Nudges for Opioid Reduction after Major Surgery (NORMS) Trial

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Table of Contents

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2.0 Background and Rationale

Prescription medications to manage pain, nausea, and related symptoms are routinely prescribed after surgery. These represent an important part of postoperative care for patients after they leave the hospital. Opioid medications, in particular, are commonly prescribed in this setting. However, postoperative prescribing patterns for opioids in the U.S. are highly variable and generally excessive relative to patient needs.[1–4] Together with the fact that larger opioid prescriptions can increase the risks of long-term use, overdose, and diversion, these issues underscore postoperative prescribing as an important area for optimization.[5–12]

There have been many efforts to try to improve opioid prescribing after surgery. Several sets of procedure-specific guidelines related to postoperative opioid prescribing have been published,[13,14] but adoption may be limited. Best practices also include multimodal pain control, both to reduce the amount of opioid medications used and to mitigate opioid-related side effects.[15]

Moreover, it has been shown from other healthcare contexts that behavioral "nudges" including electronic medical record (EMR) defaults, peer comparison feedback, and other behavioral interventions at a health systems level may be able to improve medication prescribing,[16–18] but it is not known how best to apply these to postoperative care and opioid prescribing. Additionally, the potential impact, as well as any potential unintended effects, of such interventions aimed at discharge medication prescribing on subsequent healthcare utilization during the postoperative period is not known.

3.0 Study Aims

Aim 1. Assess the feasibility of using provider-level randomization to study the impact of a behaviorally designed, EMR-based discharge medication intervention.

Aim 2. Evaluate the impact of this intervention, compared to usual care, on opioid prescribing after common surgical operations.

Aim 3. Evaluate the impact of this intervention, compared to usual care, on healthcare utilization outcomes after common surgical operations.

We hypothesize that the amount of opioids prescribed at discharge postoperatively will be lower in the intervention arm, and that any additional opioid prescribing and healthcare utilization in the following 30 days after discharge will not be significantly higher in the intervention arm.

4.0 Design and Methods

Study design: This trial is designed as a single-center, cluster-randomized, pragmatic superiority trial, with two parallel groups and a primary outcome of the opioid amount prescribed to patients at discharge after surgery. Randomization will be performed at the provider level with 1:1 randomization, and analysis will be conducted at the patient-encounter level.

Surgical providers will be randomized at the start of the study to either the intervention arm, in which they see the novel version of discharge order sets in the EMR, or the usual care arm, in which they see standard versions of these order sets. Patients eligible for the study (as detailed below) and who present for surgery during the study period will undergo the regular processes of clinical care, and ultimately be discharged by a provider who may be in the intervention or the usual care study arm. Data abstracted from the EMR will be used to compare outcomes between study arms.

Study setting: The study will be conducted within a single academic medical center, the University of Washington (Seattle, WA, USA), encompassing three physical locations: the University of Washington-Montlake, the University of Washington-Northwest, and Harborview Medical Center.

Eligibility criteria:

Inclusion criteria:

- Age ≥ 18 years
- Undergo one of these surgical operations during the index encounter:
    - Laparoscopic appendectomy
    - Laparoscopic cholecystectomy
    - Laparoscopic Nissen fundoplication
    - Laparoscopic sleeve gastrectomy
    - Laparoscopic Roux-en-Y gastric bypass
    - Laparoscopic or robotic colectomy
    - Open colectomy
    - Open small bowel resection or lysis or adhesions
    - Thyroidectomy
    - Parathyroidectomy
    - Open ventral hernia repair
- Discharge by a surgical provider included in the study (randomization)

Exclusion criteria:

- Multiple operations during the index encounter
- Death prior to discharge

4.1 Intervention

A novel discharge medications section will be placed into two existing order sets in the EMR commonly used by surgical providers for discharge orders. This includes bundles of medications with procedure-specific, pre-selected quantities and strengths of opioids, non-opioid analgesics, and other adjunctive medications to help manage nausea and opioid-related adverse effects for common surgical operations (Table 1). For each procedure type, the orders reflect evidence-based guidelines for opioid prescribing after each specific procedure,[13] recommendations for multi-modal postoperative pain management,[15] and expert consultation with providers at the study site.

