PROTOCOL DATE: July 31, 2021

OFFICIAL TITLE: Assessing Benefits of NIRAF Detection for Identifying Parathyroid Glands During Total Thyroidectomy

NCT05579782

Evaluating Impact of Near Infrared Autofluorescence (NIRAF) Detection for Identifying Parathyroid Glands during Parathyroidectomy

Short Title:

NIRAF Parathyroidectomy

Tracy S. Wang, MD, MPH

Carmen C. Solórzano, MD, FACS

Current Version Number and Date

V1 07/31/2021

Proprietary and Confidential

Title: Evaluating Impact of Near Infrared Autofluorescence (NIRAF) Detection for Identifying Parathyroid Glands during Parathyroidectomy

MCW Protocol No.: VANDERBILT-NIRAF-PARATHYROID

IRB Pro No.: PRO 40572

FDA IDE No.: DEN170056 (Class II)

Clinical trials.gov No.: NCT05579782

Principal Investigator:
Tracy S. Wang, MD, MPH
Professor
Medical College of Wisconsin
Department of Surgery
Division of Surgical Oncology
8701 Watertown Plank Road
Telephone: 414-955-1459
Email: tswang@mcw.edu

Vanderbilt University, Co-Investigator:
Carmen C. Solórzano, MD, FACS
Professor of Surgery
Vanderbilt University Medical Center
Nashville, TN 37235
1301 Medical Center Drive
Nashville, TN 37232
Email: carmen.solorzano@vumc.org

Sub-investigator/Responsible Investigator:
Sophie Dream, MD
Assistant Professor
Medical College of Wisconsin
Department of Surgery
Division of Surgical Oncology
8701 Watertown Plank Road
Telephone: 414-955-1434
Email: sdream@mcw.edu

VERSION HISTORY

Version 1, Version Date 07/31/2021

Initial submission of the protocol.

Version	Date
1	07/31/2021

TABLE OF CONTENTS

PROTOCOL SUMMARY

Title	Evaluating Impact of Near Infrared Autofluorescence (NIRAF) Detection for Identifying Parathyroid Glands during Parathyroidectomy
Principal Investigator	Tracy S. Wang, MD
Study Population	Parathyroidectomy patients
Primary Objectives	The specific aim of this study is to determine if PTeye is beneficial or not for (i) intraoperative identification of parathyroid tissues, (ii) improving efficiency of parathyroid surgeries, and (iii) minimizing risk of postsurgical complications.
Study Design	Double-arm, open-label
Study Intervention	PTeye
Number of Subjects	N = 160. Each investigator will enroll 40 subjects to the PTeye group and 40 subjects to the control group.
Estimated Time to Complete Enrollment:	Approximately 2 years

1 BACKGROUND

Parathyroid Surgery

Inability of the surgeon to identify or localize the diseased PG can occur in 5 – 10% of cases resulting in failed parathyroidectomies (1, 2). As a result, persistent hyperparathyroidism can occur in these patients resulting in unnecessary repeat surgeries that may be associated with increased morbidity and costs (3, 4). Ultrasound imaging, 99mTechnetium-sestamibi scintigraphy, and computed tomography (CT) have so far demonstrated variable efficacy in preoperative localization of diseased PGs (5, 6) and may not always correlate well with the surgical field of view as observed intraoperatively. Consequently, most surgeons rely on visual identification of PGs during surgery, whereby the accuracy of PG identification is eventually determined by her/his surgical skill and experience (7, 8). When in doubt, a surgeon routinely confirms the identity of PG tissue intraoperatively by sending the specimen for frozen section analysis that typically requires a wait time of 20–30 minutes per sample (9) and has additional costs.

By easily being able to distinguish parathyroid from other tissues intraoperatively, postsurgical complications and associated costs may be reduced. The unique discovery of near infrared autofluorescence (NIRAF) in parathyroid tissues demonstrated that optical modalities that detect NIRAF can be utilized for non-invasive and label-free identification of parathyroid tissues with an accuracy as high as 97%.(10, 11) Since then, several research groups have explored the feasibility of localizing parathyroid glands using NIRAF detection with reasonable success, resulting in FDA approval for this optical technique (12). In this study, we plan to evaluate whether an FDA-approved device called ‘PTeye’ (AiBiomed, Santa Barbara, CA) is beneficial or not, for the surgeon and patient during parathyroid operations. The results of such a study will help us to understand and assess the true impact of optical modalities such as PTeye on (i) improving the quality and efficiency of parathyroid surgeries and (ii) minimizing risk of postsurgical complications and related expenses.

