Central Neck Dissection in Patients with Clinical Node Negative Thyroid Cancer

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NCT02138214

Original Protocol Version Date: 12-Mar-2014
Revision 1 Date: 18-Apr-2014
Revision 2 Date: 04-Sep-2014
Revision 3 Date: 16-Feb-2015
Revision 4 Date: 06-Apr-2015
Revision 5 Date: 14-Sep-2015
Revision 6 Date: 23-Oct-2015
Revision 7 Date: 01-May-2016
Revision 8 Date: 20-Dec-2016
Revision 9 Date: 06-Oct-2017
Revision 10 Date: 22-Feb-2018
Revision 11 Date: 19-Jul-2018
Revision 12 Date: 13-Sep-2018
Revision 13 Date: 17-Jan-2020

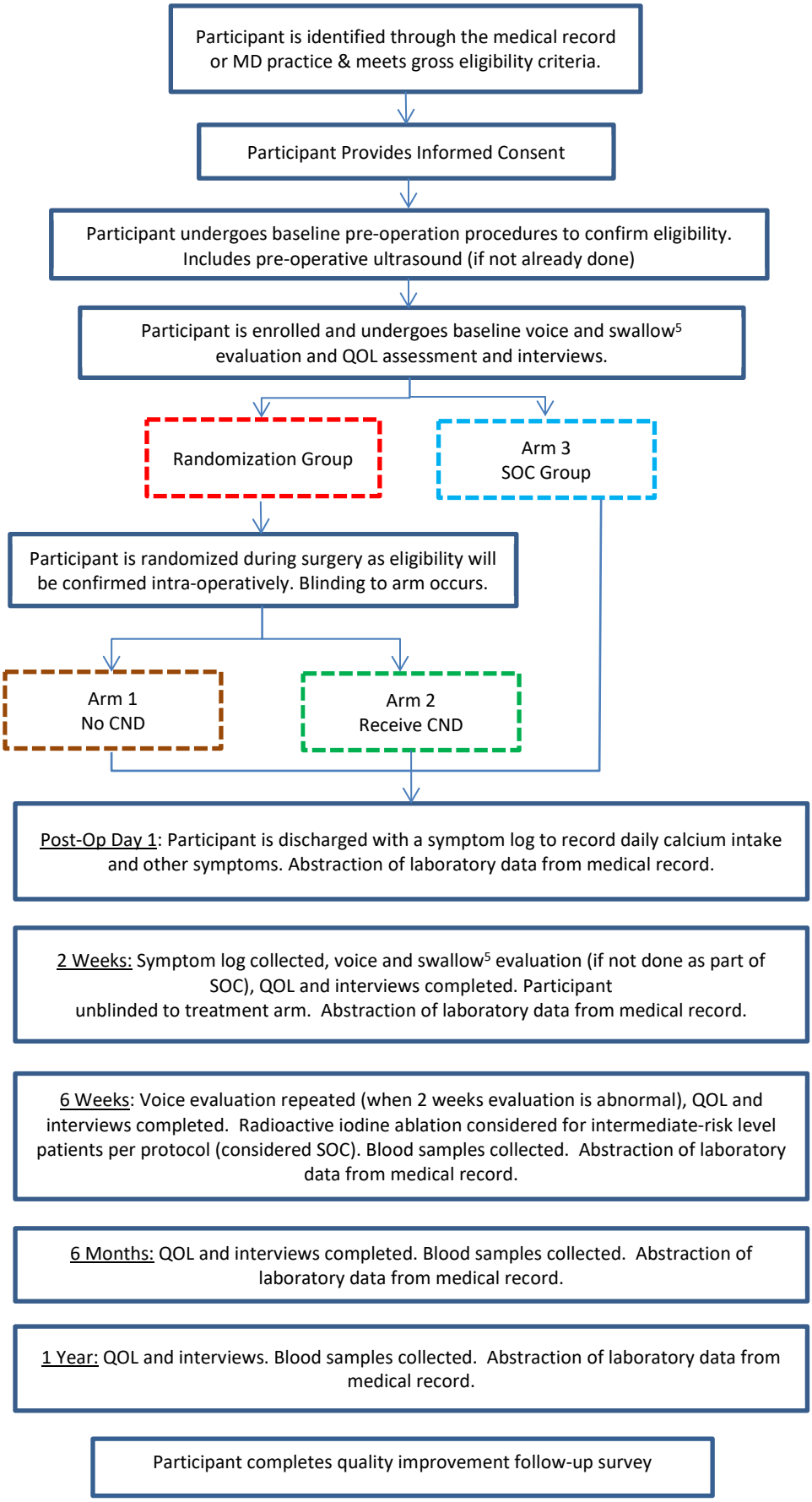
HSIRB# 2014-0391 (UW13115)

Summary

Thyroid cancer is usually treated with the complete surgical removal of the thyroid gland, but due to concerns that the cancer may recur in the future, lymph nodes in the central part of the neck may also be surgically removed. Unfortunately, the additional lymph node surgery may be associated with increased risks for complications such as inadequate calcium, problems with voice function, swallowing deficits, and generally diminished quality of life. Because the risks for these complications are poorly defined, we propose to do a clinical trial where we will compare clinical recurrence rates and complication levels in patients with papillary thyroid cancer who have thyroid gland removal alone to those who receive thyroid gland removal plus lymph node surgery in the central neck.

In this clinical trial, 70 - 140 patients undergoing surgery treatment for thyroid cancer will be enrolled into one of three treatment arms. Patients receiving total thyroidectomy for papillary thyroid cancer (PTC) with no pre-operative evidence of distant or cervical lymph node metastasis will be randomized into one of two arms: prophylactic central neck dissection or no central neck dissection. Patients who are not eligible for randomization will be enrolled into a third standard of care arm. We will then compare the three cohorts: (1) To determine the rate of transient and persistent hypocalcemia; (2) To determine the rate of voice and swallowing problems; (3) To determine the degree to which HR-QOL is compromised; (4) To determine clinical recurrence rates; (5) To determine the degree to which Natural Language Processing (NLP) tools can extract and document quality of life measures from patient interview narratives; (6) To determine the extent of correlation among quality of life measures obtained from patient interview narratives and those from traditionally administered quality of life surveys.

Figure 1: Trial overview diagram



Schedule of activities

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6	Visit 7	
	Screening	Day of Operation	Post-Op	Day 12	Week 6	Cancer Screen	Month 6	1 Year	Follow-up
Window	6 weeks-24 hours before operation		0-2 days	± 8 days	4-20 weeks	+2-7 days after Week 6	±6 weeks[1]	10 – 18 months	+10-19 months (+1-6 weeks post 1 year)
Informed Consent Obtained	X								
Venipuncture	SOC		SOC	SOC	SOC	SOC[2, 3, 4]	CI	SOC	
Calcium[3]	SOC[3]		SOC[3, 5]	SOC[3, 5]			X[5, 17]	CI [5, 17, 18]	
Parathyroid Hormone (PTH)[3]	SOC[3]		SOC[3, 5]	SOC[3, 5]			X[5, 17]	CI [5, 17, 18]	
Vitamin D[17]	CI[6, 17]								
Neck Ultrasound	SOC[7]						SOC	SOC	
Chest X-ray[8]	SOC[8]								
Comprehensive Voice Evaluation: Phonation Threshold Pressure, Dysphonia Symptom Index, CAPE-V, GRBAS, Stroboscopy, Glottal Function Index, VHI	CI[9]			CI[9]	CI[10]		CI[10]	CI[10]	
Swallow Evaluation: standardized videofluoroscopic swallow study[15]	X[11]			CI[11]	CI[11]		CI[11]	CI[11]	
Quality of Life Surveys, including: (1) the Short Form 12 (SF-12, Medical Outcomes Trust); (2) The European Organization for Research and Treatment of Cancer QOL instrument (EORTC QLQ C30); (3) The Voice Handicap Index (VHI) for assessing voice-related QOL (part of voice evaluation); (4) the EAT-10 Swallow Instrument); (5) Thyroid Cancer QOL (Thy-Ca QOL)	X			X	X		X	X	
Interviews (Audio Recorded)	X			X	X		X	X	
Participant Receives Symptom Log[3, 12]	X[3, 12]								
Randomization[13]		X[13]							
Enrolled		X							
Adverse Events Monitoring		X		X	X		X	X	
Endocrine Consult[14]				SOC[14]					
Participant Returns Symptom Log & it is Reviewed[3]				X[3]					
Participant & Study Staff Unblinded				X					
Unstimulated Thyroglobulin[15]					SOC[15, 16]		SOC[15]	SOC[15]	
Stimulated Thyroglobulin[15]						SOC[2, 15]	SOC[15]	SOC[15]	
Radioactive iodine (RAI) Whole Body Scan[2]						SOC[2]		CI[4]	
QI follow-up survey is administered via email									X

Procedure Key: **SOC** = performed as needed per Standard of Care; **X** = Research Only; **CI** = Clinically Indicated (performed SOC if warranted by patient's condition, otherwise the procedure will be done as part of research)

[1]The Month 6 time point must occur at least 4 weeks after the RAI is given, if applicable.

