Postoperative Opt-In Narcotic Treatment (POINT) Study

National Clinical Trial (NCT) Identified Number:

Principal Investigator: Dr. James Wu

Sponsor: None

Funded by: None

Version Number: 1.1

September 20th, 2020

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
9.2	Target enrollment expanded	Sample size increased in order to adequately power a subgroup analysis of pain scores

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Postoperative Opt-In Narcotics Treatment (POINT) Randomized Controlled Trial**
Study Description:	Patients who undergo outpatient thyroid or parathyroid surgery will be randomized to an opt-in program for narcotics (POINT program), where they will be empowered to choose if they want narcotic pain medication upon discharge, versus usual care. We hypothesize an opt-in program will reduce opioid consumption without increasing pain score or decreasing patient's quality of life.
Objectives:	Main Objective: To compare the impact of POINT program versus routine prescription of narcotic pain medication on postoperative pain scores and opioid consumption in outpatient cervical endocrine surgery
Endpoints:	Primary Endpoint: Daily average and maximum postoperative pain scores, postoperative days 1-7 Secondary Endpoints: • Percent of patients that do not consume opioids after surgery/discharge • Percent of patients that request rescue narcotic medication Rx • Percentage of patients that elect to use opioid pain medication • Amount of opioids consumed per patient • Quality of life in first week after operation, assessed by PROMIS-29 tool and Flourish quality of life index on postoperative day 7 • Whether score on PHQ9 preoperative depression screen predicts increased rates of opioid use and/or pain levels
Study Population:	Adults age 18 and above, estimated 100 patients (50 per arm)
Sites/Facilities Enrolling Participants:	Patients will be enrolled in 5 sites within the UC Health System in endocrinology and endocrine surgery offices.
Description of Study Intervention:	Opt-In Protocol (POINT program): Patients will receive counseling in clinic on opioid side effects, potential for abuse, and evidence that few patients require narcotics for pain relief after surgery. After surgery and prior to discharge, patients will be shown a video reiterating the same information as above, then will be asked whether they would like a narcotic prescription or not. If patients experience uncontrolled pain at home based on daily postoperative survey responses, a prescription will be electronically prescribed into their pharmacy. Usual care: Patients will receive no additional counseling or instruction. Patients will receive a prescription for 10 tabs of hydrocodone / acetaminophen (5/325 mg)
Study Duration:	6 months
Participant Duration:	1 month (preoperative visit to 7 days postop)

1.2 SCHEMA

N=100: Adult patients recommended to undergo thyroid or parathyroid surgery and consent for operation

Exclusion criteria: current opioid use, planned admission >24 hrs

Randomize

Assess pain sensitivity (BP Cuff to 180 mm Hg, score on 10-pt VAS)
Assess preoperative depression screen PHQ9

POINT Program
- Counseling on opioid side effects & abuse
- Review recent study that >90% of endocrine surgery patients do not require narcotics at home
- Will be written form reviewed with patient by MD

Usual Care
- No formal counseling

Cervical Endocrine Surgery

POINT Program
- Scripted shown video
- Instructed to alternate acetaminophen and ibuprofen for pain
- Patient chooses whether to receive narcotic Rx
- Opt-in: Rx for 10 tabs of hydrocodone / acetaminophen (5/325 mg)
- Opt-out: No narcotic Rx
- MD will be available all times to e-Rx rescue narcotics

Usual Care
- Rx for 10 tabs of hydrocodone / acetaminophen (5/325 mg)

- Daily home monitoring of pain score and opioid consumption via PRIME Application
- Will deliver PROMIS-29 and Flourish-QoL survey to patients via PRIME app to UCLA mychart on POD7

- Assessment of pain score, opioid consumption

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Visit 1 Day 0	Pre-Op	Intra-Op	PACU	Home / Clinic
Demographics	X				
Randomization	X				
Intervention: Opioid counseling	X				
Intervention: Video on opioids, study				X	
Intervention: Choose narcotic Rx (y/n)				X	
Daily monitoring via PRIME					X
Health related quality of life survey sent to patients on postoperative day 7 via PRIME					X

2 INTRODUCTION

2.1 STUDY RATIONALE

There is an ongoing opioid crisis in the United States. Surgeons have contributed to the crisis by overestimating patient's requirement for narcotic pain medication for minor procedures including thyroidectomy and parathyroidectomy. Indiscriminate routine prescription of narcotic pain medication results in waste and leaves an opportunity for abuse. A recent study in opioid naïve patients found that 6 percent of patients were still using opioids 3-6 months after their operation.[1] Empowering patients to choose whether to receive narcotics after discharge results in a dramatic reduction in opioids prescribed and wasted.[2] However, it remains unknown if patients are enduring higher levels of pain at home, and whether their quality of life is affected.

