A Clinician-Focused Nudging Intervention to Optimize Post-Surgical Prescribing

Principal Investigator:

Daniel B. Larach, M.D., M.S.T.R., M.A.

Assistant Professor of Anesthesiology, Vanderbilt University Medical Center

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1 PRÉCIS

1.1 Study Title

A Clinician-Focused Nudging Intervention to Optimize Post-Surgical Prescribing

1.2 Objectives

Overall goal: Develop pilot data for a new, easily scalable strategy to optimize post-surgical opioid prescribing.

Specific objective #1: Evaluate feasibility and acceptability of carrying out a novel nudge intervention that may reduce excess postoperative opioid prescribing by surgeons.

Exploratory objective #2: Determine whether the nudge intervention leads to changes in subsequent postoperative opioid prescribing by surgeons.

Exploratory objective #3: Determine whether this technique affects patient opioid consumption, refill requests, medical visits for pain, satisfaction with analgesia, and opioid misuse.

1.3 Design and Outcomes

Pilot single site randomized controlled trial to assess the feasibility and acceptability of a nudging intervention providing surgeons with procedure-specific feedback regarding patients' postoperative opioid prescription-to-consumption ratio in individuals 18 years of age and older.

Primary outcomes:
Feasibility:

1. Percentage of surgeons approached who agree to participate in study
2. Percentage of patients contacted who agree to participate in study

Acceptability:

1. Surgeon-reported acceptability of intervention

Exploratory outcomes: Mean pre-post percentage change in procedure-specific prescription size, mean pre-post change in patient opioid consumption, opioid refills, medical visits for pain, satisfaction with analgesia, and opioid misuse, surgeon-reported perceived usefulness of intervention.

1.4 Interventions and Duration

In the first phase, patients undergoing specific elective surgeries at the study site (Vanderbilt University Medical Center [VUMC], Nashville, TN) during study days 1-60 will be contacted by telephone or electronically 14 days postoperatively (study days 15-74) and asked to perform an opioid pill count; they will also be asked about opioid refills, satisfaction with analgesia, emergency room visits or hospitalizations for pain, and opioid misuse.

First phase data will then be analyzed and patients' surgeons randomized in a 1:1 ratio to the intervention or control arms. After study day 97, surgeons in the intervention arm will be provided procedure-specific direct feedback on opioid prescribing and consumption for their patients who had surgery during days 1-60.

After this intervention, we will assess pre-post change in opioid prescription size (measured in oral morphine equivalents) from baseline between the two groups for surgeries performed during days 108-167

We will also contact patients undergoing post-intervention surgeries (during days 108-167) 14 days postoperatively (days 122-181) to assess pre-post changes in patient opioid consumption, satisfaction with analgesia, medical visits for pain, opioid refills, and opioid misuse.

1.5 Sample Size and Population

Patients (initial phase): We anticipate successfully contacting 5 patients per day for a total of 300 patients.

Surgeons: We anticipate obtaining mean pre-post prescribing change in up to 60 surgeons (30 per group).

Patients (second phase): We anticipate successfully contacting 5 patients per day for a total of 300 patients.

2 STUDY TEAM ROSTER

Principal Investigator: **Daniel B. Larach, M.D., M.S.T.R., M.A.**
Assistant Professor of Anesthesiology
Vanderbilt University Medical Center
719 Thompson Ln. Ste. 22209
Nashville, TN 37204

Telephone (615) 322-6033
Fax (615) 322-9089
Email address daniel.larach@vumc.org

Main responsibilities/Key roles: Overall PI

Co-Investigators/Staff: **Stephen P. Bruehl, Ph.D.**
Professor of Anesthesiology
Vanderbilt University Medical Center
701 Medical Arts Building
1211 21st Ave. South
Nashville, TN 37212

Telephone (615) 936-1821
Fax (615) 936-8983
Email address stephen.bruehl@vumc.org

Main responsibilities/Key roles: VUMC site co-I

David A. Edwards, M.D., Ph.D.
Associate Professor of Anesthesiology and Neurological Surgery
Vanderbilt University Medical Center
719 Thompson Lane, Ste. 22209
Nashville, TN 37201

Telephone (615) 322-6033
Fax (615) 322-9089
Email address david.a.edwards@vumc.org

Main responsibilities/Key roles: VUMC site co-I

Sarah S. Osmundson, M.D., M.S.
Assistant Professor of Obstetrics and Gynecology
Vanderbilt University Medical Center
719 Thompson Lane, Ste. 27100
Nashville, TN 37201

Telephone (615) 343-5700
Fax (615) 343-6724
Email address sarah.osmundson@vumc.org

Main responsibilities/Key roles: VUMC site co-I

Benjamin C. French, Ph.D.

Associate Professor of Biostatistics
Vanderbilt University Medical Center
2525 West End Ave., Ste. 1100, Rm. 1137
Nashville, TN 37203

Telephone (615) 322-2001
Fax (615) 343-4924
Email address b.french@vumc.org

Main responsibilities/Key roles: Study biostatistician; will provide statistical expertise for the study, including study design, protocol development, and analysis of the results.

Tracie D. Baker, C.C.R.P.

Research Coordinator IV
Vanderbilt University Medical Center
701 Medical Arts Building
1211 21st Ave. South
Nashville, TN 37212

Telephone (615) 875-1852
Email address tracie.d.baker@vumc.org

Main responsibilities/Key roles: Study coordinator; will be responsible for carrying out study-related procedures including recruiting, consenting, and surveying patients as well as implementing the personalized feedback to surgeons in the Intervention Arm.

3 STUDY OBJECTIVES

3.1 Primary Objective

Evaluate the feasibility and acceptability of a novel nudge intervention that may reduce excess postoperative opioid prescribing by surgeons.

3.2 Exploratory Objectives

Determine whether surgeons randomized to the Intervention Arm will exhibit greater mean pre-post percentage change in procedure-specific prescription size compared to the Control Arm. Additionally, determine whether the novel nudge intervention affects patient opioid consumption, refill requests, medical visits for pain, satisfaction with analgesia, and opioid misuse.

4 BACKGROUND AND RATIONALE

4.1 Background on Condition, Disease, or Other Primary Study Focus

Among those aged 55 and older, opioids caused 8,877 deaths in the U.S. in 2017 (the most recent year for which data are available). 4,564 of these deaths were from prescription opioids.(1) The total number of U.S. opioid-related deaths in 2017 was 47,600, 17,029 of which involved prescription opioids.