[2]Patients with an elevated unstimulated thyroglobulin level (>2 ng/mL) at Week 6 and/or an intermediate or high risk level will be evaluated for standard of care radioactive iodine ablation therapy and corresponding TSH stimulated thyroglobulin lab and radioactive iodine whole body scan.

[3]Only patients who receive at least a total thyroidectomy (e.g. total thyroidectomy with central neck dissection, total thyroidectomy with lateral neck dissection)

[4]If Thyroglobulin >2ng/ml and neck US is negative (**randomized patients only)**

[5]All participants will be asked to stop their calcium and calcitriol supplementation 12 hours prior to their follow up appointment(s) so that a repeat calcium and PTH level can be checked.

[6]Vitamin D is clinically indicated if PTH is elevated or calcium is low.

[7]Ultrasounds within three months of surgery can be used for screening purposes.

[8]CXR only performed as needed at screening to rule out metastases.

[9]Voice evaluations are routinely performed pre-operatively in patients with prior neck surgery or voice complaints and post-operatively in anyone with a voice concern.

[10]Evaluations will only be obtained if results are abnormal at previous evaluation.

[11]Swallow studies were eliminated as of 12/01/2016.

[12]Between Visits 2 and 4, participants will be asked to record daily any symptoms which they think may be related to hypocalcemia (paresthesias, muscle cramps, etc). They will be asked to describe the symptoms and mark the time that the symptoms occurred and the severity of the symptoms (graded on a scale of 1-5). They will record the doses of calcium administered and how long it took the symptoms to resolve. Participants will total their daily calcium intakes. They will be instructed to contact us if they are requiring greater than 8 g /day and in such instances will be started on calcitriol 0.25 mcg twice daily to increase their intestinal calcium absorption.

[13]Randomization only performed for patients receiving total thyroidectomy with histologically confirmed diagnosis of PTC and no evidence of metastases.

[14]Only patients with histologically confirmed cancer diagnosis. Consult will occur at approximately two weeks after surgery for patients who receive total thyroidectomy and at approximately six to eight weeks after surgery for those who receive partial thyroidectomy.

[15]Thyroglobulin determinations will also include anti-thyroglobulin antibody.

[16]An unstimulated thyroglobulin level will be obtained at Week 6 to assist in decision making regarding the necessity for radioactive iodine ablation therapy.

[17] Randomization patients only. Patients enrolled into the standard of care arm will not receive special labs for research only.

[18] Calcium and PTH drawn at one year post surgery only if values for these are abnormal at month 6 time point.

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List of abbreviations and definitions

AE	Adverse event
ATA	American Thyroid Association
CAPE-V	Consensus Auditory Perceptual Evaluation of Voice
CND	Central neck dissection
CRF	Case report form
CXR	Chest x-ray
DMC	Data Monitoring Committee
EORTC	European Organization Research Treatment of Cancer
eCRF	Electronic case report form
EDC	Electronic data capture
FNA	Fine needle aspiration
HR-QOL	Health related quality of life
IRB	The institutional review board of record for the study
MSC	Mental Component Score
PCS	Physical Component Score
Permanent hypoparathyroidism	Defined as the need for either calcium or calcitriol to prevent symptoms of hypocalcemia or a serum calcium <8.0 mg/dL with a PTH <15 pg/mL at 6 months post-operatively
PRMC	Protocol Review Monitoring Committee
PTH	Parathyroid hormone
PTC	Papillary thyroid cancer
QOL	Quality of life
rTSH	Recombinant thyroid-stimulating hormone
RAI	Radioactive iodine
SAE	Serious adverse event
SOC	Standard of care
Tg	Thyroglobulin
ThyCa-QOL	Thyroid Cancer Quality of Life
UW	University of Wisconsin
VHI	Voice Handicap Index

1. Introduction

1.1. Background

Each year in the United States 46,670 new cases of thyroid cancer are diagnosed. The incidence of thyroid cancer in the United States has increased nearly 2.4-fold from 1950 to 2000. It is therefore critically important that treatments for this disease are grounded in high levels of research evidence.

Currently, complete removal of the thyroid (total thyroidectomy) is the primary treatment for papillary thyroid cancer (PTC). A prophylactic (preventative) central neck dissection to remove the lymph nodes near the thyroid is also often performed along with the total thyroidectomy.

A therapeutic central neck dissection (CND) is performed if there is evidence of lymph node involvement on pre-operative ultrasound or on intra-operative inspection. The removal of clearly involved lymph nodes is believed to provide a therapeutic benefit and to aid in local control of disease.

A prophylactic CND is somewhat different because it involves removing lymph nodes that are empirically *normal* on imaging and inspection with the belief that they may contain nascent disease, and if removed, will decrease the risk of recurrence. It is well established that central neck lymph nodes harbor microscopic lymph node involvement in 60% of cases. However, it has never been shown in a prospective study that prophylactic CND decreases recurrence or improves survival.

The role of prophylactic CND is one of the biggest clinical questions in the management of thyroid cancer today. With over 280 retrospective studies and reviews trying to address this question, there is still no consensus as to whether or not this procedure offers any real benefits. Instead, this procedure may place the patient at risk for serious and pervasive deficits in communicative function, nutrition, hydration, and health related quality of life (HR-QOL). Hypoparathyroidism can also result and may lead to life-threatening hypocalcemia that requires medications four or more times a day. These complications can be devastating, especially for young patients who will have to accommodate these consequences for the rest of their lives. However, removal of lymph nodes by means of a prophylactic CND at the initial operation may decrease the need for repeat surgery and its associated higher risks.

This debate came to the forefront when the American Thyroid Association (ATA) issued consensus guidelines in 2006 that recommended consideration of a prophylactic CND in all patients with thyroid cancer. These guidelines were based on retrospective studies using historical controls because higher levels of evidence were lacking. After the guidelines were published, there was a flurry of further retrospective studies performed in attempt to either support or refute that recommendation.
The 2006 ATA practice guidelines were partially revised in 2009 to “recommend,” based on expert opinion, an even lower level of evidence than the retrospective study designs found in the previous literature. Unfortunately, there remain limited data to either support or refute the 2009 recommendation.

The randomization arms will compare two accepted standards of care in a Phase II clinical trial. Both surgical procedures are widely practiced in the United States for the treatment of thyroid cancer, and it is not known which procedure is best. A prophylactic CND may be associated with a higher complication rate but may also provide a clinically relevant reduction in disease recurrence. Retrospective reviews have been unable to come to a consensus to answer this question adequately. In order to determine the optimal surgical management for patients with clinically node negative thyroid cancer, a randomized clinical trial is needed. A recent clinical trials planning meeting held at the National Cancer Institute picked the issue of prophylactic central neck dissection as the area of thyroid cancer that most needs a

randomized controlled trial. Since not all patients will be eligible for randomization but could provide valuable information about the impact of surgery and surgical complications on quality of life, we would like to offer patients not eligible for the randomization arms or those that are unable to be randomized intraoperatively the ability to participate in the study in the SOC arm.

Background on Natural Language Processing of patient interview narratives:

Traditionally, clinicians and researchers measure quality of life using one of several structured quality of life surveys. Such tools can become time-consuming and expensive to employ for research or clinical use. Furthermore, these surveys require patients to answer structured questionnaires about their health rather than to simply describe their experience in a more natural, narrative format.

Patient use of electronic health resources and health-related social media sites has increased significantly in the past few years. These resources offer the opportunity for patients to share their experiences in a more natural, narrative format. Making this existing information available to clinicians in a validated, standardized format will result in: 1) improved communication between patient and physician, 2) efficient longitudinal tracking of quality of life measures within an electronic medical record, and 3) retrieval and coding of quality of life data contained in narrative social media content. By applying Natural Language Processing (NLP) techniques to patient narratives collected in our qualitative interviews, we will be able to see if patients' natural language be linked to changes in their overall quality of life or other factors that could affect patient care.

1.2. Rationale and hypothesis

We propose a clinical trial in which 70 - 140 patients undergoing surgery for PTC with no pre-operative evidence of distant metastasis will be enrolled into one of three treatment arms: total thyroidectomy with prophylactic central neck dissection, total thyroidectomy without central neck dissection or standard of care. The total thyroidectomy patients will be randomized into one of the first two arms. The standard of care patients, patients who are not eligible for the randomization arms pre-operatively or are unable to be randomized intraoperatively, will be enrolled into the third study arm and will not have any aspect of their cancer care modified by study participation but will otherwise follow the same follow up study assessment schedule as the patients in the randomization arms. In the absence of this clinical trial, patients seen at our center would be offered a total thyroidectomy without central neck dissection, which is our current practice standard. At many other major academic centers, however, a prophylactic central neck dissection is the standard of care. Currently about 50% of high volume institutions are doing a central neck dissection routinely in their practice. While performing a central neck dissection may increase the risks of surgery it may also decrease the risk of recurrence. We do not know, given the presently available data, which will be greater, and therefore this study has true clinical equipoise.

Our hypothesis is that total thyroidectomy with prophylactic central neck dissection will result in a higher complication rate in comparison with total thyroidectomy alone for papillary thyroid cancer.