Our institution is a high-volume center for endocrine surgery, performing approximately 1000 endocrine surgery cases per year. Thus, we are well positioned to study an opt-in protocol for postoperative narcotic prescriptions. The results will inform treatment decisions for patients and clinicians in the future and can be expanded to other common surgical procedures to dramatically reduce opioid prescription, consumption, and abuse.

2.2 BACKGROUND

Up to 6% of opioid naïve patients have been observed to develop new long-term opioid use following thyroid surgery.[1] It is becoming clear that surgeons have played a part in the current opioid crisis in the United States. As an unintended consequence of prescribing narcotics for postoperative pain control, some patients develop chronic use, which then can lead to misuse and abuse.

For endocrine surgery procedures, we previously overestimated patient's requirement for narcotic pain medication. As a result, we have routinely overprescribed narcotics, generating waste and

opportunities for misuse of unconsumed pills. A two-institution study found that a median of 30 oral morphine equivalents (OMEs) were prescribed to patients after endocrine surgery, but 83% of patients reported consuming less than 10 OMEs at home.[3] There is little standardization in the amount of narcotics to prescribe after cervical endocrine surgery. The number of tabs of narcotic medication prescribed ranges from 0-130 OMEs.[1,3]

Newer studies are showing that the vast majority of patients can be sent home without any narcotic pain medication at all. In a study by Ruffolo et al, which first describes an "opt-in" protocol where patients must actively choose to receive a narcotic pain medication upon discharge, found that 96% of patients decline a prescription for narcotics. Furthermore, none of those patients later called for narcotics or to complain of uncontrolled pain.[2] In the absence of an opt-in protocol, approximately one third of patients choose not to use any opioids postoperatively.[4] Together, this suggests some patients may choose to use a very small amount of opioids if given a routine prescription compared to an opt-in program. It is unclear whether an opt-in program that reduces the amount of opioids prescribed and consumed results in increased pain scores at home and decreased quality of life in the first postoperative week. Some medical centers have transitioned to routinely not prescribing narcotic pain medication unless specifically requested after endocrine surgery as their usual care.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The possible risks and/or discomforts associated with this study include:

• A short duration of increased pain levels among patients that choose to be discharged without narcotic pain medication. In a previous study, there were zero patient calls complaining of excess pain or requesting rescue narcotic prescriptions, indicating the risk is low.

• The researchers will do their best to make sure that patients' information is kept confidential. Study data will be physically and electronically secured and protected by HIPAA. As with any use of electronic means to store data, there is a risk of breach of data security and possible loss of confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

Possible benefits to the patient:
The possible benefits patients may experience is a reduction in opioid consumption, with subsequent reduction in risk of opioid-related side effects and decreased risk of opioid abuse. Patients who choose to participate, regardless of which treatment arm, will receive closer outpatient postoperative monitoring via daily mobile app surveys assessing pain levels. Physician study team members will be notified if patients are having higher than expected levels of pain and contact patients for further assessment of pain.