Physician prescribing is deeply connected with opioid use disorder: Most Americans misusing prescription opioids were either directly prescribed these medications or received them from a friend or relative with a prescription,(2) and most current heroin users started opioid use with prescribed medication.(3) Surgical prescribing comprises an increasing proportion of first-start opioid prescriptions to opioid-naïve patients;(4) 6% of such patients develop new persistent opioid use postoperatively.(5) Up to 70% of prescribed postoperative opioids go unconsumed and become a reservoir for potential diversion or misuse.(6)

4.2 Study Rationale

Evidence-based postoperative prescribing guidelines have been propagated(7-10) in order to decrease both the number of surgical patients developing new persistent opioid use and the overprescribing of post-surgical opioids. Other nudging techniques like changing electronic medical record prescription size defaults have been used in the surgical setting to decrease opioid prescribing,(11) although such tactics run the risk of increasing opioid prescribing for already-low prescribers.(12)

Despite these initiatives, evidence remains limited regarding the optimal methods for reducing post-surgical opioid prescribing.(13) Our proposed project will test a novel nudging technique that has not been studied in the postoperative opioid prescribing space: direct feedback to surgeons about their patients' opioid prescription-to-consumption ratios. Direct feedback to opioid prescribers after patients suffered a fatal opioid overdose has been shown to reduce subsequent opioid prescribing significantly.(14) We believe that providing granular data to a wide population of surgical prescribers (not just those whose patients overdose) will prove similarly effective. Should our intervention decrease

surgical prescribing, we anticipate it playing a significant role in the national strategy to combat the opioid crisis.

5 STUDY DESIGN

We plan a pilot randomized controlled trial randomizing surgeons to either intervention (direct feedback) or control (no direct feedback) arms. Surgeons frequently performing specific elective general, gynecologic, orthopedic, and neurological surgeries at VUMC will be identified during a 30-day study lead-in period. Then, patients aged at least 18 years undergoing these surgeries at VUMC during study days 1-60 will be contacted by telephone 14 days postoperatively (study days 15-74) and asked to perform an opioid pill count; they will also be asked about opioid refills, satisfaction with analgesia, emergency room visits or hospitalizations for pain, and opioid misuse. The electronic medical record will be also queried for the size of the initial postoperative opioid prescription as well as evidence of any refills for each enrolled subject. We anticipate successfully contacting 5 patients per day for a total of 300 patients in this initial phase. We plan to consent patients electronically at the time of the telephone contact as consenting patients immediately after surgery may influence their subsequent opioid consumption.

Surgeons will be consented without overt discussion of the nudge intervention. Following the first block of surgeries and associated patient follow-up (study days 1-74), data will be analyzed and then surgeons will be randomized in a 1:1 ratio to the intervention or control arms. Randomization will be stratified by both surgical specialty and by mean opioid prescription size during the initial block of surgeries. After study day 97, surgeons in the intervention arm will be provided procedure-specific direct feedback on opioid prescribing and consumption for their patients who had surgery during days 1-60.

After this intervention, we will assess pre-post change in opioid prescription size (measured in oral morphine equivalents) from baseline between the two groups for surgeries performed during days 108-167. That is, mean size of post-intervention prescriptions (from electronic medical record queries) will be compared with mean pre-intervention prescription size by the same surgeon for the same procedure in order to calculate change from baseline. Primary outcomes are measures of study feasibility and acceptability given that this is a pilot study. The main exploratory outcome will be mean percentage change in procedure-specific prescription size. We will then compare mean per-surgeon percentage change in prescription size between the direct feedback and no-direct-feedback groups. Multiple regression analyses adjusting for case type and surgical specialty will also be employed to permit more granular examination of the targeted changes. To evaluate other exploratory outcomes, we will contact patients undergoing post-intervention surgeries (during days 108-167) 14 days postoperatively (days 122-181) to assess pre-post changes in patient opioid consumption, satisfaction with analgesia, medical visits for pain, opioid refills, and opioid misuse. We again anticipate contacting 5 patients per day for a total of 300 patients in this second phase.

6 SELECTION AND ENROLLMENT OF PARTICIPANTS

6.1 Inclusion Criteria

Study *surgeon* participants must meet all the inclusion criteria below to participate in the study:

- General, gynecologic, orthopedic, or neurological surgeon at VUMC during the study period performing any of the surgeries listed below

Study *patient* participants must meet all the inclusion criteria below to participate in the study:

- Aged greater or equal to 18 years
- Undergoing specified elective general, gynecologic, orthopedic, and neurological surgeries at VUMC during the specified study periods (days 1-60 for the initial patient group; days 108-167 for the follow-up patient group)
    - General: laparoscopic or open cholecystectomy, laparoscopic or open appendectomy
    - Gynecologic: abdominal hysterectomy, laparoscopic/robotic hysterectomy, vaginal hysterectomy, anterior repair/colporrhaphy, posterior repair/colporrhaphy, tension-free vaginal tape procedure, sacrospinous ligament suspension, sacrocolpopexy, uterosacral ligament suspension, colpocleisis, perineorrhaphy
    - Orthopedic: total knee arthroplasty, total hip arthroplasty, total shoulder arthroplasty, 1- or 2-level spinal laminectomy and/or discectomy (without fusion)
    - Neurological: 1- or 2-level spinal laminectomy and/or discectomy (without fusion)
- Provided opioid prescription for postoperative pain relief (verified in VUMC EMR)
- Able to understand study procedures and participate in the pill count and telephone/electronic interview process in English or Spanish
- Provide informed consent

6.2 Exclusion Criteria

There are no planned exclusion criteria for study *surgeon* participants, although those performing <3 of the specified surgeries during the first 60-day period of surgeries will not be eligible for randomization.

Study *patient* candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation:

- Opioid prescription filled (per VUMC electronic medical record [EMR] and patient self-report) between 3 months and 14 days prior to surgery
- Primary reason for surgery as assessed by chart review is cancer-related

- Surgery is a repeat/revision surgery (e.g., revision total knee arthroplasty)
- Patient has been inpatient for >3 days postoperatively prior to receiving post-discharge prescription
- Vulnerable populations: current pregnancy, prisoners
- Inability or unwillingness of patient to give informed consent
- (Partial exclusion) Prior participation in this study (e.g., a patient included in the initial patient group undergoing a left total knee arthroplasty on study day 15, followed by a right total knee arthroplasty on day 115; such a patient would be included in the initial patient group but would not be recontacted for the follow-up patient group)

6.3 Study Enrollment Procedures

During the 30-day lead-in period, study *surgeon* participants will be identified through VUMC EMR queries of historical and booked case numbers for the specific procedures listed in section 4.1, above. Given the nature of the planned behavioral nudging intervention, it is not feasible for full consent to be obtained prospectively from surgeon participants as this would very likely affect prescribing behavior in both the Intervention and Control Arms due to the Hawthorne effect. Consequently, we plan to request permission from the VUMC Institutional Review Board to utilize deception for *surgeon* participants, who will be asked to consent for participation in a study giving them information about their patients' opioid consumption (surgeons will be debriefed fully on study purposes upon completion of the study). Surgeon participants will be prospectively selected in a participant log kept by study staff. Surgeons will be randomized on a 1:1 basis to either the Intervention or Control Arms prior to administration of the nudge intervention. Enrolled surgeons must complete a minimum 3 listed cases during the initial 60-day study period (study days #1-60) to be eligible for randomization.