2. Objectives

2.1. Primary outcome and endpoints

To determine the rate of transient and permanent hypocalcemia:

- Transient hypoparathyroidism as defined by a Day 1 serum parathyroid hormone (PTH) level of <10 pg/ml
- Post-operative serum calcium (mg/dL) and PTH (pg/ml) at Day 12 and Month 6

- Total calcium consumption in first 2 weeks (total gm)
- Hypocalcemia symptoms in first 2 weeks (average episodes/day)
- Hypocalcemia symptom severity scale (range of 1-5)
- Requirement for calcium and calcitriol at Month 6 (or, if laboratory values at visit reveal calcium < 8 mg/dL and PTH <15 pg/ml)

Calcium and PTH levels, calcium intake, and hypocalcemia symptoms will be monitored post-operatively (at Day 1, Day 12, and Month 6) to examine how parathyroid function is affected by a CND. Hypoparathyroidism can lead to paresthesias and muscle cramps and is a known complication of total thyroidectomy, requiring frequent treatment with calcium and vitamin D. This risk is increased with a CND and is thus important to quantify when examining the risk/benefit ratio. Because calcium supplementation is routinely administered for symptoms of hypocalcemia in the post-operative period and this may impact the interpretation of laboratory evaluations, we will be evaluating a variety of metrics to assess the incidence and impact of hypocalcemia on patients.

2.2. Secondary outcomes and endpoints

To determine the rate of voice and swallowing problems, patients will receive videofluoroscopic swallowing studies and voice evaluations pre-operatively and post-operatively (at Day 12, Week 6, Month 6, and 1 Year visits) to examine how voice and swallow function are affected by inclusion of a CND. Voice and/or swallow evaluations may be eliminated once necessary endpoints have been satisfied or the evaluation is no longer informative.[1]

- Phonation Threshold Pressure (cm H_2O)
- Dysphonia Severity Index (DSI; +5 to -5)
- GRBAS (grade roughness breathiness asthenia strain)
- CAPE-V (0-100 on visual analog scale for voice quality parameters)
- Stroboscopy assessment (ratings 1 [most severe] to 4 [normal]) for vocal fold vibratory and movement parameters
- Glottal Function Index score
- Penetration-Aspiration Scale (0-8 score) from videofluoroscopic swallow study[1]

To determine the degree to which quality of life (QOL) is compromised, qualitative analyses of patient interview data and validated surveys of general health quality, as well as QOL surveys specific to cancer, thyroid disease, voice and swallowing will be used to assess the impact of complications on patient's lives.

- SF-12 MCS and PCS scores
- EORTC QLQ C30 scale scores
- ThyCA-QOL score
- EAT-10 dysphagia inventory score
- VHI score (collected by UW ENT department during the participant's voice evaluation, and by study personnel if no voice evaluation is needed)
- Themes, codes from interview transcripts (using qualitative research methods)

[1] With the elimination of swallow studies for patients enrolled after 12/01/2016 collection of data for this endpoint ceased.

To determine whether accurate quality of life measures can be extracted from patient interview narratives, patient interview data will be converted into usable datasets using natural language processing techniques and is then compared to QoL surveys specific to cancer and thyroid disease.

- Interview transcripts
- SF-12 MCS and PCS scores
- EORTC QLQ30 scale scores
- ThyCA-QoL score

To determine clinical recurrence rates, measures of thyroglobulin levels (a reliable surrogate marker for future recurrence), and clinical evidence of recurrent disease (using either I-131 imaging or neck ultrasound), will be made at Month 6 and 1 Year visits.

- Percent of patients with a 1 Year recombinant thyroid-stimulating hormone (rTSH) stimulated Thyroglobulin level <1 ng/ml
- Unstimulated Thyroglobulin just prior to beginning the Week 6 radioactive iodine treatment
- Stimulated Thyroglobulin at the time of Week 6 radioactive iodine treatment (if RAI is given)
- Unstimulated Thyroglobulin at Month 6 >1 ng/mL
- Stimulated Thyroglobulin at 1 Year >2 ng/mL
- Biopsy-proven disease identified on neck ultrasound or I-131 uptake at either Month 6 or 1 Year post surgery, and reevaluated annually while enrolled in the study

For those patients who do experience thyroid cancer recurrence, this typically does not manifest until 10 to 20 years after their initial treatment. For this reason, in order to capture true clinical recurrence rates, participants who receive a diagnosis of PTC, as confirmed by final surgical pathology, and continue to receive care within the University of Wisconsin Hospital system will be followed through chart review in Health Link as well as University of Wisconsin's endocrine surgery outcomes database until their cancer recurs or they are lost to follow up.

Radioactive iodine treatment, ultrasound, and thyroglobulin monitoring are all part of the standard treatment and follow up of thyroid cancer for nodules >1cm. The only test that will be done for research purposes is to check the thyroglobulin level prior to radioactive iodine, so that we can assess the completeness of surgical excision prior to administering radioactive iodine.

3. Study design

This study will compare total thyroidectomy which is the standard of care treatment for PTC at the University of Wisconsin with total thyroidectomy with prophylactic CND to also remove the lymph nodes near the thyroid. Both surgical procedures are widely practiced in the United States for the treatment of thyroid cancer and it is not known which procedure is best.

Participant Identification and Eligibility:
Participants will be primarily identified from all of our University of Wisconsin endocrine surgery and otolaryngology clinics.

Eligible patients will have a thyroid nodule >1 cm in size that is consistent with or suspicious for PTC on a pre-operative biopsy. All biopsies will be reviewed by pathology to confirm eligibility. Patients with T4 (tumor of any size that extends beyond the thyroid) tumors, history of degenerative neurological diseases, pre-operative vocal cord paralysis or other vocal cord pathology will be excluded. All patients will undergo a comprehensive neck ultrasound to evaluate for lymphadenopathy by an experienced thyroid radiologist. A comprehensive evaluation of lymph nodes in levels 1-6 will be performed. If the patient is proven to have lymph node involvement they will be ineligible for the randomization arms.

Patients without evidence of nodal involvement on pre-operative imaging will be eligible for the randomization arms of the trial and consented pre-operatively. Per standard of care at our institution and the recommendations of the ATA, thyroid cancer patients are offered various surgical treatments depending on the nature of their disease. For example, for those whose cancer is limited to only one side of the thyroid, a partial lobectomy may be the appropriate treatment. For this reason, we will only approach patients who have elected to undergo total thyroidectomy for the randomization arms. Patients who are eligible for the trial but not for randomization (i.e. have evidence of lymph node disease or are choosing a thyroid lobectomy) will be approached for consent into the standard of care arm.

Pre-Operative Screening and Testing: Pre-operative laboratory testing will include calcium, PTH, and Vitamin D testing (Aim 1), a comprehensive voice and swallow[1] evaluation (Aim 2), and a complete quality of life evaluation using validated questionnaires and semi-structured interviews (Aim 3). Patients eligible for the randomization arms will then be randomly assigned - after intraoperative confirmation of no suspicious adenopathy or gross local invasion - to one of two treatments on the day of surgery; Arm 1: total thyroidectomy alone, or Arm 2: total thyroidectomy with ipsilateral prophylactic CND. Randomization will be stratified by both age and tumor size to allow appropriate comparisons between groups. Allocation schedule will not be known to study staff prior to consenting.

Operative Procedure: Total thyroidectomy will be performed using standard techniques in all patients potentially eligible for randomization. An open technique will be used to remove the entire thyroid including pyramidal lobe and all visible thyroid tissue. Care will be taken to visualize and preserve both recurrent laryngeal nerves and to preserve all parathyroids in situ. All removed specimens will be carefully examined for any parathyroid tissue and any devascularized or resected normal parathyroid glands will be confirmed by frozen section and autotransplanted into the sternocleidomastoid muscle.

For randomization patients who do not have a pre-operative diagnosis confirming PTC, a frozen section of the suspicious nodule(s) will be performed intra-operatively. If frozen section confirms PTC, the surgical procedure will continue and the patient will be randomized. If frozen section does not confirm cancer, randomization will not occur, and the operative procedure will continue according to clinical indication. During surgery, unexpected and suspicious lymphadenopathy will be biopsied. If lymph node metastases are found, then a CND would be performed at the discretion of the treating surgeon, and the patient will not be randomized. If lymph node metastases are not found in the biopsy, and the surgeon would not otherwise perform a CND based on the observed suspicious lymph node, the participant will be randomized per protocol. Once a patient has met both pre-operative intra-operative inclusion criteria and the randomization envelope is opened, he or she is enrolled in the study. Patients who screen fail intraoperatively will continue their participation with the study as part of the standard of care arm.

Patients randomized to Arm 2 will be receive total thyroidectomy with an ipsilateral CND. The CND will be performed as described by a consensus conference of the ATA. This will include removal of the prelaryngeal nodes, the pretracheal nodes, and the paratracheal lymph nodes. The paratracheal dissection will be bounded superiorly by the cricoid cartilage and inferiorly by the innominate artery on the right and on the left by the axial plane where the innominate crosses the trachea. The superior parathyroid gland will be preserved in situ along with its primary blood supply from the superior branch of the inferior thyroid artery. The inferior parathyroid gland will be reflected laterally along with its blood supply from the inferior thyroid artery. Parathyroid autotransplantation will be performed if the glands are devascularized during dissection. Paratracheal tissue specimens will be examined for parathyroid glands that may be salvaged and transplanted before being removed from the sterile field. Suspected parathyroid glands will be confirmed by frozen section biopsy prior to autotransplantation.