Possible benefits to others or society:
The possible benefits to others or society from being in this study include decreasing unused narcotic medication at home, decreasing wasteful prescription and purchasing of unused opioids. Establishing whether a bundle of evidence-based practices can lessen postoperative pain and opioid consumption after cervical endocrine surgery.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This study presents minimal risks beyond what the patient would be exposed to if not enrolled in the study. There is the potential risk of breach of data security. These minimal risks are outweighed by the benefit to patients and society as reducing opioid waste and reducing opportunities for abuse are of paramount importance.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Compare an opt-in protocol to routine prescription of narcotic pain medication, with respect to postoperative pain scores	Postoperative pain scores in the first week following endocrine surgery	The success of an opt-in program requires a reduction in opioids prescribed and opioids consumed without an excessive increase in postoperative pain scores. Scores will be compared using hierarchical regression.
Secondary		
Determine whether an opt-in program reduces amount of opioid medication prescribed and consumed	(1) Percent of patients in POINT program that request narcotics (2) Among patients that receive a narcotic prescription, amount of opioids consumed per patient	We expect the POINT program to dramatically reduce the number of patients that receive a prescription for narcotics and subsequently reduce consumption as well
Compare quality of life during postoperative recovery period between patients in POINT program versus usual care	(1) Scores from PROMIS-29 survey and Flourish Quality of Life Index sent to patients on postoperative day seven, inquiring about experiences over past 7 days	To measure if there are intangible elements not captured by pain score that affect quality of life (i.e. pain restricting normal activity or decreasing enjoyment of regular activity)
Determine risk factors for requiring opioids for pain management, including positive scores on PHQ9 depression screen	(1) Determine patient factors that may predict need for opioids on multi-variable regression (2) Determine if scores on PHQ9 depression screen predict need for opioids or opioid consumption	It is important to identify clinical factors that may predict which patients are more likely to request and/or consume opioids.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The purpose of this study is to compare the level of postoperative pain experienced by patients when randomized to a program in which patients must opt-in to receive narcotic pain medication (aka POINT program) instead of being routinely prescribed narcotics.

This is a single-center, randomized clinical trial comparing the POINT program to routine prescription of narcotic pain medication. All patients who consent to outpatient cervical endocrine surgery will be asked to participate during the clinic visit when informed consent is obtained. Those who enroll will be randomized to the POINT program versus routine narcotic prescription using sealed envelopes randomly mixed in a 1:1 ratio. Patients randomized to the POINT program will receive counseling regarding the side effects of opioids, potential for abuse, and will be informed that a majority of patients determined they did not require narcotics for pain control at home. If patients have iphones or ipads suitable for PRIME app, study team members will facilitate download of the PRIME for Patients mobile app onto their personal devices for daily survey administration after surgery. Patients who decline use of the PRIME app or do not have compatible devices will receive daily phone calls by team members after surgery instead. Patients will be offered a $50 gift card if they complete all study surveys, which will be given to patients at their postoperative visit.

All patients will receive acetaminophen 1000 mg PO prior to surgery in the pre-treatment unit. All patients will receive a bilateral cervical plexus block with 10 cc with 0.25% bupivacaine for each side, as well as 5 cc infiltration of planned incision with 0.25% bupivacaine with epinephrine 1:200. In post anesthesia care unit patients will have a standing order for acetaminophen 500 mg PO q6 hours, hydrocodone / acetaminophen (5/325 mg) 1 tab PO PRN pain score 4 or above, morphine 2 mg IV q2 hours PRN breakthrough pain.

<u>Usual Care:</u>

In the post anesthesia recovery unit (PACU), once deemed ready for discharge, patients will receive prescriptions for 10 tabs of hydrocodone/acetaminophen 5/325 mg. If patients have a history of non-tolerance to hydrocodone/acetaminophen (nausea and/or vomiting or altered mental status), 10 pills of codeine/acetaminophen 30/300 mg will be offered instead. If patients experienced uncontrolled pain (pain scores higher than 8) in PACU despite hydrocodone, we will offer to prescribe 10 tabs of oxycodone / acetaminophen instead. They will be provided with written and verbal instructions with the following message: “We recommend taking Tylenol if your pain score is 3 or less and taking Norco if 4 or above. It is okay to also take Ibuprofen for pain, which works differently than Tylenol. Doses of the same medication should be taken six hours apart. If you take Norco, please note each Norco tablet contains 325 mg of Tylenol, also known as acetaminophen. You should not exceed 3000 mg of Tylenol (acetaminophen) in 24 hours due to a risk of liver injury.”

Patients who contact the study team with complaints of uncontrolled pain will be advised to maximize intake of alternating acetaminophen and ibuprofen. Patients who have continued pain despite maximum doses of these two medications and have consumed all 10 tabs will be prescribed an additional 10 tabs of their originally prescribed narcotic medication. If patients complain of uncontrolled pain (score 8 or higher) despite taking maximum doses of hydrocodone / acetaminophen, patients will be prescribed 10 tabs of oxycodone / acetaminophen (5/325 mg).