Study *patient* candidates will be identified through VUMC EMR queries of performed surgical cases for study surgeon participants. All patient candidates including procedures by study surgeons will be sent a pre-recruitment letter by the VUMC Department of Anesthesiology informing them that may be contacted by telephone postoperatively regarding the study. Study team members contacting patients will be blinded to the surgeon randomization assignments. All patient candidates undergoing included procedures by study surgeons and otherwise meeting inclusion/exclusion criteria will be contacted 14 days postoperatively by telephone or electronic messaging and asked to complete an opioid pill count and a brief verbal questionnaire relating to postoperative opioid use and analgesia. Because preoperative or immediate postoperative consenting for the study might affect patient participants' subsequent opioid consumption, we plan to obtain electronic informed consent from *patients* at the time of contact. Study research coordinators will securely document the consent process. Study personnel will also maintain a screening log containing records for all evaluated candidates as well as reasons for study ineligibility and non-participation of eligible candidates.

Additionally, at the request of the study Data and Safety Monitoring Board, a third participant population will comprise *all* patients undergoing surgery *of any kind* by

surgeons in the nudge intervention group for 60 days following receipt of the nudge intervention. This will entail only EHR queries on POD #10 and #30 (on a rolling basis) for pain-related medical concerns and healthcare visits. This is to determine whether surgeon prescribing practices changed sufficiently following nudge relief to compromise postoperative analgesia and potentially harm patients. These patients will not be contacted by study staff unless they otherwise meet inclusion criteria for the study as listed above.

7 STUDY INTERVENTIONS

7.1 Interventions, Administration, and Duration

The one-time contact of *patient* participants will take place on postoperative day 14 (or no later than postoperative day 19) for the initial contact group. After verifying eligibility and documenting consent, patients will be asked to obtain their prescribed opioid pill bottle and conduct a pill count. If the patient consumed the entirety of the prescription and disposed of the bottle, this will be documented. If the patient does not have their pill bottle readily available, arrangements will be made to follow up with the patient by telephone or secure electronic messaging later to complete this aspect of the query. Patient participants will also be asked to answer several questions related to our exploratory outcomes:

- Overall satisfaction with postoperative analgesia (numeric rating scale)
- To select from the following answers: "I received a) too many opioid pills, b) the right amount of opioid pills, c) too few opioid pills."
- Whether patient required any medical visits primarily due to postoperative pain (office visits, emergency department visits, or hospital admissions)
- Whether additional opioid refills were prescribed after the initial postoperative prescription (this will also be evaluated through EMR queries)
- Evidence of opioid misuse (Current Opioid Misuse Measure-9 [COMM-9])

The one-time intervention for *surgeon* participants in the Intervention Arm will take place on approximately study day 97. This will entail procedure-specific direct feedback (through electronic communication) on patients' opioid consumption-to-prescription ratio. E.g., "Your abdominal hysterectomy patients were prescribed a mean 60 opioid pills last month. These patients consumed a mean 20 pills (33%)." Surgeon participants who perform more than one of the specified procedures (see section 4.2, above) will receive nudging communications for each individual procedure. Since the data on opioid consumption provided to surgeons is based on self-report data from consented patients, surgeons will be specifically informed that the data is self-reported through inclusion of the following statement: "This is based off self-reported pill counts. The information is self-reported and not validated so it could be erroneous."

Surgeon participants randomized to the Control Arm will not be contacted directly at any time during the study.

7.2 Handling of Study Interventions

The one-time contact of *patient* candidates will take place as follows: (1) Initial contact of patients by research coordinators through telephone or secure electronic message; (2) consent process and electronic documentation of consent; (3) pill count and questionnaire by telephone or secure electronic message (REDCap Twilio).

The one-time intervention for *surgeon* participants in the Intervention Arm will be delivered by text message, paging or e-mail on the same day.

7.3 Concomitant Interventions

7.3.1 Allowed Interventions

All drugs and treatments/interventions are permitted.

7.3.2 Required Interventions

There are no required interventions.

7.3.3 Prohibited Interventions

There are no prohibited drugs and treatments/interventions.

7.4 Adherence Assessment

No formal adherence assessment is planned.

8 STUDY PROCEDURES

8.1 Schedule of Evaluations

Assessment	Days -30 to 0	Days 1-60 Group #1 PT Surgeries	Days 15-74 Patient Phone calls	Day 75-93 Surgeon prescribing practice review	Day 97Surgeon Nudge Arm notification	Days 108-167 Group #2 PT Surgeries	Days 122-181 Patient Phone calls	Days 181+ Surgeon survey
Identification of Surgeon Participants	X							
Preliminary Screening of Patient Candidates (EMR/PDMP) – Initial Patient Group		X	X					
Inclusion/Exclusion Criteria – Initial Patient Group			X					
Consent of Patient Candidates – Initial Patient Group			X					
Pill Count – Initial Patient Group			X					
Exploratory Outcome Questions – Initial Patient Group			X					
Assessment of Pre-Intervention Opioid Prescribing by Surgeon Participants				X				
Randomization of Surgeon Participants				X				

Nudging Intervention					***x***			
Assessment of Post-Intervention Opioid Prescribing by Surgeon Participants						***x***	***x***	
Screening of Patient Candidates (EMR/PDMP) – Follow-Up Patient Group							***x***	
Inclusion/Exclusion Criteria – Follow-Up Patient Group							***x***	
Consent of Patient Candidates – Follow-Up Patient Group							***x***	
Pill Count – Follow-Up Patient Group							***x***	
Exploratory Outcome Questions – Follow-Up Patient Group							***x***	
Acceptability Questions - Surgeons								***x***
Adverse Events				***x***	***x***	***x***	***x***	***x***

8.2 Description of Evaluations

Figure 1: Study Flow Diagram (Days -30 through 0)

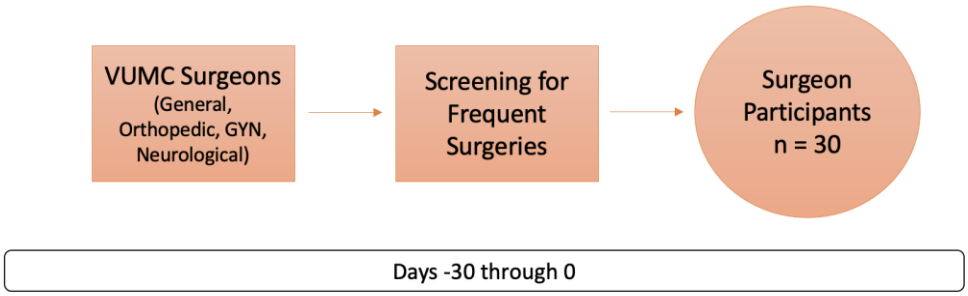


Figure 2: Study Flow Diagram (Days 1 through 60)