Blinding: Both surgical procedures are performed through the same incision and post-operative care is identical. As such, the neck dressings are identical, allowing both the patients and study staff to be masked with regard to treatment arm randomization. Participants will remain blinded to treatment arm until the Day 12 follow-up appointment, at which point their pathology report will be reviewed with them, and unblinding will occur. Because subjective symptoms and calcium intake are two of our secondary endpoints, we will minimize participant and researcher bias in the description and treatment of post-operative symptoms in the immediate post-operative period. Because the risks of the two procedures and the post-operative instructions are identical for both arms, there is no risk associated with blinding the patients until their Day 12 follow-up. Participants who screen fail intra-operatively will be notified as to which procedure(s) was conducted immediately following surgery. The surgeon performing the procedure cannot and will not be blinded to the participant's treatment arm at any time.

Post-operative follow-up: Post-operative follow-up will be done in the hospital on post-operative Day 1, and clinic follow up will occur at Day 12, Week 6, Month 6, and 1 Year. Patients will be discharged with thyroid hormone that will be administered at 1.5-1.7 mcg/kg daily. Patients will be provided a hypocalcemia symptom log and will be requested to record their calcium intake and symptoms daily. When they have symptoms they will be asked to record the time of the symptoms, what the symptoms were, the severity of the symptoms (scale of 1-5), the amount of calcium taken to treat the symptoms, and the time to symptom resolution.

All patients will be seen in follow up in the clinic in approximately 2 weeks. A calcium and PTH level will be obtained at that visit. Patients will be asked about their calcium intake and their symptoms of hypocalcemia, and their symptom log will be reviewed by study staff (Aim 1). Their symptom log will be collected at the two-week appointment and abstracted by study staff to determine the total volume of calcium supplementation consumed, the type and frequency of hypocalcemia symptoms, and the severity of those symptoms when they occurred.

Comprehensive voice and swallow[5] evaluations will also be performed at the Day 12 visit, and these evaluations will be repeated at Week 6, Month 6, and 1 Year visits (Aim 2) if abnormalities or complaints were noted at the previous time point. All of the voice assessments listed in section 2.2 are part of a standard voice evaluation which is done routinely for patients with a history of previous neck surgery or any voice concerns, either pre-operatively or post-operatively. The video swallow exam is normally only done if there are concerns with voice or swallow function post-operatively. If deficits are observed at Day 12, appropriate treatment will be provided. This may include watchful waiting, behavioral therapy, diet modification, use of injectables, or further surgery. Follow-up assessments at Week 6, Month 6, and 1 Year will, in these cases, provide preliminary data on treatment outcomes. Patients will also complete QOL surveys and interviews to determine the effects (if any) of post-operative complications on overall well-being at each visit (Aim 3).

It is difficult to coordinate voice and swallow evaluations with regularly scheduled patient visits. If the study team is unable to schedule these procedures on the same day, the subject is given the option of returning on a different day of his or her choosing or waiving the evaluation(s) in question at that time point. If an exam is missed, the exam will be scheduled at the subject's next time point. To adequately address the secondary endpoints of the study, the study staff only needs to know if the vocal cord is working and, if it is not working, if it recovers; this can be assessed with only one post-operative time point. Ideally, the study team also hopes to understand the time course of recovery after surgery; therefore, we aim to evaluate patients at each time point. The research-only voice and swallow evaluations do not affect clinical care for thyroid cancer patients.

Subjects will receive an unstimulated thyroglobulin test approximately 6 weeks after surgery. Thyroglobulin reaches its nadir 3-4 weeks post-operatively in most patients, making the Week 6 time point ideal for collection. In multivariate analysis, the postoperative thyroglobulin level is often found to be an independent predictor of persistent or recurrent disease with a level above 0.2 ng/mL considered "elevated". Based on this result as well as the pathology report, the subject's treating endocrinologist will determine his or her risk status. According to the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, RAI remnant ablation is not routinely recommended after thyroidectomy in low-risk patients, although consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preference are relevant to decision making regarding RAI. We will not require low-risk patients to undergo RAI remnant ablation in accordance with these guidelines; instead, their low risk status and thyroglobulin level < 0.2 ng/mL will classify their response to therapy as excellent. Should low-risk patients choose to undergo RAI remnant ablation, they will follow the protocol outlined below.

In all intermediate- and high-risk subjects and low-risk subjects who choose to undergo RAI remnant ablation therapy, radioactive iodine will be administered at 4-20 weeks post-operatively and will be administered with rTSH. For consistency all subjects will be treated with 50 mCi of radioactive iodine unless it is strongly recommended otherwise based on specific features of the individual patient. Microscopic nodal involvement found on pathologic review will not influence the treatment dose of radioactive iodine, but the presence or absence of micrometastatic versus macrometastatic disease will be tracked for future analyses. Thyroglobulin levels will be checked after the rTSH stimulation in order to assess the burden of disease prior to radioactive iodine treatment. Following radioactive iodine administration, levothyroxine will be administered to maintain TSH < 0.5 uIU/mL. Labs will be checked at 6-8 week intervals until TSH level is in the goal range and stable.

At Month 6 and 1 Year visits, TSH, unstimulated thyroglobulin and anti-thyroglobulin antibody will be measured. Additionally, all patients will receive a neck ultrasound at these time points to further evaluate for recurrence.

If the subject underwent RAI remnant ablation, recombinant TSH will be administered and a blood sample testing for the stimulated thyroglobulin level will be obtained at the 1 Year visit. If the stimulated thyroglobulin is greater than 2 ng/mL and the neck ultrasound is negative, a whole body scan will be obtained. Elevated thyroglobulin and/or positive whole body scanning will prompt further evaluation with ultrasound, CT, MRI, or CT-PET as needed. All participants will be followed for a minimum of 1 year after treatment. Long term follow-up tracking the incidence of disease recurrence will be conducted throughout the entirety of the study, with the goal of tracking patients beyond the active study phase through our prospective endocrine surgical database.

Long-term follow-up: Participants who receive a diagnosis of PTC, as confirmed by final surgical pathology, and continue to receive care within the University of Wisconsin Hospital system will be followed through chart review and the endocrine surgery outcomes database until their cancers recur or they are lost to follow up. Clinical documentation of cancer recurrence only, if it occurs, will be abstracted from their electronic medical records.

At each time point (pre-operatively, post-operative, 6 weeks after surgery, 6 months after surgery, and 1 year after surgery), a semi-structured qualitative interview will be conducted by a trained interviewer who is not a member of the clinical staff. Interview guides were developed in consultation with clinical

staff and piloted prior to use; guides include both prompted and unprompted open-ended questions aimed at understanding patient experience with various components of thyroid cancer treatment and subsequent care. All interviews will be transcribed verbatim and any identifiers will be removed from transcripts prior to coding. Data will be coded using a catalogue of focused codes developed through analysis of emergent themes in a representative subset of interview transcripts. Qualitative Health Research Consultants (QHRC), a NIH approved subcontract consisting of Dr. Cameron Macdonald, Dr. Jason Orne, and their employees, will assist with data collection and analysis associated with qualitative aims.

Patients will also be contacted after their one year study time point to complete an electronic questionnaire about their study participation for the purposes of quality improvement, to better understand patient's perceptions of their participation in a clinical trial, and to give patients to opportunity to receive updates on study-related research in the future.

Additionally, we would like to use the coded transcripts from the interviews to customize Natural Language Processing (NLP) tools; Doing this will provide a usable training dataset from coded quality of life (QOL) surveys that the patients completed on the day of each interview. We will train NLP algorithms to turn patient narratives (transcribed interview text) into quality of life measures. That is, we aim to predict how a person would fill out a given quality of life survey tool based on their interview text. The following describes the development process:

1. The interview recordings will be transcribed by trained transcriptionists employed through the Wisconsin Surgical Outcomes Research Program (WiSOR) or an outside contractor with a business associate agreement that has been approved by UW Legal Services/Privacy Officer for HIPAA compliance. Transcriptionists have been instructed to remove identifying information from the transcripts. The audio recordings and transcripts will be shared through a secure server that only the transcriptionists and study team members have access to.

2. The completed interview transcripts will be stored on the secure network within the Wisconsin Surgical Outcomes Research Program (WiSOR). The main levels of security for this data application server housed at the SMPH Computer Center include: being securely located behind the UW-Madison campus firewall; having data directory access controls; having physical server security; and having virtual server security. The participants' names and identifying information will be stored separately from the interview transcripts. The only link between the transcripts and the identifying information will be a subject identification number contained in both data files.

3. The transcripts will be reviewed and patient narratives pertinent to quality of life will be extracted.

4. Natural language processing (NLP) tools will be used to parse the patient narratives and extract quality of life measures. A variety of parsing and machine learning strategies will be employed to maximize accuracy. Collaborators in the Department of Journalism and Mass Communications will assist with the development of these tools. All resulting data files will be stored on secure and encrypted servers.

5. The accuracy of the NLP tools will be evaluated by comparing computer generated quality of life responses to the actual patient responses and collected QoL surveys

6. The NLP tools will be customized as needed to make extraction as accurate as possible. Again, a variety of software packages and/or machine learning programming will be employed.

4. Study population

4.1. Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study.