In the first 7 days after surgery, patients will be asked to answer daily surveys via the PRIME app or by phone call to assess their pain levels and pain medication usage in the prior 24 hours. We will assign a physician (resident or attending) member of the study group to review survey responses and always be available for patient calls following discharge. If patient-reported pain levels are marked as 8 or higher,

the monitoring physician will contact patients to evaluate. Patients will be asked their current pain score, if there were any inciting events that caused increased pain, and if they have been using non-narcotic adjuncts. Patients with pain levels of 8 or higher despite maximal doses of prescribed narcotics and non-narcotic adjuncts will be offered 10 pills of Percocet 5/325 mg electronically prescribed to their local pharmacy.

On the 7th postoperative day, we will assess quality of life during the first postoperative week by administering patients the PROMIS-29 and Flourish questionnaires via the PRIME app, which are loaded into patient's mychart. If patients declined UCLA mychart, questionnaries will be administered over the phone.

POINT Program:

In the PACU, patients who have met criteria for discharge will be shown a scripted video. This video will 1) summarize the adverse effects of opioids, 2) state once again that the vast majority of patients in a previous study declined narcotics with zero patients requesting rescue narcotics after the fact, and 3) reassure patients that if they decline a narcotic prescription at this time, they will be given a direct line to a study physician to request a narcotic prescription be electronically prescribed to the patient's local pharmacy. Patients randomized to POINT will then be asked whether they would like a narcotic pain prescription.

Patients in the POINT program will be given written and verbal instructions with the following message: "If you have pain, we recommend taking 1 tablet (500 mg) of acetaminophen every six hours. If your pain persists, we recommend taking 3 tablets (600 mg) of ibuprofen in addition to acetaminophen, alternating the two medications every three hours. Doses of the same medication should be taken six hours apart."

In the first 7 days after surgery, patients will be asked to answer daily surveys via the PRIME app or by phone call to assess their pain levels and pain medication usage in the prior 24 hours. We will assign a physician (resident or attending) member of the study group to review survey responses and always be available for patient calls following discharge. If patient-reported pain levels are marked as 8 or higher, the monitoring physician will contact patients to evaluate. Patients will be asked their current pain score, if there were any inciting events that caused increased pain, and if they have been using non-narcotic adjuncts.

On the 7th postoperative day, we will assess quality of life during the first postoperative week by administering patients the PROMIS-29 and Flourish questionnaires via the PRIME app, which are loaded into patient's myUCLAhealth. If patients declined enrollment in myUCLAhealth, questionnaries will be administered over the phone.

At follow-up visit, patient will be asked if they are still taking narcotic or non-narcotic pain medication, and asked for their pain score.

Patient Requests Narcotic Rx (Opt-In):

Patients randomized to POINT who request narcotics will be prescribed 10 tabs of hydrocodone-acetaminophen 5/325. If patients have a history of non-tolerance to hydrocodone/acetaminophen (nausea and/or vomiting or altered mental status), 10 pills of codeine/acetaminophen 30/300 mg will be offered instead. If patients experienced uncontrolled pain (pain scores higher than 8) in PACU despite hydrocodone, we will offer to prescribe 10 tabs of oxycodone / acetaminophen instead.

In addition to instruction on acetaminophen and ibuprofen as written above, patients will be instructed: "If pain greater than 3 persists despite acetaminophen and ibuprofen, then take a tablet of [prescribed narcotic]. If you take [prescribed narcotic], please note each [prescribed narcotic] tablet contains [300 vs 325 mg] of acetaminophen. You should not exceed 3000 mg (Or 3 grams) of acetaminophen total in 24 hours due to a risk of liver injury."

Patients who contact the study team with complaints of uncontrolled pain will be advised to maximize intake of alternating acetaminophen and ibuprofen. Patients who have continued pain despite maximum doses of these two medications and have consumed all 10 tabs will be prescribed an additional 10 tabs of their originally prescribed narcotic medication. If patients complain of uncontrolled pain (score 8 or higher) despite taking maximum doses of hydrocodone / acetaminophen, patients will be offered a prescription of 10 tabs of oxycodone / acetaminophen (5/325 mg).