Animal Studies and Previous Human Studies

Modalities that rely on NIRAF detection for label-free parathyroid identification have been successfully validated in several studies (13-16). FDA approval for this application was recently granted to Fluobeam (a commercially available imaging system) and PTeye (a commercial fiber probe-based system) in 2018 (12). Certain outcome studies have reported that imaging-based systems for NIRAF detection such as the PDE Neo II system was able to reduce the number of frozen sections required during parathyroid procedures (15). However, other studies have reported that they observed no benefit from imaging-based systems in parathyroid localization (17). In a recent study, Thomas et al. demonstrated that a fiber probe-based system – the PTeye – was more sensitive in parathyroid identification compared to the imaging-based system by PDE Neo II (18). To date, there has been no studies that determine the impact of a fiber probe-based system (i.e. PTeye) during parathyroid surgeries in minimizing a number of frozen sections obtained intraoperatively or postsurgical complications.

Known Risks and Potential Benefits

The proposed study is designed to collect NIRAF measurements from neck tissues with a commercial device called PTeye during a parathyroidectomy. The device that will be used for NIRAF measurements is an FDA-approved device.

Each PTeye measurement takes less than 2 seconds, with the whole set of measurements not adding more than 5 minutes to the surgical procedure. Thus, there is a minimal increase of risk of surgery due to the potential five extra minutes of anesthesia time associated with the study. In addition, the participating surgeon will evaluate the eligibility of the patient based on his or her medical condition. Patients with high anesthetic risks will not be asked to participate in the study.

Since the power of near infrared light from PTeye will be extremely low, no side effects should be introduced to the patient.

There should not be any discomforts, inconveniences, and/or risk resulting from this study.

The study should not increase the risk of infection as a disposable sterile probe is used for each patient.

The PTeye device used in this study has been FDA-approved. The FDA approval is granted based on the caveat that necessary precautionary measures will be taken by the surgeon to minimize the probable risks (as listed in the device brochure). The PTeye may be associated with unknown/unforeseen risks as with any other FDA-approved medical devices used during surgical procedures.

2 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

The goal of this study is to assess whether using PTeye – a NIRAF detection modality – can improve patient outcomes and reduce healthcare associated costs after parathyroid surgeries.

By being able to quickly and definitively locate parathyroid glands while in the operating room, the duration of surgical procedure could be further reduced. In addition, the number of frozen section biopsy and associated costs can be minimized. Furthermore, repeat surgeries as a result of missing a diseased parathyroid gland at the time of the initial parathyroidectomy for hyperparathyroidism could potentially be avoided.

2.1 Primary Objective

The specific aim of this study is to determine if PTeye is beneficial or not for (i) intraoperative identification of parathyroid tissues, (ii) improving efficiency of parathyroid surgeries, and (iii) minimizing risk of postsurgical complications.

2.2 Primary Outcome Measures

2.2.1 Persistent hyperparathyroidism (Immediate)

Failure of intra-operative parathyroid hormone (PTH) to normalize (defined as failure of PTH to drop > 50% of its baseline value at final intra-operative PTH assay and/or failure of PTH to drop < 65 pg/ml or 6.9 pmol/L). [Time Frame: During parathyroidectomy (PTx) procedure]

2.2.2 Persistent hyperparathyroidism or hypercalcemia (transient)

Elevated blood calcium levels (total blood calcium level > 10.5 mg/dL or 2.6 mmol/L) with/without elevated parathyroid hormone (PTH) (serum intact PTH > 65 pg/ml or 6.9 pmol/L) at first postoperative visit. [Time Frame: 5-14 days after PTx procedure]

2.2.3 Persistent hyperparathyroidism or hypercalcemia (failed parathyroidectomy)

If blood calcium with/without parathyroid hormone (PTH) has not normalized at 1st post-operative visit, calcium and/or PTH is subsequently measured as necessary. Patient is defined to have a failed parathyroidectomy if hypercalcemia/hyperparathyroidism (defined as total blood calcium level > 10.5 mg/dL or 2.6 mmol/L, with/without elevated serum intact PTH > 65 pg/ml or 6.9 pmol/L) persists at or after the 6th postoperative month. [Time Frame: 6 months after PTx procedure]

2.3 Secondary Outcome Measures

2.3.1 Overall number of parathyroid glands identified

Overall number of parathyroid glands identified (Experimental Group: Glands identified with naked eye + NIRAF;Control Group: Glands identified with naked eye) [Time Frame: Immediate. During PTx procedure.]