1. Pre-operative diagnosis or suspicion of papillary thyroid cancer, usually by FNA
2. No pre-operative evidence of cervical lymph node metastases on neck ultrasound **(Randomization arms ONLY)**
3. No evidence of distant metastases
4. Age 21-73 years
5. Ability to read and write in English

4.2. Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Largest papillary thyroid carcinoma <1 cm in size on ultrasound
2. Previous thyroid surgery
3. Concurrent active malignancy of another type
4. Age <21 or >73 years
5. Inability to give informed consent or lacks decision making capacity
6. T4 tumor
7. Pre-existing vocal cord paralysis
8. Chronic neurologic condition which affects voice or swallow (for instance, multiple sclerosis or Parkinson disease)
9. Baseline laryngeal pathology that would warrant intervention that could affect voice or swallow function
10. Becomes pregnant before surgery or at any time while on study

4.3. Intra-operation exclusion criteria (Randomization arms ONLY)

1. Evidence of nodal involvement identified in the OR
2. Failure to confirm diagnosis of cancer in participant

4.4. Protected populations

We will not be including any vulnerable populations, such as children, prisoners, those without decision making capacity or women known to be pregnant in this study.

5. Trial interventions

The intervention portion of this study is the assignment to Treatment Arm 1 (no CND) or Treatment Arm 2 (CND). SOC arm patients will not undergo any specific treatment intervention.

5.1. Treatment Arm 1 (No CND)

Arm 1: total thyroidectomy alone.

5.2. Treatment Arm 2 (CND)

Arm 2: total thyroidectomy with ipsilateral prophylactic CND

5.3. Treatment Arm 3 (SOC)

Arm 3: no specific trial intervention, treated as per patient and physician preference

5.4. Allocation to intervention

Patient allocation will be randomized by using a permuted block randomization stratified by age (≥ or < age 45) as the staging of thyroid cancer is different based on patient age, and tumor size (T1-T2 vs. T3) as the benefit of prophylactic central neck dissection may be greater in patients with T3 tumors. We have no predefined recruitment goal for participants ≥ or < age 45. For tumor size we would like to recruit 25% of patients with T3 tumors (size > 4 cm or minimal extrathyroidal extension); this is estimated to be 25% of our eligible population, so we believe that this goal is achievable. Randomization will occur on the day of surgery in the operating room after confirming no suspicious adenopathy and will only be known by the operating surgeon. Participants will be blinded to their treatment allocation until their 2-week follow up appointment at which time their pathology report will be reviewed and they will be told of their treatment allocation.

6. Participant recruitment and consent

6.1. Participant identification

We will recruit patients from the University of Wisconsin Endocrine Surgery and Otolaryngology Clinics. We will also promote the study to endocrinologists throughout the state, specifically targeting endocrinologists in areas with a greater proportion of underrepresented minorities than found in the Madison area. We have well established referral patterns from Winnebago County, IL, which has a significantly higher proportion of underrepresented minority patients than Dane County where our institution is based.

We will work closely with referring endocrinologists to perform the needed long-term follow up for the participants in the study. We will try to condense all study visits to 4 time points, which are already established for routine clinical follow up. Because participation in the study will require additional time at these appointments we will provide a small monetary reimbursement for participation in each of the study visits ($20). The cost of all study procedures that are not the standard of care will be covered as part of participation in the clinical trial.

6.2. Screening

A member of the study staff will assess patient eligibility using the Prepatory to Research provision, as approved by the institutional review board (IRB). All protected health information used during the screening process of a potential participant will be the minimum necessary for the conduct of this study. Any protected information recorded will be destroyed at the end of the screening process. The clinical care team of the potential participant will be aware of the potential participation in this study as they will be the ones who refer the participant.

After consent is obtained, if any pre-operative procedures were not captured in the medical record, these will be conducted as necessary per standard of care prior to surgery. The study team will record the necessary data from these standard of care procedures.

A participant is enrolled prior to surgery and will undergo baseline testing of voice and swallow[5] function and QOL assessment. They will be randomized during surgery after confirmation that there is no evidence of nodal involvement.

6.3. Recruitment and consent

The human subjects participating in this study will be recruited from the University of Wisconsin Endocrine Surgery and Otolaryngology Clinics as well as patients referred to the clinic by regional endocrinologists. A participant's decision whether or not to participate will not affect the care he or she receives as a patient. Participants will be treated according to the standard of care for their disease until

consent for the study is obtained. Participants must meet inclusion and exclusion criteria as listed above. Participants will be selected without consideration of socio-economic background or insurance status.

Following explanation of the consent form, each potential participant will be given an opportunity to read it thoroughly. Before being allowed to sign the consent form, potential participants also will be given an opportunity to ask questions. The investigator will emphasize the fact that the participant can terminate involvement at any time without any consequences. Once the consent form has been signed, the study pre-operative procedures will be performed if not already captured in the medical record.

7. Activities and measurements

Enrollment: Participants will be enrolled after signing the informed consent form.

Pre-operative visit: The pre-operative visit will include a study-required baseline assessment of every participant's voice and swallow[5] function and a QOL survey. A baseline assessment of vocal function will be considered clinically indicated in those patients with existing voice complaints or prior neck surgery. If patients are found to have some abnormality on their vocal evaluation that would warrant intervention, they will not proceed to randomization. These pre-operative study evaluations will be coordinated with the standard collection of the participant's pre-operative medical history, physical exam, and laboratory evaluation.

Day of surgery: Once the surgeon visually confirms there is no evidence of nodal involvement intraoperatively, the participant will be randomized. Study arm randomization will be computer generated by Dr. Glen Leverson of the UW Department of Surgery Biostatistics Office and communicated to the surgeon via sealed envelope. Participants will be blinded to their treatment arm until the Day 12 visit.

Post-operative care in hospital: After surgery, participants will remain in the hospital overnight per surgeon preference and laboratory evaluations will be performed per standard of care.

Post-operative Day 1: The participant will be educated on the signs and symptoms of hypocalcemia and be given detailed instruction on how to treat these symptoms per standard of care. They will be given a study log to fill out which will allow them to record the frequency and severity of symptoms and the number of doses of calcium taken. This will be completed and returned to study staff at the Day 12 visit.

Day 12 visit: Physical and laboratory evaluations will be performed per standard of care. A comprehensive voice and swallow[5] evaluation will be conducted; this will be considered a research procedure unless the participant is experiencing difficulty swallowing or there is evidence of vocal fold dysfunction. The participant will also complete a QOL survey and participate in a qualitative interview per study protocol.

Week 6 visit: 48 hours prior to the Week 6 visit day, participants will have a blood sample drawn to establish post-operative thyroglobulin levels and assess response to treatment. During the visit, participants will complete QoL surveys and participate in a qualitative interview. If the patient's voice or swallow function was impaired at the Day 12 visit, additional voice and swallow[5] evaluations will also be performed.

At this time the treating endocrinologist will assess the subject's risk profile based on the criteria outlined in section 3 of the protocol. If the patient is classified as intermediate- or high-risk or if the patient is classified as low-risk but chooses to undergo RAI remnant ablation, he or she will be treated according to the following standard schedule:

Day 1: rTSH injection
Day 2: rTSH injection
Day 3: 50 mCu I-131 therapy administered[2]
Day 5: Stimulated thyroglobulin lab
Day 5-17: Whole Body Scan performed

Month 6 visit: Physical and laboratory evaluations, as well as an ultrasound of the neck, will be performed per standard of care. PTH and calcium samples required for the study will be drawn at this time. A QOL survey and qualitative interview will be completed. If the patients' voice or swallow function was impaired at the Week 6 visit, additional voice and swallow[5] evaluations will also be performed.

1 Year visit: Patients will receive a neck ultrasound and labs per standard of care. If a patient underwent RAI remnant ablation, a stimulated thyroglobulin level after rTSH administration will be obtained to assess response to therapy. A QOL survey and qualitative interview will be completed. If the patients' voice or swallow[5] function was impaired at the Month 6 visit, additional voice and swallow evaluations will also be performed.

Follow-up: Patients will receive a quality improvement follow-up survey between 1 and 6 weeks after the completion of their last study activity. Patients who meet criteria for long term follow-up will continue to be followed through chart review and the endocrine surgery outcomes database.

Time required for study procedures: 120 minutes for voice and swallow evaluation[3, 5]
15-30 minutes for QOL survey
60-90 minutes for qualitative interview

7.1. Table: Time points for data collection

		Time Points for Data Collection					
Variable	**Unit**	**Pre**	**Post-Op Day 1**	**Post-Op 2 Weeks**	**Post-Op 6 Weeks**	**Post-Op 6 Mo**	**Post-Op 12 Mo**
Phonation Threshold Pressure	mmHg or cmH20	X		X	Performed only if prior exam is abnormal		
Dysphonia Symptom Index	Score	X		X	Performed only if prior exam is abnormal		
CAPE-V Global Dysphonia	Rating	X		X	Performed only if prior exam is abnormal		
CAPE-V Rough	Rating	X		X	Performed only if prior exam is abnormal		
CAPE-V Breathy	Rating	X		X	Performed only if prior exam is abnormal		
CAPE-V Strain	Rating	X		X	Performed only if prior exam is abnormal		

[2] Since no patient will have significant nodal involvement, low-dose ablation should be appropriate for all patients. No RAI will be required for participants determined to be low-risk
[3] If voice and swallow are normal at any post-op visit, then evaluations will not be performed at subsequent follow up time points.