At follow-up visit, patient will be asked if they are still taking narcotic or non-narcotic pain medication and asked for their pain score.

Patient Declines Narcotic Rx (Opt-Out):

In addition to instruction on acetaminophen and ibuprofen as written above, patients will be instructed: "If pain persists despite acetaminophen and ibuprofen, please contact us."

Patients who contact the study team with complaints of uncontrolled pain will be advised to maximize intake of alternating acetaminophen and ibuprofen if not already done. Patients will be offered a prescription of 10 tabs of hydrocodone / acetaminophen regardless of pain level or intake of acetaminophen / ibuprofen. If patients have a history of non-tolerance to hydrocodone/acetaminophen (nausea and/or vomiting or altered mental status), 10 pills of codeine/acetaminophen 30/300 mg will be offered instead.

If patient contact study team again, and experienced uncontrolled pain (pain scores higher than 8) despite hydrocodone, we will offer to prescribe 10 tabs of oxycodone / acetaminophen instead.

At follow-up visit, patient will be asked if they are still taking narcotic or non-narcotic pain medication and asked for their pain score.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study was designed as a single-institution, randomized clinical trial to evaluate an opt-in program to receive postoperative narcotics versus routine narcotic prescription. To date, no randomized trial has examined the impact of an opt-in program after routine endocrine surgery, and no studies have closely examined daily pain scores and quality of life in the postoperative period at home. Though previous studies have established a large majority of patients are able to control their pain without narcotic pain medication at home, it remains unknown whether if patients who decline narcotic pain medication are bearing higher pain scores at home, and whether there is an impact on patient's quality of life.

We believe a non-inferiority design is optimal, since it allows to determine whether we can dramatically reduce opioid prescription and opioid use without increasing pain scores. We purposefully minimized interventions among patients randomized to usual care, since we wanted to truly compare implementation of the POINT program to current standard of care. The impact of the POINT program includes the counseling performed in clinic, setting expectations after surgery, and instructions on maximizing non-narcotic pain medications at home. Using a standardized video in the POINT arm limits variation in counseling and nonverbal communication that may influence a patient's choice to receive a narcotic prescription for home.

It was not possible to blind trial participants to treatment allocation. The surgical and healthcare team will not be involved in any trial assessments and the primary outcome data will be either entered independently by patients into the PRIME app or collected by phone by non-treatment team study personnel.

4.3 JUSTIFICATION FOR DOSE

Prior studies of narcotic use after thyroid surgery report that over 80% of patients use less than 10 oral morphine equivalents following surgery, with many who do not take narcotics at all. The UCLA perioperative pain recommendations also suggest the prescription of 10 tabs of Norco following thyroidectomy. Thus, we chose to prescribe 10 tabs of hydrocodone / acetaminophen in usual care patients, as well as patients in the POINT program that "opt-in" for narcotics.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study after they have completed their follow-up visit

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, aged 18 and older
2. Consented for cervical endocrine surgery
3. English-speaking (all counseling, written, and video materials to be provided in English)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current opioid use or history of opioid dependency or abuse
2. Inpatient admission >23 hours after surgery, due to more extensive surgery or perioperative complications

5.3 LIFESTYLE CONSIDERATIONS

None

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of failure to meet inclusion or exclusion criteria will not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients who consent for cervical endocrine surgery within the UCLA Health system at 5 eligible clinic sites will be screened. Patients who fully complete all administered surveys and questionnaires will be awarded with a $50 Amazon gift card. No compensation will be given for partial completion. Patients will be provided with a reminder of the compensation during the daily PRIME postoperative surveys.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION

6.1.1 STUDY INTERVENTION DESCRIPTION

POINT program – preoperative and postoperative counseling about adverse effect of opioids, empower patients to choose whether or not to receive narcotic medication on discharge.