2.3.2 Number of parathyroid glands identified with NIRAF

Number of parathyroid glands identified with NIRAF, which was not seen with surgeon's naked eye [Time Frame: Immediate. During PTx procedure.]

2.3.3 Number of frozen sections sent for analysis

Number of frozen sections sent for analysis during the procedure to confirm potential parathyroid tissue [Time Frame: Immediate. During PTx procedure.]

2.3.4 Number of diseased parathyroid glands identified versus preoperatively localized glands

Number of diseased parathyroid glands identified intra-operatively versus glands localized preoperatively using sestamibi, CT or ultrasound [Time Frame: Preoperative to immediate during PTx procedure.]

2.3.5 Number of intra-operative parathyroid hormone (PTH) assays sent

Number of intra-operative parathyroid hormone assays sent during the procedure [Time Frame: Immediate. During PTx procedure.]

2.3.6 Duration taken to identify first parathyroid gland

Duration taken to identify 1st parathyroid gland in PTx procedure – timed from skin incision to finding PG. [Time Frame: Immediate. During PTx procedure.]

2.3.7 Duration taken to identify last parathyroid gland

Duration taken to identify last parathyroid gland in PTx procedure – timed from skin

incision to finding the last PG.[Time Frame: Immediate. During PTx procedure.]

2.3.8 Duration of parathyroidectomy (PTx) procedure

Duration of PTx procedure – timed from skin incision until the surgeon notifies the anesthesia team to awaken the patient [Time Frame: Immediate. During PTx procedure.]

2.3.9 Duration taken for intraoperative parathyroid hormone (PTH) to normalize

Time taken for PTH to attain cure criteria or normalize - timed from skin incision until the PTH levels drops > 50% of its baseline value and/or PTH drops < 65 pg/ml or 6.9 pmol/L. [Time Frame: Immediate. During PTx procedure.]

2.3.10 Number of nights spent in the hospital after parathyroidectomy

Number of nights spent for postoperative recovery in the hospital after the surgical procedure. [Time Frame: 0-72 hours after PTx procedure.]

2.3.11 Number of 'false positive' tissues excised by surgeon

Number of tissues that were excised by surgeon assumed to be parathyroid tissue, but is later validated as nonparathyroid tissue (false positive) by histology [Time Frame: Immediate to 10 days after PTx procedure.]

2.3.12 Number of doctor visits/emergency department visits or hospital admissions

Number of doctor visits/emergency department visits or hospital admissions due to persistent hypercalcemia and/or associated symptoms after parathyroidectomy procedure [Time Frame: Up to 6 months after PTx procedure.]

2.3.13 Number of patients who have had repeat parathyroidectomy (PTx) procedure

Number of patients with repeat PTx procedure performed after the current procedure [Time Frame: 6 - 12 months after PTx procedure.]

3 STUDY DESIGN

3.1 General Description

This study is a diagnostic study. Patients will be randomly allocated the patient to the experimental arm (where the surgeon will use PTeye) or a control arm (where the surgeon will not use PTeye). Patients will be allocated via ‘Random Allocation Software’ (http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html). The primary outcome of the protocol is designed to evaluate the efficacy of PTeye.

Primary Completion

The study will reach primary completion (complete enrollment) approximately 12-18 months from the time the study opens to accrual.

3.2 Study Completion

The duration of the study is expected to be approximately two years from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
- Screening: period after consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibly criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- On follow-up: from last day of treatment to the end of follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local principal investigator.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent, but are not subsequently assigned to the study intervention or enrolled in the study. MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Eligibility Confirmation

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

4.5 Eligibility Criteria

*No waivers of protocol eligibility will be granted.

All inclusion and exclusion criteria should be explicitly stated as applying to the subject in the source material (e.g., “The patient has been postmenopausal since 2010”).

4.6 Inclusion Criteria

1. All adults (i.e., ≥ 18 years old) patients with primary hyperparathyroidism who will be undergoing parathyroid surgery

2. All adults (i.e., ≥ 18 years old) patients with persistent primary hyperparathyroidism after having undergone a failed prior parathyroid surgery who will be undergoing repeat parathyroid surgery

3. Ability to understand a written informed consent document, and the willingness to sign it.

4.7 Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Children and minors

2. Pregnant women

3. Patients with concurrent parathyroid and thyroid disease that require total thyroidectomy

4. Patients with secondary or tertiary hyperparathyroidism

“I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible.”