		Time Points for Data Collection					
Variable	**Unit**	**Pre**	**Post-Op Day 1**	**Post-Op 2 Weeks**	**Post-Op 6 Weeks**	**Post-Op 6 Mo**	**Post-Op 12 Mo**
CAPE-V Pitch	Rating	X		X	Performed only if prior exam is abnormal		
CAPE-V Loudness	Rating	X		X	Performed only if prior exam is abnormal		
CAPE-V Other	Rating	X		X	Performed only if prior exam is abnormal		
GRBAS Grade	Rating	X		X	Performed only if prior exam is abnormal		
GRBAS Rough	Rating	X		X	Performed only if prior exam is abnormal		
GRBAS Breathy	Rating	X		X	Performed only if prior exam is abnormal		
GRBAS Asthenia	Rating	X		X	Performed only if prior exam is abnormal		
GRBAS Strain	Rating	X		X	Performed only if prior exam is abnormal		
Stroboscopy Edge Left & Right	Rating	X		X	Performed only if prior exam is abnormal		
Stroboscopy Phase Symmetry	Rating	X		X	Performed only if prior exam is abnormal		
Stroboscopy Amplitude, L & R	Rating	X		X	Performed only if prior exam is abnormal		
Stroboscopy Vibratory	Rating	X		X	Performed only if prior exam is abnormal		
Glottal Function Index	Rating	X		X	Performed only if prior exam is abnormal		
Penetration Aspiration Scale[1]	Rating	X		X	Performed only if prior exam is abnormal		
SF-12 MCS	Score	X		X	X	X	X
SF-12 PCS	Score	X		X	X	X	X
EAT-10	Score	X		X	X	X	X
EORTC QLQ-30	Score	X		X	X	X	X
THYCA-Qol	Score	X		X	X	X	X
Voice Handicap Index Total	Score	X		X	X	X	X
Voice Handicap Index Function	Score	X		X	X	X	X
Voice Handicap Index Emotion	Score	X		X	X	X	X
Voice Handicap Index Physical	Score	X		X	X	X	X
Interview	Codes, Themes	X		X	X	X	X
Calcium	Lab	X	X	X		X	Performed only if month 6 value is abnormal
PTH	Lab	X	X	X		X	Performed only if month 6 value is abnormal

		Time Points for Data Collection					
Variable	**Unit**	**Pre**	**Post-Op Day 1**	**Post-Op 2 Weeks**	**Post-Op 6 Weeks**	**Post-Op 6 Mo**	**Post-Op 12 Mo**
Vitamin D (if PTH is high)	Lab	X					
Neck ultrasound	Imaging	X				X	X
FNA result	Lab	X					
Hypocalcemia symptom log	Rating			X			
TSH & repeat TSH (if needed)	Lab				X	X	X
Radioactive Iodine scan dose and scan results (**randomized patients only**)	Imaging				X[4]		If indicated clinically
Unstimulated Tg level	Lab				X	X	X
Stimulated Tg level	Lab				X[5]		X[5]

7.2. Blood sample collection

For patients enrolled in the randomization arm, blood drawn for research purposes will be collected at the patient's standard of care blood draws whenever possible, which should result in only one additional venipuncture being necessary (at the Week 6 visit). Lab results from the research samples will be entered into the patient's chart and reported to the patient. About 15 mL (one tablespoon) of additional blood will be taken; no research samples will be saved or banked for future testing. No additional blood for research purposes only will be drawn from patients enrolled in the standard of care arm.

7.3. Data entry

Data will be collected electronically and on paper. The following will be captured electronically: (1) data from the electronic medical record (see data collection sheet); (2) voice and swallow evaluation video and audio recordings and clinician reports/summaries; (3) audio recordings of participant interviews and electronic codes for content themes. Paper data collection will consist of the QOL instruments (SF12, EAT-10, EORTC, ThyCa-QOL, and VHI). Raw data will be scored or otherwise evaluated as necessary and entered into a study-specific Microsoft Access database as soon as possible after data collection.

Voice and videostroboscopy recordings collected during this study may not be immediately destroyed after all research procedures have been completed, as this data could be of value to a follow up or related study. IRB approval will be sought for any use of this data outside of the study parameters described in this protocol.

7.4. Participant withdrawals

Participants have the right to withdraw from the study at any time for any reason, either before or after the surgical procedure. Additionally, any participant may be discontinued from the study at any time at the discretion of the investigator if she feels it is in the best interest of the participant. If a participant withdraws or is withdrawn from one aim (i.e. voice and swallow), they may continue to participate in the other aims.

Study participation may be terminated early under the following circumstances:

If voice and swallow are normal at any post-op visit, then evaluations will not be performed at subsequent follow up time points.

remnant ablation at Week 6

(1) the participant does not meet all inclusion criteria and is deemed a screen failure
(2) the participant meets any of the exclusion criteria (including intra-operative criteria) and is deemed a screen failure
(3) the participant does not adhere to protocol requirements (e.g., completing QOL questionnaires or the Symptom Log, refusing permission to have interview recorded, etc.)
(4) the participant experiences an AE which in the investigator's opinion requires their withdrawal from the study[6]
(5) the participant is lost to follow up
(6) death of the participant

The investigator will document the reason(s) for withdrawal of each participant in source documents and in the eCRF.

Participants that withdraw or are withdrawn prior to Day 12 will be replaced. Their pre-operative data may be used to establish baseline function for comparison. Participants that withdraw from any aspect of the study will continue to be cared for per the standard of care.

7.5. Stopping rules (By the Data Safety and Monitoring Committee)

The DSMC shall have authority to stop a research protocol in progress and remove individual human participants from a research protocol. The Data Safety and Monitoring Committee may request enrollment be suspended due to safety concerns.

8. Data analysis and statistical considerations

8.1. Sample size determination

At the beginning of this study, we anticipated randomizing 140 patients with clinically node negative thyroid cancer, with the goal of 116 participants completing the study. Patients will be recruited from the Endocrine Surgery and Otolaryngology Clinics at the University of Wisconsin Hospitals and Clinics. This is a high volume tertiary care center with a large thyroid practice, performing approximately 350 thyroid operations per year. Thyroid cancer accounts for 30% of thyroidectomy cases at our institution and this is the pool from which the patients will be identified (approximately 105 patients/year). Approximately 15% of thyroid cancer cases will have a positive pre-operative ultrasound, thus decreasing our pool of eligible participants to approximately 89 patients per year. With an accrual goal of 140 participants within 4 years, we would need to recruit 39% of eligible patients each year.

Permanent complications in thyroid surgery are uncommon, but these complications can be disastrous for a patient that is affected. Permanent hypoparathyroidism occurs in 1-2% of patients after a total thyroidectomy and the risk may be as high as 14% when a CND is performed. The best surrogate marker to predict an increase in permanent morbidity is the incidence of transient hypoparathyroidism, which is substantially more common than permanent hypoparathyroidism. For example, transient hypoparathyroidism occurred in 12% of our last 270 patients undergoing a total thyroidectomy. The rate of transient hypoparathyroidism in patients treated with a CND has been shown in the literature to be significantly higher. The rate of transient hypoparathyroidism in recent large retrospective studies was reported to be between 38-51%.

We assumed a power of 0.8 and an alpha of 0.05. For sample size calculations we made the assumption that the incidence of transient hypoparathyroidism after a total thyroidectomy alone is 12% and that an increase to 36% (or tripling of the risk) is clinically significant. The rate of hypoparathyroidism in Arm 1 is based upon our last 270 patients and is a reliable estimate. The incidence in the CND arm is based on a

review of the literature and we purposely chose a number on the lower end of quoted ranges to ensure that we are not underestimating our sample size. With these assumptions the sample size is 116, with 58 patients per arm. Due to the short follow up for our primary endpoint (post-operative day 1) and for our secondary endpoints (<12 months), we anticipate no significant loss to follow up. For our secondary aims, we chose the Dysphonia Severity Index (DSI) as representative and found a prior thyroid surgery study (45) showing that as few as 8 patients in a negative voice outcome group were sufficient to detect clinically meaningful differences on this measure versus patients with normal vocal functioning at 6 months post-op. Thus, the sample size in our study should be adequate to address our secondary aims even if there is attrition/ loss to follow-up.

The number of patients who must be consented will be larger than the final sample size because a portion of patients that are enrolled and evaluated pre-operatively may not be randomized the day of surgery (because malignancy is not proven intraoperatively, suspicious adenopathy is identified, or there is gross local invasion). We aim to increase the sample size by 20% to accommodate for this.

We have found in our examination of preliminary data that our objective measures are not effectively capturing the impact of surgery on patients and that the most critical and meaningful data that we are obtaining from our study is from the in-depth patient interviews. Given the value of our qualitative data, we need to ensure that we are capturing adequate qualitative data to identify differences between the objective and patient-reported evaluations of experiences with hypocalcemia and voice and swallowing problems caused by transient or permanent nerve injury. Ultimately, we plan to make our existing study aims even more robust by incorporating both objective and subjective data into each of our primary and secondary outcomes measures.

