and surname
- 2) Location (city and state) and date of birth
- 3) Social Security Number
- 4) Current residential address and best contact phone number
- 5) Medical record number for Yale New Haven Hospital

- b. How will the research data be collected, recorded and stored?

Data will be collected from both direct patient interview and extraction from the medical record. These data will be input into the OnCore clinical trials management system directly from the medical record. Patient surveys, which are completed in paper format, will be stored in a single, locked file cabinet and kept separate from all the remaining study documents; these data will be input into the OnCore clinical trials management system. An electronic database will be created from the data contained in OnCore. This database will serve as a standalone product to allow us to track participants and samples. It will be stored on the limited-access Yale secure server. The data in OnCore will be kept indefinitely; the research database will be de-identified one year after the end of the study and the data kept in this anonymous form indefinitely on the secure server.

- c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☒ Desktop Computer ☐ Other
- d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
- Do all portable devices contain encryption software? ☒ Yes ☐ No
- If no, see <http://hipaa.yale.edu/guidance/policy.html>

All electronic data files for this study will either be stored as password-protected files on an encrypted, password-protected computer, in the Yale Clinical Trials Management System (OnCore), or on the limited-access secure Yale ITS server. OnCore is accessed through Yale-networked computers and access is granted only to appropriate study personnel. Any files that contain protected health information will be maintained separately from the rest of other data files and only on the secure server or in OnCore.

The research database that contains the participant data will be maintained on the secure Yale server and will be de-identified at the end of the study. Access to this database will be restricted to the small subset of individuals responsible for study operations. In this manner, we hope to minimize the risk of breach of confidentiality by limiting access to the PHI and its link to the anonymous unique identifiers.

- e. What will be done with the data when the research is completed? Are there plans to destroy identifiable data?

At the end of the study, personally identifiable data in the research database will be de-identified or deleted using specific software to “securely” delete a selective file. Information regarding this software will be obtained from ITS at the time that it is needed. Personally identifiable data that exists in OnCore cannot be de-identified or destroyed. Access to the OnCore data will remain restricted.

- f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

All of our paper survey forms will be stored in a single locked file cabinet located in the Department of Surgery. Access to the file cabinets will be limited to Dr. Glenda Callender, PI of the study, and Dr. Jennifer Malinowski, Administrative Coordinator of the study.

All electronic data will be kept either in the Yale OnCore clinical trials management system or on secure Yale servers with access limited to study personnel. PHI in OnCore cannot be destroyed or de-identified; access to the OnCore data is restricted. PHI in the research database will be de-identified after the study conclusion. This anonymized research data will be maintained on the secure Yale server.

- g. If appropriate, has a [Certificate of Confidentiality](#) been obtained?

We are not collecting data that would require a Certificate of Confidentiality.

- h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview - incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

No.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

An ongoing debate exists as to the optimal management of patients with PTMC. Options vary from total thyroidectomy to thyroid lobectomy to observation only. Many patients undergo total thyroidectomy; it is considered the standard-of-care treatment in the United States. However, morbidity is a concern in thyroid surgery. Surgical complications, such as hoarseness or hypoparathyroidism, and postoperative metabolic/psychological disturbances (that can occur in spite of adequate hormone replacement) can profoundly impact patient quality of life. It has been shown that the majority of patients with PTMC can be followed safely with observation close surveillance, without a significant difference in patient outcome. The option of percutaneous ethanol ablation allows for actual treatment of the

cancer, which is an advantage over observation, but it is considerably less invasive than total thyroidectomy.

We are offering a new treatment option for patients with PTMC, which could fundamentally change patient management. Percutaneous ethanol ablation is an established tool for the management of metastatic thyroid cancer or patients with benign primary thyroid conditions who are not ideal surgical candidates. By introducing this approach for patients with PTMC, we can potentially change current patient management and avoid the more invasive procedure in many patients (i.e. total thyroidectomy) by treatment of the cancer with a minimally invasive and low risk intervention.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

Total thyroidectomy, thyroid lobectomy, or observation (observation is currently only performed as part of a protocol).

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

None

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

The treatment in this study may be considered standard of care and it is anticipated that the patient's health insurance will cover all expenditures for the procedure, i.e percutaneous ethanol ablation. The follow-up visits will be performed by an endocrine surgeon from our department and the follow-up tests and visits are routine tests that are standard of care for surveillance of PTC.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.

- a. Will medical treatment be available if research-related injury occurs?

Yes

- b. Where and from whom may treatment be obtained?

If a patient is injured as a direct result of this research, he/she will receive treatment. The study investigators will assist in the coordination of care with caregivers close to the subject's residence. The patient or their health insurance will be expected to cover the cost of the treatment. No additional compensation for injury or lost wages is provided.

- c. Are there any limits to the treatment being provided?

There are no limitations.

- d. Who will pay for this treatment?

The patient or their health insurance.

- e. How will the medical treatment be accessed by subjects?

Patients are instructed to call our office (available 24/7) with any questions or concerns.