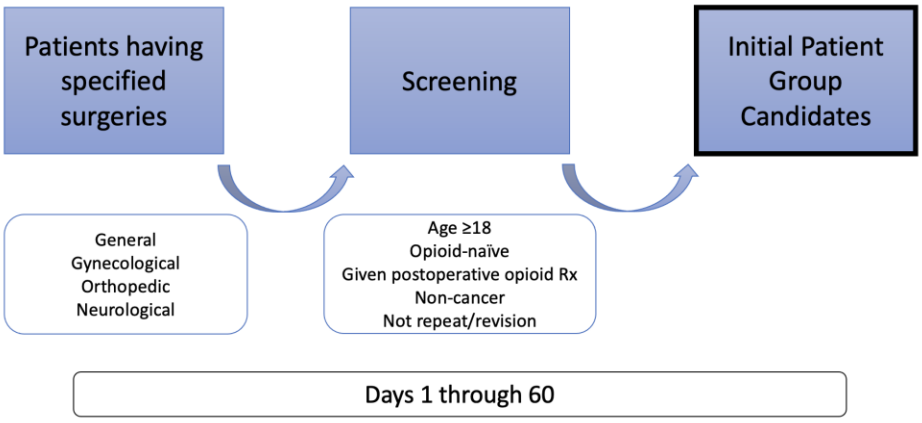


Figure 3: Study Flow Diagram (Days 15 through 74)

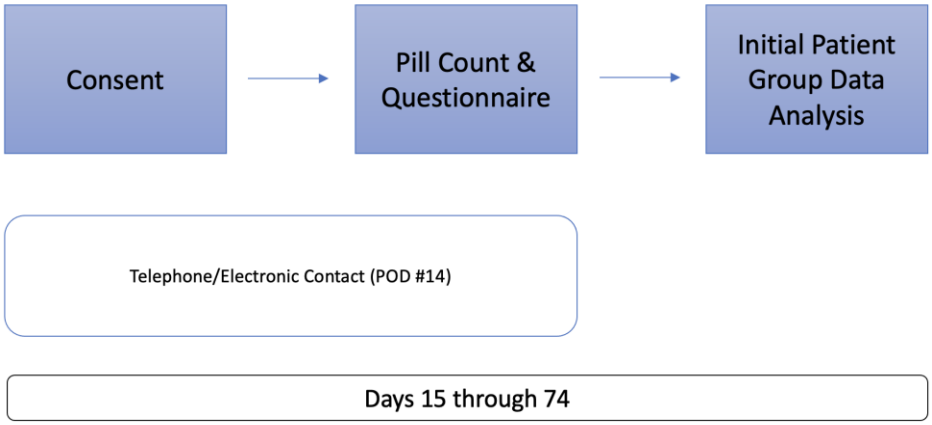


Figure 4: Study Flow Diagram (Days 97 through 167)

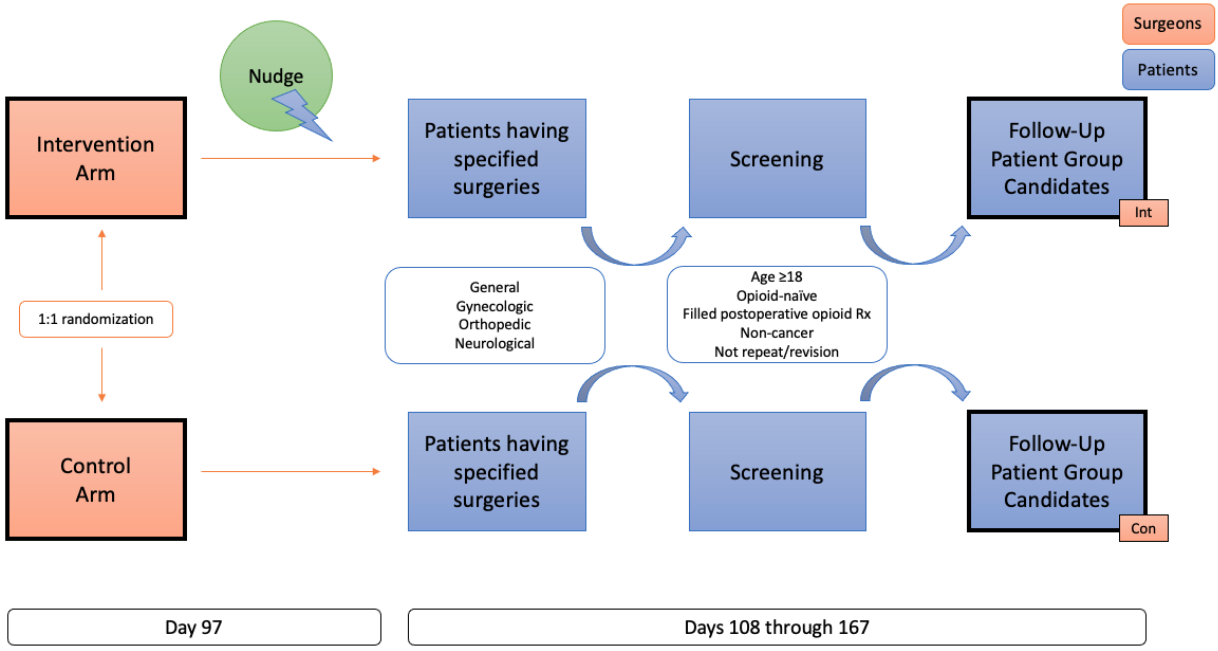
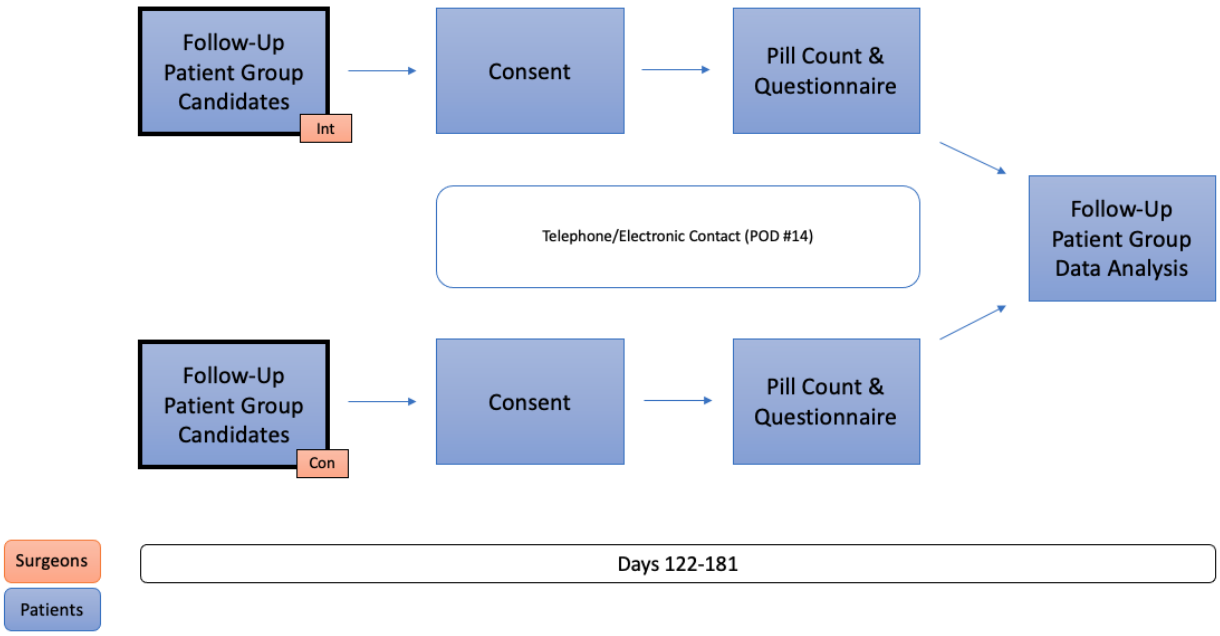