Based on our experience with qualitative research and the rates of objective complications in the patients enrolled to date, we've determined that we need to enroll at least 62 patients in order to obtain an adequate dataset to examine the impact of hypocalcemia and 70 patients in order to obtain an adequate dataset to examine the impact of vocal cord dysfunction. While we will continue to recruit as many patients as feasible, based on these calculations, if we are able to enroll at least 70 patients, this should give us the data necessary to evaluate all of our study aims.

Therefore, we will plan to randomize 70 - 140 patients. We will plan to recruit patients up until year 5 of the study as the primary recurrence endpoint will be at 1 year. Given the fact that we anticipate having at least 89 eligible patients per year, we should meet our recruitment goal while allowing for at least 1 year of follow up in all study patients.

8.2. Analysis of endpoints

For all primary aims, data will be analyzed using a mixed model two-way analysis of variance examining the effects of treatment group, time and factor interactions, such as radioactive iodine dose. Evaluation time periods (pre-surgery, Day 12, Week 6, Month 6, and 1 Year) will serve as between subjects factor and treatment group (prophylactic CND versus no CND) will serve as the between subjects factor. Experiment-wise error will be controlled with an appropriate adjustment to the alpha-level. Prior to each analysis, we will plot all data and carefully examine each analysis to ascertain that the assumptions of ANOVA are not violated. Data will be transformed as necessary to better conform to the assumptions. Nonparametric statistics will be used when assumptions for ANOVA are not achieved. Statistical support for the study design and analysis will be performed by Dr. Glen Leverson who will perform analyses with SAS statistical software (SAS Institute Inc., Cary, NC).

9. Risks and benefits of trial participation

9.1. Potential risks

Risks associated with surgical procedures

The two surgical approaches to be compared are both widely adopted as standard of care for the treatment of thyroid cancer. There are risks to these surgical procedures and the risks include injury to the recurrent laryngeal or superior laryngeal nerves leading to decrements in voice and swallow function, injury to the parathyroid glands leading to transient or permanent hypocalcemia, bleeding, and infection. The risks of both surgical arms are the same, but the frequency may be higher in one arm versus another and this is the primary aim of this study.

Risks associated with lab testing

Much of the testing and post-operative monitoring included in this project is considered the standard of care in the treatment of thyroid cancer and there is no added risk to participating in this study for the participants. These tests include: lab testing, pre-operative and post-operative ultrasound, thyroid hormone replacement at suppressive doses, and radioactive iodine ablation.

Risks associated with videofluoroscopic (VF) swallow study[5]

There are some small risks associated with the videofluoroscopic (VF) swallow study and the complete voice evaluations. However, these evaluations are considered routine evaluation method for patients with voice and swallowing disorders and thus can be considered minimal risk. That is, the probability and magnitude of harm or discomfort anticipated with these evaluations are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102).

With VF there are small levels of radiation exposure. The UW-IRB has previously determined that prior research from our department involving VF is minimal risk. Participants will likely be exposed to radiation from the fluoroscopy unit for approximately 240 seconds. According to dose-area product measurements, a standard videofluoroscopic evaluation yields an average effective dose to the patient of 0.85 mSv, which is considered a low associated risk (1/16,000). Participation in this study does not prevent the participant from undergoing any medical procedure that would require further exposure to X-ray. Bolus volumes to be used are considered safe even in severely dysphagic patients and all participants will be carefully observed in the controlled radiology environment

Potential risks of the VF swallow study include gagging, choking, and fainting. There is minimal discomfort and minimal risk associated with the endoscopy procedures used during the evaluations. The rigid endoscope is simply inserted into the mouth, without the need for any topical anesthesia. It is possible that the participant may feel a slight amount of anxiety due to having something placed into his/her mouth, although in our experience this is very rare. There may be discomfort with the face mask or feelings of unease or anxiety during the airflow recordings due to the facemask or the tube in the participant's mouth. The likelihood of these risks occurring is small and further reduced by providing the participants adequate time to rest between tasks. Medical staff will be immediately on hand in our hospital setting if these events should occur.

Risks associated with psychological stress

Participants will be discussing their experiences and any adverse outcomes they have experienced in the post-operative period. This may cause changes in thought processes and emotion. These changes will mostly be transitory; however they may be recurrent, or even permanent.

Risks associated with loss of confidentiality

There is a risk that information recorded about participants will be shared with people who would not normally have access to this information.

Risk of radioactive iodine standardization
There is a risk that health care providers following standard of care procedures would treat a study-eligible patient with higher doses of radioactive iodine (usually 100 mCi) than is allowed under this protocol. This theoretical under treatment could possibly contribute to a recurrence or persistence of the original disease, requiring either additional surgery or radioactive iodine treatment(s) in the future. If there are concerns about the dosing of radioactive iodine the case will be presented at our multidisciplinary tumor board and a joint decision made by all providers whether it is appropriate for the patient to remain on the protocol or not and this will be communicated to the patient so they can decide how they would like to proceed.

Unknown risks
This study may involve risks to the participant which are currently unforeseeable. We will inform participants as soon as possible if we discover any information that may affect the participant's health, welfare, or decision to be in this study.

9.2. Mitigation of potential risks

Mitigation of risks associated with surgical procedures
The risks associated with the surgical procedures are clinical risks not specific to the research because participants are receiving surgery due to clinical necessity and both types of surgery are considered standard of care. These risks are described in detail to the patient as part of the informed consent process for surgery and the risks are the same for both proposed procedures, although the magnitude of the risk may be different. While inclusion of a prophylactic CND may increase the risks of surgery it also may provide a clinical benefit to the patient by decreasing the risk of recurrence. This is one of the issues to be examined in the proposed research.

Mitigation of risks associated with lab testing
The risks of these tests are clinical risks and not research risks. The PI will be aware of the clinical risks and these risks will be explained to the patient as part of the informed consent process.

Mitigation of risks associated with videofluoroscopic (VF) swallow study[5]
The likelihood of these risks occurring is small and further reduced by providing the participants adequate time to rest between tasks. Medical staff will be immediately on hand in our hospital setting if these events should occur.

Mitigation of risks associated with psychological stress
The participant showing signs of psychological stress will be reminded of the voluntary nature of the clinical trial they are participating in, and that they can stop at any time without punishment or loss of care. The Primary Investigator will be made aware of any participants displaying these signs by the research staff, and will refer them to appropriate resources as needed.

Mitigation of risks associated with loss of confidentiality
All information obtained and associated data files will be confidential and will be kept in a locked file or password protected computer. The risk of breach of confidentiality regarding participation in the study outside of the scope of the research will be handled by carefully controlling access to study data only to personnel on the research team.

Confidentiality will be protected further by: (1) using a participant log form that contains only the minimum necessary protected health information (PHI) concerning participants, and storing this log in a locked area when not in use, (2) not sharing PHI with any outside institution, (3) coding data collection forms with a consecutive participant number that is not derived from any participant personal identifiers, and linking that data collection form to the participant log, and (4) storing the participant log and data collection forms separately.

It is highly likely that these measures will result in avoidance of breach of confidentiality outside of the research. In addition, the data to be collected are not sensitive to participants. A data and safety monitoring board will also be in place.

Mitigation of risks of radioactive iodine standardization

It is not clinically possible to know if a recurrence was due either completely (or in part) to the slightly lower dose of radioactive iodine. All participants will be followed rigorously according to current guidelines, and if recurrence or persistence occurs, detection of the disease at an early stage will facilitate appropriate treatment.

9.3. Potential benefits and risk-to-benefit ratio

Potential benefits to the individual participant

Individual benefits to participants are not guaranteed, as this study is seeking to determine which of the two accepted standard of care treatments participants could receive will yield the best clinical benefits. We do not anticipate any direct benefits to participants as a result of the evaluation of natural language processing of patient interview narratives.

Potential benefit to society

Over 60,000 thyroid operations are done each year in the United States for the treatment of thyroid cancer. By following the ATA recommendations and changing the recommended surgical approach from a total thyroidectomy to a total thyroidectomy with a prophylactic CND this would alter the treatment of over 50,000 patients each year. Many practitioners have already adopted this change in practice without solid evidence to support it. In order to ensure that this change in practice does not lead to a significant increase in potentially devastating morbidity, it is essential that we clarify the true risks of this intervention in a systematic fashion. Enhancing our understanding of the risks and benefits of a prophylactic CND will help us to improve the care of patients diagnosed with thyroid cancer by minimizing morbidity and ensuring the efficacy of our treatments.

In addition, our unique qualitative data analysis, including evaluating the use of natural language processing, could potentially lead to the development of a novel way for clinicians and researchers to measure quality of life in patient populations. The specialized natural language processing tools developed through this project could be used to more easily extract quality of life information from health-related social media sites and electronic health resources. This could lead to more patient-centered care. It could also reduce the need to administer structured quality of life surveys, which can be time-consuming and may miss important quality of life indicators that may come out in an unstructured patient narrative.

Risk-to-benefit ratio

Although individual benefits to participants are not guaranteed, it is anticipated that considerable societal benefit will result from the proposed studies. Currently both surgical approaches proposed are accepted standards of care. While the risks associated with a CND may be higher, that risk is offset by a potential clinical benefit to the patient. The reason this study is essential is that currently the evidence

cannot support one treatment over another and therefore we feel that this study has true equipoise. The results of this study can be used to help guide the treatment of thyroid cancer and help provide solid evidence to support future guidelines.