6.1.2 ADMINISTRATION

Thyroid enhanced recovery after surgery program – bundle of practices to reduce perioperative pain after cervical endocrine surgery

- Preoperative oral acetaminophen
- Intraoperative bilateral cervical plexus nerve block
- Infiltration of incision with local anesthetic prior to incision
- Discussion to select smallest possible endotracheal tube
- Postoperative scheduled oral acetaminophen

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients will be randomized to POINT program versus routine prescription of narcotic after surgery. There will be a number of sealed envelopes allocating enrollees to POINT program versus usual care mixed in a 1:1 ratio. As stated above, it was not reasonable to blind trial participants to treatment allocation. The surgical and healthcare team will not be involved in any trial assessments and the primary outcome data will be either entered independently by patients into the PRIME app or collected by phone by non-treatment team study personnel.

6.3 STUDY INTERVENTION COMPLIANCE

Recovery room staff will receive initial orientation to the study. Patients status as study subject will be noted in patients paper chart once patient arrives in PACU. Patients will be reminded to input their postoperative outpatient data by daily notifications via the PRIME app or daily phone calls from study personnel.

6.4 OUTCOMES MEASUREMENT

PRIME for Patients – mobile application developed at UCLA by Dr. Anne Lin now used by several surgery subspecialties at UCLA. We created customized questions that patients will answer on a daily basis regarding their postoperative pain.

6.4.1 RESCUE

If patients report uncontrolled pain via PRIME app or phone survey, defined as pain score of 8 or higher, an alert will be sent to a pre-assigned “on-call” provider. This provider will assess that patient’s pain, exacerbating factors, and help optimize use of non-narcotic medication.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Criteria for discontinuing study intervention includes any perioperative complications or more extensive surgery that requires additional hospitalization beyond 23 hours. Because the study involves minimal risk, follow up of participants who discontinue the study intervention will not be pursued.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Because the study involves minimal risk, we do not foresee that an investigator may discontinue or withdraw a participant from the study for reasons other than patient request.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to present for postoperative clinic visit and / or fails to answer daily phone call, email, or text message for >5 days.

The following actions must be taken if a participant fails to present for postoperative clinic visit

- The site will attempt to contact the participant and reschedule the clinic visit.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Screening: Endocrine surgeons consenting patients for cervical endocrine surgery at UCLA Health sites (UCLA Endocrine Center, Westwood, CA; UCLA Santa Monica Endocrinology, Santa Monica, CA; UCLA South Bay Endocrinology, Torrance, CA; UCLA Westlake Village Endocrinology, Westlake Village, CA; UCLA Encino; UCLA Toluca Lake, UCLA Encino) will identify patients satisfying inclusion and exclusion criteria listed above and determine patients' willingness to participate in the trial.

Pain sensitivity score: During preoperative clinic visit, patient will have blood pressure cuff inflated to 180 mm Hg and patients will be asked to rate the pain of that sensation on a 10-point visual analog scale.

PHQ-9: During the preoperative clinic visit, patient will fill out this questionnaire. This is a validated tool to assess for symptoms of depression.[5]

Preoperative counseling on adverse effects of opioids: Patients enrolled in the study will receive counseling by study personnel. Study personnel will be guided by written documents that will be handed to the patient following the counseling session.

Postoperative video: Once meeting criteria for discharge in the PACU, patients will be shown a pre-recorded video that summarizes main points from the counseling above. This video will also emphasize that the vast majority of patients do not require narcotics for pain control after endocrine surgery.

Finally, it will reassure patients that they will be provided a direct line to a study physician following discharge. If patients decline narcotics on discharge, they will be able to contact a physician for consultation and a narcotics prescription if needed.

PRIME for Patients: Patients will be given an option to be contacted by the PRIME app, email or phone call. They will also be asked if study personnel can contact them by means other than their primary choice. This is a mobile application created by UCLA Health. Study team members will assist patients who consent to use the app to download it onto their personal devices. Patients will receive daily notifications in the morning to complete the survey.