Figure 5: Study Flow Diagram (122 through 181)



8.2.1 Preliminary Evaluations (Days -30 to 0)

Identification of Surgeon Participants

- Up to 60 general, gynecologic, orthopedic, and neurological surgeons at VUMC regularly performing the following procedures:
    - General: laparoscopic or open cholecystectomy, laparoscopic or open appendectomy
    - Gynecologic: abdominal hysterectomy, laparoscopic/robotic hysterectomy, vaginal hysterectomy, anterior repair/colporrhaphy, posterior repair/colporrhaphy, tension-free vaginal tape procedure, sacrospinous ligament suspension, sacrocolpopexy, uterosacral ligament suspension, colpocleisis, perineorrhaphy
    - Orthopedic: total knee arthroplasty, total hip arthroplasty, total shoulder arthroplasty, 1- or 2-level spinal laminectomy and/or discectomy (without fusion)
    - Neurological: 1- or 2-level spinal laminectomy and/or discectomy (without fusion)
- EMR query will be utilized to identify surgeons most frequently performing these surgeries historically at VUMC

- The date of screening and of enrollment of surgeon participants will be kept in the password-protected and encrypted research database.

Preliminary Screening of Patient Candidates (EMR/PDMP) – Initial Patient Group

- Age ≥18 years
- Undergoing specified surgeries with surgeon participants between study days 1-60
- Provided opioid prescription that was subsequently filled
- Opioid-naïve (no prior opioid prescriptions between study days -90 to -14)
- Non-cancer surgery
- Non-repeat/revision surgery
- Demographic information, including gender and race/ethnicity, will be collected
- Screening date will be recorded in the password-protected and encrypted research database

8.2.2 Initial Patient Group Contacts and Surgeon Pre-Intervention Prescribing Evaluation (Days 1-74)

Inclusion/Exclusion Criteria – Initial Patient Group

- Confirmation of inclusion/exclusion criteria first assessed during preliminary screening
- Assessment of other inclusion/exclusion criteria:
    - Able to understand study procedures and participate in pill count and interview process in English or Spanish
    - Not a member of a vulnerable population (current pregnancy, prisoners)
    - Able to give informed consent

Consent of Patient Candidates – Initial Patient Group

- Identified patient candidates will be contacted by telephone or electronically by trained research coordinators.
- After description of study is provided and risks reviewed, telephone or electronic consent will be obtained.
- Documentation of electronic consent and enrollment of patient participants will be made by the research coordinator and stored in the password-

protected, encrypted research database.

Pill Count – Initial Patient Group

- Consented patients will be asked to physically obtain their prescribed opioid pill bottle and conduct a pill count.
- Patients who report having consumed the entirety of their prescription and disposed of the bottle will be considered to have a pill count of 0; absence of the empty bottle will be documented in the patient's study record.
- For patients who consent to participate but do not have their pill bottle readily available, arrangements will be made to follow up with the patient by telephone or secure electronic messaging later to complete this aspect of the query.
- All data will be stored in a password-protected and encrypted research database.

Exploratory Outcome Questions – Initial Patient Group

- Patient participants will be asked several questions related to exploratory outcomes:
    - Overall satisfaction with post-discharge adequacy of analgesia (Likert scale)
    - Whether patients felt they received too many, too few, or the proper amount of opioid pills
    - Whether patient required any medical visits primarily due to postoperative pain (office visits, emergency department visits, or hospital admissions)
    - Whether additional opioid refills were prescribed after the initial postoperative prescription (this will also be evaluated through EMR queries)
    - Evidence of opioid misuse (Current Opioid Misuse Measure-9 [COMM-9])

Assessment of Pre-Intervention Opioid Prescribing by Surgeon Participants

Baseline pre-intervention opioid prescribing by surgeon participants in both the Intervention and Control Arms will be assessed through VUMC EMR queries for all patient participants who complete the screening, consent, and pill count processes.

Randomization of Surgeon Participants

1:1 randomization of surgeon participants between Intervention and Control Arms

will be completed prior to the study intervention on approximately study day 97

8.2.3 Nudging Intervention (Day 97)

- On approximately study day 97, surgeon participants randomized to the Intervention Arm will receive the one-time nudging intervention.
- Procedure-specific direct feedback on patients' opioid consumption-to-prescription ratio delivered through text message, paging or email message
- Example: "Your abdominal hysterectomy patients were prescribed a mean 60 opioid pills last month. These patients consumed a mean 20 pills (33%)."

8.2.4 Follow-Up Patient Group Contacts and Surgeon Post-Intervention Prescribing Evaluation (Days 108-181)

Screening of Patient Candidates (EMR/PDMP) – Follow-Up Patient Group

- Age ≥18 years
- Undergoing specified surgeries with surgeon participants between study days 4108-167
- Provided opioid prescription that was subsequently filled
- Opioid-naïve (no prior opioid prescriptions between 14 and 90 days prior to the date of surgery)
- Non-cancer surgery
- Non-repeat/revision surgery
- Not a prior participant in the Initial Patient Group of this study
- Demographic information, including gender and race/ethnicity, will be collected
- Screening date will be recorded in the password-protected and encrypted research database

Assessment of Post-Intervention Opioid Prescribing by Surgeon Participants

Post-intervention opioid prescribing by surgeon participants in both the Intervention and Control Arms will be assessed through VUMC EMR queries for all patient participants who complete the *screening* process (primarily to exclude patients who are not opioid naïve and who may have participated earlier in the study).

Inclusion/Exclusion Criteria – Follow-Up Patient Group

- Confirmation of inclusion/exclusion criteria first assessed during preliminary screening

- Assessment of other inclusion/exclusion criteria:
    - Able to understand study procedures and participate in pill count and interview process in English or Spanish
    - Not a member of a vulnerable population (current pregnancy, prisoners)
    - Able to give informed consent (or for legal guardian/representative to do so)

Consent of Patient Candidates – Follow-Up Patient Group

- Identified patient candidates will be contacted by telephone or electronically by trained research coordinators.
- After description of study is provided and risks reviewed, electronic consent will be obtained.
- Documentation of electronic consent and enrollment of patient participants will be made by the research coordinator and stored in the password-protected, encrypted research database.