10. Adverse events and unanticipated problems

10.1. Adverse event definitions

Adverse event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence in a human participant including any abnormal sign, symptom, or disease temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research. Adverse event collection will begin at Day of Operation and continue through the last assessments. Untoward medical occurrences or acute conditions that occur between screening and surgery will be recorded as medical history.

Serious adverse event (SAE)

A serious adverse event is defined as any adverse event that meets one of the following criteria:

- Results in death; OR
- Is life-threatening; OR
- Requires hospitalization or prolongs existing hospitalization; OR
- Results in significant or persistent disability or incapacity; OR
- Results in a congenital anomaly/birth defect; OR

Unanticipated problem (UP)

An unanticipated problem is defined as an event that meets all of the following criteria:

(1) unexpected in severity, nature, or frequency given the research procedures and the characteristics of the participant population (i.e., problems that are not described in this protocol or other study documents); AND

(2) related or possible related to participation in the research; AND

(3) suggests that research places participants or others at a greater risk of harm related to the research than was previously known or recognized.

10.2. Severity assessment

The severity of all adverse events will be assessed according to the following scale:

- Mild = does not interfere with the participant’s usual function
- Moderate = interferes to some extent with the participant’s usual function
- Severe = interferes significantly with the participant’s usual function

10.3. Causality assessment

The PI will determine the relationship of adverse events to the research intervention using the following scale:

- Definite = AE is clearly related to the study procedures
- Probable = AE is likely related to the study procedures
- Possible = AE is possibly related to the study procedures
- Unlikely = AE is doubtfully related to the study procedures
- Unrelated = AE is clearly not related to the study procedures

10.4. Procedures for recording and reporting adverse events

All adverse events will be recorded for the duration of participation in the study, which is 1 year post treatment. Since the adverse events being tracked are associated with both treatment arms, it will be difficult to know if the adverse event is truly related to the intervention of not. The frequency of events will be monitored bi-annually by the DSMC. Ongoing study-related risks to patients include: the qualitative interviews; QOL surveys; and the voice and swallow[5] assessment(s). It is anticipated that there will be very few adverse events attributable to this follow up care.

Adverse events recording will cease after patients' final study visits at 1 year post treatment, i.e. these events will not be tracked during long term recurrence follow up.

11. Trial safety monitoring

11.1. Data Safety Monitoring Committee

Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff
- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC

Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOWG meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOWG

[5] Swallow evaluations were discontinued for patients enrolled after 12/01/2016

meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

11.2. Review and oversight requirements

Serious Adverse Event – reported within 24 hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

See Section 11.3 for detailed instructions on SAE reporting.

Serious Adverse Event – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.
If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

See Section 11.3 for detailed instructions on SAE reporting.

Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

11.3. Expedited reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table [#] below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to the subsequent sections if the SAE occurred at the UWCCC.

FDA reporting requirements for Serious Adverse Events (21 CRF Part 312)[6, 7]

NOTE: Investigators MUST immediately report to the UWCCC and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect

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[6] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 events

[7] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6)

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

<u>Expedited AE reporting timelines are defined as:</u>

- 24-Hour; 5 Calendar Days – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report
- 10 Calendar Days – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

SAE requiring [24] hour reporting occurs at UWCCC:

<u>Report to the UWCCC:</u>

Reference the SAE SOP (Standard Operating Procedure) and the SAE Reporting Workflow for DOWGs on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. A follow-up report is required to be submitted within 10 days of the initial [24] hour report.

For this protocol, the following UWCCC entities are required to be notified:

(1) DSMC (saenotify@uwcarbone.wisc.edu)
(2) UWCCC Study PI
(3) UWCCC Treating MD
(4) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

<u>Report to the IRB:</u>

The timing and format for submitting an AE report to the IRBs depends on whether: (a) the event suggests an adverse alteration in the risks to subjects or others; (b) the event is reasonably related to study participation; (c) the event is unexpected; (d) there is a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC); (e) the event occurred at sites or to subjects under UW purview; (f) the event results in or is expected to result in a change to the protocol, consent documents, and/or dissemination of new information to subjects (e.g., letter or telephone call to subjects); and (g) whether an investigational device is involved.

Immediate Report to the IRB

An AE, regardless of where it occurred, which meets all three of the following conditions must be reported to the IRB immediately:

- Unexpected
- Immediately life threatening or severely debilitating to other current subjects, and
- Caused by or probably related to the treatment or study intervention

The IRBs expect that these reports will be rare. AEs that meet these conditions must be reported to the IRB Chair or IRB Director via telephone as soon as possible, but no later than 1 business day after the local research team becomes aware of the event. The research team will then discuss with the IRB Chair or IRB Director what action needs to be taken related to the occurrence (e.g., suspension of study enrollment, change in treatment regimen) to prevent further harm from occurring. This initial report to the IRB Chair or IRB Director must be followed within 2 business days with a submission of an Adverse Event Report Form to the IRB Office.

SAE requiring [10] day reporting occurs at UWCCC:

Report to the UWCCC:

Reference the SAE SOP and the SAE Reporting Workflow for DOWGs on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for [10] day reports.

For this protocol, the following entities are required to be notified:

(1) DSMC (saenotify@uwcarbone.wisc.edu)
(2) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

Report to the IRB:

The timing and format for submitting an AE report to the IRBs depends on whether: (a) the event suggests an adverse alteration in the risks to subjects or others; (b) the event is reasonably related to study participation; (c) the event is unexpected; (d) there is a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC); (e) the event occurred at sites or to subjects under UW purview; (f) the event results in or is expected to result in a change to the protocol, consent documents, and/or dissemination of new information to subjects (e.g., letter or telephone call to subjects); and (g) whether an investigational device is involved.

Report to the IRB within Fourteen (14) Business Days

Any other AE as described above Adverse Events that are Reportable to the IRBs must be reported to the IRB within fourteen (14) business days.

Report to the IRB at Continuing Review

AEs that meet the criteria below should be reported at the time of continuing review. Events reported at continuing review must meet ALL of the following criteria:

- occurred locally (i.e., at sites under UW IRB purview);
- are related to the research study but unexpected;
- were not assessed as placing subjects or others at increased risks (including physical, psychological, economic, or social harm) than was previously known or recognized;
- were not assessed as resulting in new information that needed to be disseminated to participants; and
- occurred on studies that do not have a formal DSMB or DMC

Other Reporting Requirements

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

12. Administrative requirements

12.1. Good clinical practice

The study will be conducted in accordance with FDA and ICH guidelines for Good Clinical Practice. All study staff will be thoroughly familiar with the contents of this protocol and associated trial materials.

12.2. Data quality assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data will be entered into an electronic case report form (eCRF) by site personnel. Any changes made to study data will be made to the CRF.

12.3. Study monitoring

Due to financial and staff limitations there are no formal plans to monitor data for this study; however there remains a possibility for this if deemed necessary by the DSMC, HS-IRB, or study team.

12.4. Ethical consideration

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the participants. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent form, written information given to the patients, safety updates, annual progress reports and any revisions to these documents will be provided to the IRB by the investigator.

12.5. Patient confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the participant of the following:

- what protected health information (PHI) will be collected from participants in this study
- who will have access to that information and why
- who will use or disclose that information
- the rights of a research participant to revoke their authorization for use of their PHI

All participants will be assigned a study-specific ID number. We will maintain a master list linking each participant's medical record number (MRN) with a study-specific ID number. This list is to be maintained in a location separate from any study data. Only study staff listed on the IRB application shall have access to the list.

All information obtained and associated data files will be confidential and will be kept in a locked file or password protected computer. The risk of breach of confidentiality regarding participation in the study outside of the scope of the research will be handled by carefully controlling access to study data only to personnel on the research team.

Confidentiality will be protected further by: (1) using a participant log form that contains only the minimum necessary protected health information (PHI) concerning participants, and storing this log in a locked area when not in use, (2) not sharing PHI with any outside institution, (3) coding data collection forms with a consecutive participant number that is not derived from any participant personal identifiers, and linking that data collection form to the participant log, and (4) storing the participant log and data collection forms separately.

All study data will be kept for 10 years after publication of study findings. All data will be destroyed by deletion from computer files and/or shredding.

12.6. Investigator compliance

The investigator will conduct the trial in compliance with the protocol approved by the IRB. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants.

12.7. Participant cost and payment

Cost

Participants are not expected to incur additional costs from participation as clinical care costs that are not considered standard of care will be covered for all participants.

Payment

Participants will be provided $20 in reimbursement for each completed study visit (participants completing the study will have 5 visits).

Clinical care costs that are not considered standard of care will be covered for all participants including 6 month calcium and PTH testing. For consistency all pre-operative ultrasounds for lymph node staging will be performed by a dedicated radiologist at the University of Wisconsin and this expense will be covered by the trial.

For our primary recurrence endpoint we would like to have all patients undergo recombinant TSH stimulated thyroglobulin testing.

13. Funding sources

This study is being funded by an R01 Grant.

14. Publication policy

This study will be registered with ClinicalTrials.gov.