_____ _____

(Local Investigator Signature and Date)

4.8 Enrollment

Subject enrollment logistics are defined as follows:

- OnCore® enrollment entry must occur within 24 hours of eligibility confirmation.
- A case/subject/sequence number is assigned in OnCore® from the MCW staff in sequence (i.e., inputted from the site staff, not generated by OnCore®).
    - Sites enter the case number according to the following template “XXX-XXX-001” or “XXX-001” (unless otherwise specified by MCW OnCore® Staff), where the “XXX” sections are abbreviations are determined by MCW OnCore® Staff, and “001” is the sequential subjects who consented to the trial at the site (e.g., the first enrolled case number would be XXX-XXX-001, but the second would be XXX-XXX-002).

4.9 Screening

The screening procedures and assessments must be completed on the day of consultation for parathyroidectomy.

- Patient demographics
- Blood chemistry assessment of serum calcium, ionized calcium, parathyroid hormone (PTH) levels, and 25-OH vitamin D levels

Day of Parathyroidectomy

To be completed within 30 days of the last dose of the study drug.

- Patient demographics
- Duration of surgery
- Number of frozen section analyses performed
- Frozen section and permanent histology reports of all excised tissues

Follow-Up Visits

Patients will be followed for six months following parathyroidectomy. The visits will be within 5-14 days after surgery and at 6 months after surgery.The following procedures will be performed at the follow-up visit(s):

- Physical examination
- Vital signs
- Blood chemistry assessment of serum calcium, ionized calcium, parathyroid hormone (PTH) levels, and 25-OH vitamin D levels
- Concomitant medications
- History of visits to the Emergency room, hospitalization, or repeat surgery due to high calcium levels

- Documentation of postsurgical complications

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow its IRB of record's SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal with no study follow-up.

- Selective consent withdrawal from interventional portion of the study, but agree to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.10 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered
      AND
    - A letter to the participant's last known mailing address goes unanswered.
      AND
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore® (follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the participating site study team, the subject should be considered in follow-up again.

4.11 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® tracks accrual throughout the study.

- If the study must be suspended, OnCore® is updated to a 'suspended' status.
- When the accrual number is reached, OnCore® notifies staff of study closure.

4.12 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

4.13 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study principal investigator, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB) and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

5.1 Definitions

5.1.1 Adverse Event (AE) and Serious Adverse Events (SAE)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to adverse event reporting. This information may be found on the Human Research Protection Program website.

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- **Death.** Results in death.
- **Life threatening**. Is life threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

5.1.2 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

5.1.3 AE Attribution and Grading

Adverse Event Grading

Grade	Description
0	No AE (or within normal limits).
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention (e.g., packing cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Adverse Event Attribution

Attribution is an assessment of the relationship between the AE and the medical intervention.

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

Relationship Assessment: In-Depth Definitions

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

5.2 Monitoring and Recording an Adverse Event

Definition. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

Reporting source. AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

Prior to the trial. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

Pretreatment events following signed informed consent. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Treatment events. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Not serious AEs. For non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management 30 days following the last dose of the study drug or treatment or until they are resolved, if they are related to the study treatment.

5.2.1 Procedure for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant, or suspects that she is pregnant, while participating in this study, she must inform the investigator immediately and permanently discontinue the study drug. The sponsor-investigator must notify the DSMC by email. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately notify the DSMC by email. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (a sample is provided in the appendices)

5.2.2 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the sponsor and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a sponsor representative. Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

5.2.3 Routine Reporting Procedures for AEs

Expedited Reporting Procedures for SAEs, SARs, UPIRSOs and DLTs.

Since this is an investigator-initiated study, the principal investigator, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor-investigator's IRB. Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to the DSMC as soon as possible, but no later than five calendar days of the sponsor-investigator's observation or awareness of the event.

Signs or symptoms reported as adverse events will be graded and recorded by the investigator, according to the CTCAE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

The investigator will assess all adverse events and determine reporting requirements to the MCWCC Data and Safety Monitoring Committee (DSMC) and MCW's Institutional Review Board, and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA), if it meets the FDA reporting criteria. The investigator will report SAEs to any regulatory agency and to the sponsor-investigator's IRB.

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®.

Reporting to the Data and Safety Monitoring Committee

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to the DSMC as soon as possible, but no later than five calendar days of the sponsor-investigator's observation or awareness of the event.