PROMIS-29: This is a validated tool to assess patient global quality of life after thyroid surgery.[6,7]

Flourish: This is a separate validated tool that assesses quality of life based not solely on the absence of disease or disability but rather focuses on patient's perception that they are able to continue to grow and prosper in ways that are most meaningful to the patient.[8]

8.2 SAFETY AND OTHER ASSESSMENTS

See Section 8.1

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Study personnel will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study

participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

8.3.5 ADVERSE EVENT REPORTING

Type of Event	When to Report
ADVERSE EVENTS (AE)	
INTERNAL (on-site) AE that PI determines to be 1) unexpected, 2) related or possibly related, ***and*** 3) places subjects or others at greater risk of harm than previously known or recognized (i.e. serious) ***OR*** 1) expected ***and*** 2) related ***but*** 3) indicates a higher frequency of occurrence or higher level of severity than was previously known or recognized	Within **10 working days** of UCLA PI awareness.
EXTERNAL (off-site) AE that UCLA PI determines to be 1) unexpected, 2) related or possibly related, ***and*** 3) places subjects or others at greater risk of harm than previously known or recognized (i.e. serious) ***Note:*** Submit event if all subjects have completed participation, if previously-enrolled subjects must be notified of potential risk	Within **10 working days** of UCLA PI awareness.
For interventional studies only*:** Internal (on-site) death that PI determines to be 1) unexpected ***and 2) related or possibly related	Within **3 working days** of UCLA PI awareness
For interventional studies only: Internal (on-site) death that PI determines to be 1) expected ***and*** 2) related or possibly related	At time of continuing review
External adverse event that UCLA PI determines does not meet the 10-working-day reporting criteria	Reporting not required
OTHER TYPES of EVENTS or UPDATED STUDY SAFETY INFORMATION	
Updated Investigator Brochure or Device Brochure	Within **10 working days** of UCLA PI awareness
Audit or monitoring report, DSMB Report, or Interim Study Results	
Other **updated safety information or publication** that addresses the risk or benefit of the research	
Suspension, Hold or Termination of study activities	Within **3 working days** of UCLA PI awareness
PROTOCOL VIOLATIONS, DEVIATIONS and INCIDENTS, including SUBJECT COMPLAINTS	
Violation, deviation or incident that is 1) unexpected, 2) related or possibly related to the study ***and*** 3) places subjects or others at greater risk of harm than previously known or recognized. See reporting form for examples	Within **10 working days** of UCLA PI awareness
Emergent protocol deviation to eliminate apparent immediate hazard to subject	Within **3 working** days of event
Violation, Deviation or Incident that the UCLA PI determines does not meet 10 or 3-day reporting requirements	Report at time of continuing review

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Postoperative Pain Scores Through POD7, Maximum and Daily Average
Null hypothesis: There is/are no significant difference(s) in pain scores in patients randomized to POINT program versus usual care, as defined as a 2 point difference on a visual analog scale from 0 to 10.

Alternative hypothesis: There is/are significant difference(s) in pain scores in patients randomized to POINT versus usual care

- Secondary Efficacy Endpoint(s):

Opioids Prescribed and Consumed
Null hypothesis: There is no significant difference in number of opioids prescribed and consumed in patients enrolled in POINT program versus usual care

Alternative hypothesis: There is a significant difference in number of opioids prescribed and consumed in patients enrolled in POINT program versus usual care

Health-related Quality of Life
Null hypothesis: There is/are no significant difference(s) in HR-QoL metrics between patients enrolled in the POINT program versus usual care

Alternative hypothesis: There is/are significant difference(s) in HR-QoL metrics between patients enrolled in the POINT program versus usual care.

9.2 SAMPLE SIZE DETERMINATION

This is a prospective study including all patients undergoing cervical endocrine surgery in our health system. We chose a non-inferiority design and defined minimal clinically important difference as a difference of 2 points on an 11-point numeric rating scale of pain.

A power analysis for sample size was calculated. In order to achieve 90% power to establish noninferiority with a margin of 2 points on the numeric rating scale for pain (0-10) comparing group 1 versus group 2 at an alpha level of 0.05 (1-sided) for each comparison using a standard deviation of 2, 18 patients per treatment arm will need to be enrolled.

Based on our interval analysis, half of patients in the POINT group opted in for opioids. Our power analysis indicates that 100 patients undergoing cervical endocrine surgery will adequately power our study to detect a significant difference in pain score in the POINT group (projected 25 patients to opt in, 25 patients to opt out). A 15% margin was added for drop out.

9.3 POPULATIONS FOR ANALYSES

The comparison groups will be patients randomized to the POINT program versus routine narcotic prescription.