Pill Count – Follow-Up Patient Group

- Consented patients will be asked to physically obtain their prescribed opioid pill bottle and conduct a pill count.
- Patients who report having consumed the entirety of their prescription and disposed of the bottle will be considered to have a pill count of 0; absence of the empty bottle will be documented in the patient's study record.
- For patients who consent to participate but do not have their pill bottle readily available, arrangements will be made to follow up with the patient by telephone or secure electronic messaging later to complete this aspect of the query.
- All data will be stored in a password-protected and encrypted research database.

Exploratory Outcome Questions – Follow-Up Patient Group

- Patient participants will be asked several questions related to exploratory outcomes:
    - Overall satisfaction with postoperative analgesia (Likert scale)
    - Whether patients felt they received too many, too few, or the proper amount of opioid pills
    - Whether patient required any medical visits primarily due to

postoperative pain (office visits, emergency department visits, or hospital admissions)

- Whether additional opioid refills were prescribed after the initial postoperative prescription (this will also be evaluated through EMR queries)
- Evidence of opioid misuse (Current Opioid Misuse Measure [COMM-9])

Acceptability Questions – Surgeons

- At the study's conclusion, surgeon participants will be informed of the nature of the nudge intervention and asked several questions related to study acceptability:
  - Yes/no response to question involving perceived acceptability of receiving feedback on patients' opioid consumption
  - Surgeon-reported perceived usefulness of intervention
- All randomized surgeons will be provided with feedback on their patients' opioid use across the entire study at the end of the study.

9 SAFETY ASSESSMENTS

9.1 Risk/Benefit Profile and Risk Mitigation

Potential risks: We anticipate that this will be a minimal risk study. There is a small risk that people who are not connected with this study will learn a participant's identity or their personal information through violation of HIPAA compliance and established research protocols. There is also a small risk that physicians may experience some discomfort in learning the opioid consumption patterns of their patients, or that deception was used in the initial vague description of the purpose of the study. Finally, there is a small risk that surgeon participants in the Intervention Arm may, following the intervention, prescribe insufficient amounts of postoperative opioids and consequently that patients undergoing surgery with these physicians after the intervention may be at higher risk of pain-related medical visits.

Potential benefits: There may be no direct benefits to patients participating in this study. Providers may benefit from the post-surgical opioid prescribing guidelines disseminated during the intervention. Prescribers may also be more likely to exercise more careful use of opioids after they have been made aware of discrepancies between opioids prescribed and consumed. They may also be more likely to adjust their prescribing practices, discuss opioid prescribing with colleagues, and identify careful use of opioids with their self-image in the future.

Risk mitigation: Study staff will protect the privacy of study participants. We do not

anticipate greater than minimal risk to patients or surgeons given that patient contact consists only of a pill count and several questions related to postoperative pain and the surgeon contact consists only of feedback regarding opioid prescription/consumption ratio and published prescribing guidelines. Differences in pain-related medical visits will be evaluated as described below. The consent process informs a volunteer about the study, indicates the participation is voluntary and he/she has the right to stop at any time. Risks are described during the consent process. Surgeons will be fully debriefed on the purpose of the study as soon as deception is no longer necessary (upon completion of the study).

Only designated members of the research team will have access to study data. Only data from eligible subjects will be analyzed. All data will be stored on password-protected computers and accessible only accessible to study personnel with appropriate password authorization. These measures should be effective in minimizing breaches of confidentiality. Prior to study initiation, approval will be obtained from the Institutional Review Board at Vanderbilt University Medical Center. This approval will be reevaluated each year as part of the Human Subjects Committee annual review process, paying particular attention to patient confidentiality and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

For this single-site minimal risk intervention pilot study, the study staff and principal investigator will be responsible for ensuring participants' safety daily and for monitoring and responding to any adverse events or unanticipated problems and for reporting them to the IRB, DSMB, and the NIA Program Officer. No formal safety parameter analyses are planned, but study staff will monitor for differences in pain-related medical visits between the Intervention and Control Arms.

9.3 Adverse Events and Serious Adverse Events

We will monitor for specific unanticipated problems during the study period that might be related to the study intervention. At any time, clinicians can report an adverse event or unanticipated problem potentially related to the study to study staff, the Safety Officer, or the DSMB. We do not expect there to be adverse events directly influenced by the clinical guidance being delivered in this study. All study interventions encourage clinicians to follow well-established national guideline recommendations and known best practices. While the expectedness of adverse events is very low, we will investigate every numerator case identified in all safety measures described above.

As requested by the DSMB, we will perform EHR queries for all patients in the follow-up intervention patient groups (that is, patients having surgery after the one-time study has been delivered to the surgeon intervention and control arms) at approximately postoperative day 14. The purpose of these EHR reviews will be to assess for evidence of uncontrolled pain through review of hospital admissions,

emergency department visits, clinic visits, and patient phone calls/electronic portal messages.

For cases identified by the safety monitoring measures, we will perform manual physician chart review to examine the clinical circumstances and to make a judgment (1) the expectedness of the event (unexpected, expected), (2) the likelihood that the safety event was study related (not related/possibly related/definitely related) and (3) judge the event's severity (abnormal clinical finding without symptoms/symptoms requiring clinical intervention/short term disability or hospitalization/death AND separately define the severity as mild, moderate, or severe).

These will be conducted only by authorized study personnel. Study personnel will interview patients' treating clinicians when needed to obtain additional information. Each case identified will have a case report form with these variables and will be signed and dated by study staff completing the form. These forms will be stored in a locked office. Each adverse event will be given an identification number. If study personnel believe that a patient that experienced an adverse event would benefit from seeing or communicating with their prescribing surgeon, the PI will within 2 business days reach out to this clinician advising them to contact the patient as soon as possible. All study personnel will be trained in HIPAA-compliant procedures. Data will be kept on a password protected drive on a secure network, to which study personnel will have restricted access.

Adverse events will be defined as: Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. For this study, we will only be collecting adverse events involving the study interventions, pain, or opioid use. Other post-surgical complications or adverse events will not be captured.

Adverse events will be assessed by a qualified medical professional using the following guidelines 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".

Additionally, Serious Adverse Events will be defined as any adverse event that: (1)

Results in death; (2) Is life threatening, or places the participant at immediate risk of death from the event as it occurred; (3) Requires or prolongs hospitalization; (4) Causes persistent or significant disability or incapacity; (5) Results in congenital anomalies or birth defects; or (6) Is another condition which investigators judge to represent significant hazards.

Additionally, all Adverse Events and Serious Adverse Events will be assessed for their relationship to study procedures as follows:

- 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 study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.

- Possibly related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the trial intervention or patient contact). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).