Report Method: The investigator will use email to report SAEs to the DSMC. The SAE report must include event term(s), serious criteria and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE as a guideline whenever possible.

The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Reporting to MCW Committee Institutional Review Board

The principal investigator must report events to the MCW IRB within five business days of his/her awareness of the event.

[Guidance on Adverse Event Reporting to the IRB is available online at MCW IRB Policies and Procedures.]

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the sponsor-investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The sponsor-investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **seven calendar days** after the investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Suggested Reporting Form:

- US FDA MedWatch 3500A:
  http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

Any other form deemed appropriate by the sponsor-investigator.

Event Type	Report Recipients					
	PI/Study Chair/ Coordinating Center	Institutional Review Board	DSMC	FDA	CTO Regulatory Office	Other
Serious Adverse Event	ASAP	5 days (or annual CPR)[1]	5 days	7 or 15 days[2]	ASAP	
Unanticipated Problems Involving Risks to Subjects of Others	ASAP	5 days (or annual CPR)[1]	5 days	7 or 15 days[2]	ASAP	
Evidence of Causal Relationship between Drug and AE	ASAP	5 days (or annual CPR)[1]	5 days	7 or 15 days[2]	ASAP	
Dose-Limiting Toxicity	ASAP	5 days (or annual CPR)[1]	5 days	7 or 15 days[2]	ASAP	

Contacts					
Role	**Name**	**Entity/Department**	**Institution**	**Telephone**	**Email**
Sponsor-Investigator			MCW	414-	
Research Coordinator			MCW	414-	
IRB Representative			MCW	414-	
DSMC			MCW	414-	
Regulatory Contact			MCW	414-	
FDA			FDA		

Footnotes
[1] Consult MCW IRB Policies (contact your regulatory representative)
[2] FDA guidelines: Suspected adverse reaction, Unexpected and Serious = 7 Days; If not = 15 days

6 STATISTICAL CONSIDERATIONS

Benmiloud et al. studied the impact of NIRAF-based identification of parathyroid glands which comprised of a group of 93 patients where NIRAF was used by a surgeon for parathyroid identification and a control group of 153 patients where NIRAF was not used (19). Their study reported that mean parathyroid glands identified by surgeon with NIRAF imaging was significantly higher at 3.1±0.9, while that of same surgeon without NIRAF imaging was 2.6±0.1 (p=0.0001). Based on this data (mean difference: 0.5 and standard deviation: 1.0), it was determined that in order to observe a statistically significant difference (i.e. for an expected mean difference: 0.7 and expected standard deviation:1.0), 33 patients would be required per group (for a 95% powered study). Since this study may involve patient follow-up for data up to 6 months after surgery, we will thus assume an approximate data attrition rate of 20%, thus requiring a recruitment of 40 patients per group. Therefore, a total of 80 patients (study and control arm) should be recruited per surgeon for this study at this study site.

7 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

7.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

7.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

7.3 Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

7.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the subject (and legally authorized representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, hospital staff was present for consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients who require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

7.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it

confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked Clinical Research Office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the case report forms contain the study identifiers, subject initials, date of birth and date of service.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study. Data/PHI would not be destroyed until permission is granted by the sponsor to destroy the records.

The sponsor-investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review and regulatory inspections.

The study monitor or other authorized representatives of the sponsor-investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

7.6 Protection of Human Subjects

7.6.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

7.6.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

7.7 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

7.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

8 DATA HANDLING AND RECORD KEEPING

8.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

8.2 Data Management Responsibilities

8.2.1 Principal Investigator

The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication and investigational product(s), measurements, exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

8.2.2 Research Coordinator

A research coordinator creates, collects and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

8.2.3 Research Nurse/Medical Staff

The research nurse and medical staff document protocol-required care or assessment of the subject's outcomes, adverse events and compliance to study procedures.

8.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

8.3 Handling and Documentation of Clinical Supplies

The MCWCC principal investigator will maintain complete records showing the receipt, dispensation, return or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The principal investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the principal investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

8.4 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

The source documents for this protocol are as follows:

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

8.5 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific case report forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The clinical research coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered in CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

8.6 Study Record Retention

The duration of the study is expected to be approximately two year and will depend on patient availability. The data acquired from this study will be preserved indefinitely, as it may influence the future development of the entire research project. However, the data will not be accessible to anyone other than the participants of this study. All original paper records, record sheets, preoperative and postoperative lab investigations, drug/medication history, post-surgical medical history, histopathological diagnoses of the investigated tissue samples, will be collectively retained by the PI or Key Study Personnel. The data of this study will be stored in a password protected computer, and only users with permission from the PI can access the data base.