There will also be a subgroup analysis of patients that were randomized to POINT that elected to go home with narcotics versus those who did not. There will also be a separate analysis of the patients that initially declined narcotics but later asked for a rescue prescription.

There will also be further analysis of patients that did not consume opioids regardless of randomization group versus patients that did consume opioids to determine what risk factors may predict opioid usage and / or increased pain.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive continuous data will be summarized as medians and interquartile ranges. Descriptive categorical data will be summarized as percentages. Comparisons of baseline demographics between groups will be made using standardized differences to estimate effect sizes between groups. P values < 0.05 and 95% confidence intervals will be used as thresholds for statistical significance. All tests will be two sided.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Postoperative pain scores

Postoperative pain score will be captured on initial arrival to PACU, then twice hourly, then immediately prior to discharge. Once patients have returned home, we will ask for daily maximum pain score and average pain score from discharge until postoperative day 7. Final pain score will be assessed at post-operative visit.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Opioid consumption

Opioids consumed in the PACU will be recorded in the electronic medical record. Following discharge we will determinate opioid consumption by patient reporting. Units will be standardized into oral morphine equivalents.

Opioids requested and prescribed

We will analyze risk factors for requesting narcotics within the patients randomized to the POINT program, including age, sex, BMI, prior history of narcotic use, PHQ-9, preoperative cancer diagnosis, surgical procedure, inpatient pain medication administered, and inpatient postoperative pain scores. We will also compare the total amount of opioids prescribed (both initial and rescue) among patients randomized to POINT program and to routine narcotic prescription.

Health-related Quality of Life

HR-QoL will be estimated using a PROMIS-29 and Flourish surveys administered on postoperative day 7 via PRIME app or telephone call.

9.4.4 SAFETY ANALYSES

The UCLA IRB deemed our study to involve minimal risk to patients based on 45 CFR 46.166(c) and (d). All practices and procedures in our study are consistent with standard of care, the intervention is simply the introduction of patient choice when receiving narcotics. No AEs will be considered related to the study intervention and will not be analyzed.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics to be compared between patients randomized to the POINT program versus usual care include age, sex, history of depression/anxiety, history of substance abuse, pain sensitivity score. Continuous variables will be summarized with medians and interquartile ranges, while categorical variables will be summarized with percentages. Differences in baseline characteristics between groups will be compared by calculating the standardized difference between groups.

9.4.6 PLANNED INTERIM ANALYSES

Interim analysis will be performed after 3 months of enrollment.

9.4.7 SUB-GROUP ANALYSES

There will also be a subgroup analysis of patients that were randomized to POINT that elected to go home with narcotics versus those who did not. There will also be a separate analysis of the patients that initially declined narcotics but later asked for a rescue prescription.

There will also be further analysis of patients that did not consume opioids regardless of randomization group versus patients that did consume opioids to determine what risk factors may predict opioid usage and / or increased pain.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer's IB, package insert, and device labeling.

1. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surg.* 2017;152(6):e170504.
2. Ruffolo LI, Jackson KM, Juviler P, et al. Narcotic Free Cervical Endocrine Surgery: A Shift in Paradigm. *Ann Surg.* 2019.
3. Lou I, Chennell TB, Schaefer SC, et al. Optimizing Outpatient Pain Management After Thyroid and Parathyroid Surgery: A Two-Institution Experience. *Ann Surg Oncol.* 2017;24(7):1951-1957.
4. Chen Y, Nwaogu I, Chomsky-Higgins K, et al. Postoperative Pain and Opioid Use After Thyroid and Parathyroid Surgery-A Pilot, Prospective SMS-Based Survey. *J Surg Res.* 2019;240:236-240.
5. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *Cmaj.* 2012;184(3):E191-E196.
6. Goswami S, Mongelli M, Peipert BJ, Helenowski I, Yount SE, Sturgeon C. Benchmarking health-related quality of life in thyroid cancer versus other cancers and United States normative data. *Surgery.* 2018;164(5):986-992.
7. Craig BM, Reeve BB, Brown PM, et al. US valuation of health outcomes measured using the PROMIS-29. *Value in Health.* 2014;17(8):846-853.
8. VanderWeele TJ, McNeely E, Koh HK. Reimagining health—flourishing. *JAMA.* 2019;321(17):1667-1668.