- Not related: The AE is completely independent of study intervention administration/patient contact, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by a qualified medical professional.

9.3.1 Reporting Procedures

Should a serious, unanticipated, and possibly or definitely related adverse event, unanticipated problem or safety analysis occur, we will notify the Safety Officer, DSMB Chair, NIA Program Officer, and theVUMC IRB within 48 hours of the study team becoming aware of the event. Our report will include appropriate identifying information for the study, a detailed description of the unanticipated, possibly/definitely related, serious adverse event, and a description of any changes to the protocol or other corrective actions that have been taken or are proposed. If an unanticipated, possibly/definitely related, serious adverse event occurs, we will review relevant clinical decision support and ensure others are not at a greater risk of harm than was previously known or recognized.

Patient deaths related to this study are not expected. However, should we identify a possibly related or definitely related patient death in safety measures described above we will report the death to the Safety Officer, NIA Program Officer, DSMB chair, and the VUMC IRB within 48 hours of our knowledge of the death.

The summary of all SAEs (both anticipated and unanticipated) and safety measures will be reported and shared with the Safety Officer, NIA Program Officer, DSMB chair, and the VUMC IRB quarterly throughout the duration of the project, unless otherwise requested. In addition, the summary for reporting all reportable adverse

events (including a report of all numerator cases to all safety measures identified in this report) will be shared with the Safety Officer, NIA Program Officer, DSMB chair, and VUMC IRB quarterly, unless more frequent reports are requested by the NIA, DSMB, or IRB.


Adverse Event Occurs
Is the event associated with the study interventions, pain, or opioid use?
No
Do not record this event
Yes
Did the event occur between discharge and when the subject completes the study?
No
Do not record this event
Yes
Is the event in a participant that was in the Nudge intervention group?
No
This will be an unrelated adverse event that will be captured in REDCap and reported quarterly.
Yes
Is the event Serious?
No
This will be an adverse event that will be captured in REDCap and reported quarterly. PI will assess relatedness
Yes
Is the event Unanticipated?
No
This will be a serious adverse event that will be captured in REDCap and reported quarterly. PI will assess relatedness
Yes
Is the event determined by the PI to be possibly or definitely related to the study
No
This will be an unrelated serious adverse event that will be captured in REDCap and reported quarterly
Yes
This event should be reported to the safety officer, DSMB Chair, NIA Program Officer, and the IRB within 48 hours

9.3.2 Follow-up for Adverse Events

The occurrence of a reportable 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 reportable 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, qualified medical professional'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 reportable AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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.

The study team will record all reportable events on consented patients with start dates occurring any time post-discharge until the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

9.4 Safety Monitoring

For this single-site minimal risk intervention pilot study, the study staff and principal investigator will be responsible for ensuring participants' safety daily and for monitoring and responding to any adverse events or unanticipated problems and for reporting them to the Safety Officer, IRB, DSMB, and the NIA Program Officer. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. As the NIA has requested the oversight of a DSMB, we will utilize the oversight of the standing Roybal Centers DSMB. The study team will prepare safety reports quarterly to be reviewed by the NIA and DSMB for recommendations for or against the trial's continuation, as well as any modification to the study. The DSMB will meet at least biannually either in-person or by teleconference call to review study progress, data quality, and participants safety.

10 INTERVENTION DISCONTINUATION

There are no formal criteria for discontinuing the study, although the discovery of any unanticipated adverse event would warrant immediate consideration of this.

Study participation for patient participants is anticipated to last no longer than a day, and in most cases approximately 15-30 minutes. Subjects may withdraw voluntarily from

participation in the study at any time and for any reason. Subjects who withdraw from the study will not be replaced. For any subject who withdraws from the study due to an AE or SAE, every effort will be made to collect safety data related to the AE or SAE and ensure the study receives appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

11 STATISTICAL CONSIDERATIONS

11.1 General Design Issues

This is a pilot randomized controlled trial assessing the effect of a brief behavioral nudging intervention on surgeons' postoperative opioid prescribing. In addition to determining feasibility and acceptability, we are chiefly interested in obtaining precise estimates of mean and variance to aid in planning a larger, sufficiently powered efficacy trial.

Exploratory hypotheses include that (1) surgeons in the Intervention Arm will exhibit a larger pre-post percentage change in procedure-specific prescription size (measured by oral morphine equivalents [OMEs]) compared with surgeons in the Control Arm who do not receive the nudging intervention and (2) there will be no pre-post difference between the Intervention and Control Arms in terms of patient opioid consumption, opioid refills, medical visits for pain, satisfaction with analgesia, and opioid misuse.

11.2 Sample Size and Randomization

We anticipate obtaining mean pre-post prescribing change in up to 60 surgeons (30 per group). This exceeds the suggested rule-of-thumb threshold of 12 per group for an adequately precise estimate of the variance of a continuous variable to use in future studies.(16)

11.2.1 Treatment Assignment Procedures

For randomization, a list of all surgeon participants will be generated. Using random.org's sequence generator, a true random integer sequence derived from atmospheric noise will determine order in the list. Randomization will be stratified by surgical specialty (e.g., neurological surgery) and by mean opioid prescribing amount during the first 60-day surgical period prior to randomization (greater or equal to median vs. below median). We will at minimum ensure an even or near-even split among the four overall major surgical divisions (general, orthopedic, gynecologic, and neurological) across the intervention and control arms.

11.3 Interim analyses and Stopping Rules

We will assess study measures and safety measures in the middle of the study. There are no interim analyses planned that would trigger early stopping for this pilot study as it involves only a single communication with surgeons and a single communication with participating patients. As noted in section 8, above, the discovery of any adverse event would prompt immediate evaluation by the study team (including study statistician and, if necessary, DSMB statistician) to review the events by group to determine whether there

are statistical and/or clinical concerns. The statistician would report their findings to a closed session of the DSMB and/or NIA. Findings would be used to determine what steps would be taken.

11.4 Outcomes

11.4.1 Primary outcomes

- Percentage of surgeons approached who agree to participate in study (goal: >50%)
- Percentage of patients contacted who agree to participate in study (goal: >50%)
- Surgeon-reported acceptability of intervention (goal: >75% respond "Yes" to question regarding perceived acceptability of nudge intervention)

11.4.2 Exploratory outcomes

- Mean pre-post percentage change in procedure-specific prescription size, as measured by OMEs. Mean size of post-intervention prescriptions (from electronic medical record queries) will be compared with mean pre-intervention prescription size by the same surgeon for the same procedure in order to calculate change from baseline.
- Pre-post change in patient opioid consumption, as measured by OMEs
- Pre-post change in satisfaction with overall postoperative analgesia, as measured by patient-reported numeric rating scale
- Pre-post change in patient satisfaction with general amount of opioids prescribed
- Pre-post change in incidence of medical visits for pain (office visits, emergency department visits, and/or hospital admissions)
- Pre-post change in number of subsequent opioid refills after the initial postoperative prescription (from EMR/PDMP data)
- Surgeon-reported perceived usefulness of intervention (goal: median response to question "Do you think the nudge intervention would be useful?" ≥4 on 0-5 scale, where 0 is "not at all" and 5 "extremely."