The PI at each participating site is required to prepare and maintain adequate records of the disposition of study materials and case histories that record all observations and other data pertinent to the investigation on each individual administered the materials in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all data entry forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

9 REFERENCES

1. Simental A, Ferris RL. Reoperative Parathyroidectomy. Otolaryngologic Clinics of North America. 2008 2008/12/01/;41(6):1269-74.
2. Cron DC, Kapeles SR, Andraska EA, et al. Predictors of operative failure in parathyroidectomy for primary hyperparathyroidism. The American Journal of Surgery. 2017;214:509-14.
3. Doherty GM, Weber B, Norton JA. Cost of unsuccessful surgery for primary hyperparathyroidism. Surgery. 1994;116(6):954-8.
4. Wachtel H, Cerullo I, Bartlett EK, et al. What Can We Learn from Intraoperative Parathyroid Hormone Levels that Do Not Drop Appropriately? Annals of Surgical Oncology. 2015 June 01;22(6):1781-8.
5. Mohebati A, Shaha AR. Imaging techniques in parathyroid surgery for primary hyperparathyroidism. American Journal of Otolaryngology. 2012 12/07;33(4):457-68.
6. Ahuja AT, Wong KT, Ching ASC, et al. Imaging for primary hyperparathyroidism — what beginners should know. Clinical Radiology. 2004 11//;59(11):967-76.
7. Sosa JA, Powe NR, Levine MA, et al. Thresholds for Surgery and Surgical Outcomes for Patients with Primary Hyperparathyroidism: A National Survey of Endocrine Surgeons. The Journal of Clinical Endocrinology & Metabolism. 1998;83(8):2658-65.
8. Chen H, Wang TS, Yen TWF, et al. Operative Failures after Parathyroidectomy for Hyperparathyroidism: The Influence of Surgical Volume. Annals of Surgery. 2010;252(4):691-5.
9. Novis DA, Zarbo RJ. Interinstitutional comparison of frozen section turnaround time. Archives of pathology & laboratory medicine. 1997;121(6):559.
10. McWade MA, Sanders ME, Broome JT, et al. Establishing the clinical utility of autofluorescence spectroscopy for parathyroid detection. Surgery. 2016 1//;159(1):193-203.
11. McWade MA, Paras C, White LM, et al. A novel optical approach to intraoperative detection of parathyroid glands. Surgery. 2013 12//;154(6):1371-7.
12. The United States Food and Drug Administration. FDA permits marketing of two devices that detect parathyroid tissue in real-time during surgery. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624982.htm. Accessed November 3, 2018.
13. Ladurner R, Sommerey S, Arabi NA, et al. Intraoperative near-infrared autofluorescence imaging of parathyroid glands. Surgical Endoscopy. 2016:1-6
14. Falco J, Dip F, Quadri P, et al. Increased identification of parathyroid glands using near infrared light during thyroid and parathyroid surgery. Surgical Endoscopy. 2017 September 01;31(9):3737-42.
15. Squires MH, Jarvis R, Shirley LA, Phay JE. Intraoperative Parathyroid Autofluorescence Detection in Patients with Primary Hyperparathyroidism. Annals of Surgical Oncology. 2019;26:1142-8.
16. Thomas G, McWade MA, Paras C, et al. Developing a clinical prototype to guide surgeons for intraoperative label-free identification of parathyroid glands in real time. Thyroid. 2018;28(11):1517-31
17. DiMarco A, Chotalia R, Bloxham R, et al. Autofluorescence in Parathyroidectomy: Signal Intensity Correlates with Serum Calcium and Parathyroid Hormone but Routine Clinical Use is Not Justified. World journal of surgery. 2019 Jun 15;43(6):1532-7.
18. Thomas G, Squires MH, Metcalf, T., et al. Imaging or a Fiber Probe-based Approach? Assessing Different Methods to Detect Near Infrared Autofluorescence for Intraoperative Parathyroid Identification. Journal of the American College of Surgeons. 2019; (in press)
19. Benmiloud F, Rebaudet S, Varoquaux A, et al. Impact of autofluorescence-based identification of parathyroids during total thyroidectomy on postoperative hypocalcemia: a before and after controlled study. Surgery. 2018; 163(1):23-30