11.5 Data Analyses

Primary feasibility and acceptability outcomes will be assessed on a descriptive basics among both the intervention and control surgeon groups (each group will be given a full explanation of the nature of the study following completion). After the intervention, we will also assess pre-post change in opioid prescription size (measured in oral morphine

equivalents) between the two groups. We will compare postoperative prescription size from the baseline (surgeries performed during days 1-60) to prescription size for surgeries performed during days 108-167. The specific exploratory outcome will be mean percentage change in procedure-specific prescription size. That is, mean size of post-intervention prescriptions (from electronic medical record queries) will be compared with mean pre-intervention prescription size by the same surgeon for the same procedure in order to calculate change from baseline. We will then compare mean per-surgeon percentage change in prescription size between the Intervention and Control Arms. We will plan a multiple regression analysis adjusting for case type and surgical specialty to further explore the targeted intervention effects.

To evaluate our other exploratory outcomes, we will assess pre-post changes across groups in patient opioid consumption, satisfaction with analgesia, medical visits for pain, opioid refills, and opioid misuse.

Additionally, we will examine differential consent rates between patients in the follow-up intervention patient group vs. those in the follow-up control patient group using descriptive statistics. This is due to the potential for varying consent rates among patients who are more or less satisfied with their postoperative analgesia following delivery of the one-time study intervention to surgeons.

We will not undersample or oversample surgeons who are women and/or members of minority racial and ethnic groups, so we expect to enroll them in proportion to their population prevalence at VUMC. We will use VUMC EMR data to assess sex/gender and race/ethnicity of patient participants, and will conduct analyses to investigate any differences between groups (including any sex/gender or race/ethnicity differences in willingness to participate in the study).

12 DATA COLLECTION AND QUALITY ASSURANCE

12.1 Data Collection Forms and Data Management

Trained research coordinators with appropriate clearances will contact, consent, and interview each patient participant; they will extract pertinent information from VUMC EMR data (after obtaining appropriate IRB approval) into Case Report Forms utilizing a password-protected, encrypted REDCap database. Study team members, including the study biostatistician, will perform outcome assessments as described above.

12.2 Quality Assurance

12.2.1 Training

All project personnel handling study data will be certified by the Collaborative IRB Training Initiative (CITI) program, which consists of courses in the Protection of Human Research Subjects for Biomedical Research and Quality Control.

12.2.2 Metrics

It is the primary responsibility of study staff to record surgeon and patient provider data in a secure, password-protected database at VUMC and track surgeon

participants in regard to intervention status. Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study.

12.2.3 Protocol Deviations and Monitoring

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 2 working days of identification of the protocol deviation. All deviations will be addressed in study source documents, reported to NIA Program Official. Protocol deviations will be sent to the VUMC Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

13 PARTICIPANT RIGHTS AND CONFIDENTIALITY

13.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

13.2 Informed Consent Forms

Electronic patient participant consent procedures and templates will be IRB-approved and the participant will be asked to review their content as appropriate. The investigator/clinical research staff will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Live Spanish translation services will be provided for Spanish-speaking subjects participating in the consent process that do not speak and/or understand English. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice, and that the quality of their medical care will not be adversely affected if they decline to participate in this study. Participants will have the opportunity to ask questions prior to

giving consent. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. A copy of the signed informed consent document will be sent to the participants for their records.

Permission to engage in deception for surgeon participants will be obtained from the VUMC IRB.

13.3 Participant Confidentiality

Every effort will be made to avoid the risk of people not connected with the study learning participants' identities or personal information. The minimum necessary data will be extracted to address our study objectives. Study staff will protect the privacy of study participants. Only designated members of the research team will have access to study data. Only data from eligible subjects will be analyzed. All data will be stored on password-protected computers and accessible only accessible to study personnel with appropriate password authorization. All study staff will undergo mandated VUMC training on appropriate research conduct, including HIPAA compliance and protection of participant information. These measures should be effective in minimizing breaches of confidentiality.

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

13.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

14 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with VUMC's clinical research standards that meet regulations relating to Good Clinical Practice (GCP). These standards adhere to the following guidelines:

Good Clinical Practice: ICH Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).

United States (US) Code of Federal Regulations (21 CFR) dealing with human subject protection and conduct of investigational clinical studies (21 CFR parts 50, 54, 56, 312, and 314).

Declaration of Helsinki, concerning medical research in humans ("Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects," Helsinki 1964, amend Tokyo 1975, Venice 1983, Hong Kong 1989, revised version of Somerset West, Republic of South Africa, October, 1996 and Scotland, 2000).

15 COMMITTEES

Not applicable

16 PUBLICATION OF RESEARCH FINDINGS AND DATA SHARING

We will adhere to the USC Roybal Center Master Dissemination Plan to ensure that our study findings and interventions are quickly and widely shared:

In accordance with recommended practice for clinical trials, we will register this study with ClinicalTrials.gov within the recommended timeframe (not later than 21 calendar days after the enrollment of the first participant). We will also ensure that results information is submitted in adherence with the timeframes (no later than one year following study primary completion date) outlined in ClinicalTrials.gov policies to facilitate timely dissemination of study findings. Likewise, we will ensure that informed consent documents include a specific statement relating to the posting of clinical trial information at ClinicalTrials.gov. VUMC also has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

This study will be conducted in accordance with the following publication and data sharing policies and regulations: National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Timeframe for data sharing is discussed in the Clinical Trial Dissemination Plan, above. All data and resources generated through this study will be available for replication on a website or repository hosted on the Vanderbilt research cloud. This will include pilot study protocols (with detailed information on recruitment, randomization, and workflow specifications), intervention language, and any other study specific resources necessary to facilitate replication. The PI will share with the scientific community these data in a timely manner, and no later than the online publication date of any publications related to the project. It will be available for download from a repository hosted on the Vanderbilt research cloud, and will include a "readme" file that explains how a researcher can get access to the data and a description of the files and a data dictionary that will guide a researcher through potential replication of the study.

Data will be a HIPAA-compliant, limited data set. Prior to sharing of data, data use agreements will be executed and data will only be made accessible to key project staff.

The data use agreement will include language requiring the user(s) to certify that no attempt will be made to reidentify participants from de-identified data. There are restrictions with sharing this data. Some data will be extracted from the BioVU electronic medical record at Vanderbilt University Medical Center. Data may be made available through data use agreements among researchers interested in using the data. Patient and physician data will be recorded in a secure, electronic database (REDCap), and maintained by study analysts. Data will be entered, tracked, edited, updated and reported by pre-approved analysts with the appropriate clearance. Shared data will be fully deidentified following HIPAA and VUMC IRB procedures. Study documents will be retained for a minimum of 3 years after of study completion. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable.

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

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