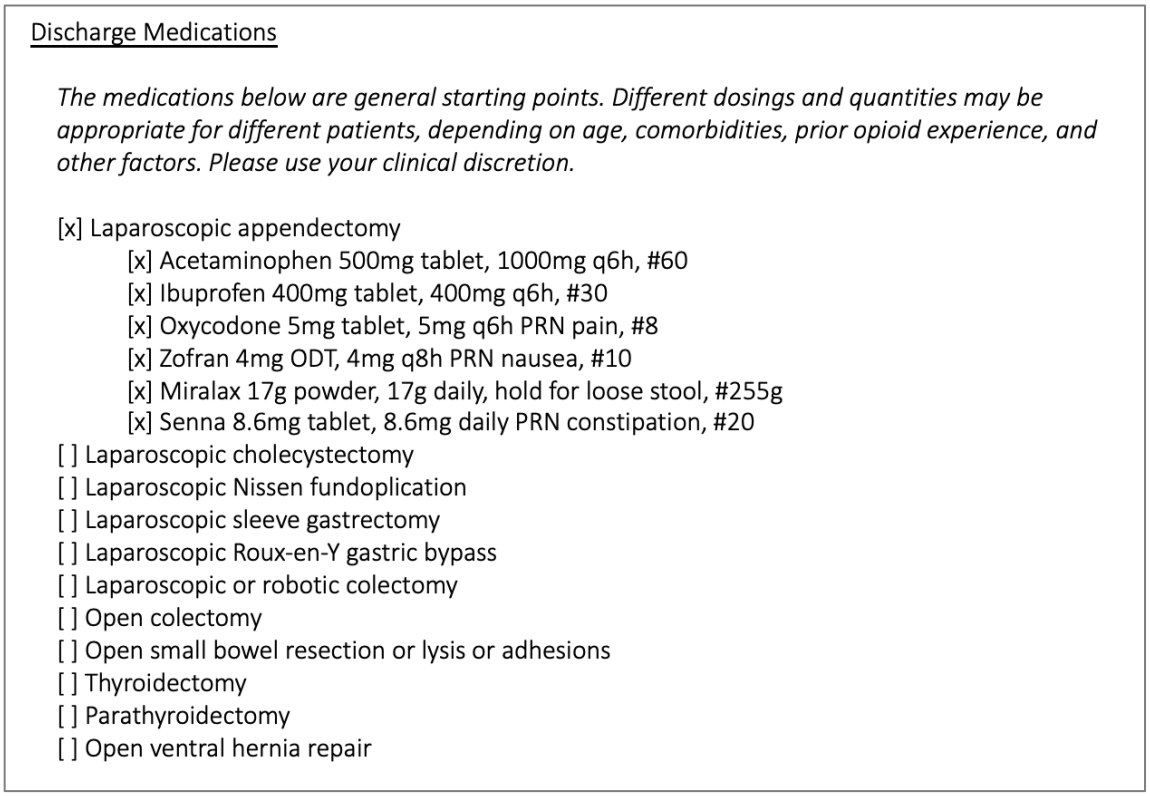
In practice, providers in the intervention arm will be able to select the relevant procedure for a given patient encounter, and the corresponding medications would pre-populate as discharge prescriptions (Figure 1). All individual orders remain editable by providers, and providers can also order medications outside of the order sets as in the usual care situation.

Table 1. Discharge medications by surgical procedure in the intervention

Procedure	**Discharge Medications**
Laparoscopic appendectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, #60 [x] Ibuprofen 400mg tablet, 400mg q6h, #30 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #8 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #20
Laparoscopic cholecystectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, #60 [x] Ibuprofen 400mg tablet, 400mg q6h, #30 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #8 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #20
Laparoscopic Nissen fundoplication	[x] Acetaminophen 500mg tablet, 1000mg q6h, #60 [x] Ibuprofen 400mg tablet, 400mg q6h, #30 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #10 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #20
Laparoscopic sleeve gastrectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, crush, #60 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, crush, #10 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #15 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Omeprazole 20mg tablet, 20mg daily, crush, #30 [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, crush, #20
Laparoscopic Roux-en-Y gastric bypass	[x] Acetaminophen 500mg tablet, 1000mg q6h, crush, #60 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, crush, #10 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #15

	[x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Omeprazole 20mg tablet, 20mg daily, crush, #90 [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, crush, #20
Laparoscopic or robotic colectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, #60 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #10 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10
Open colectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, #80 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #15 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10
Open small bowel resection or lysis or adhesions	[x] Acetaminophen 500mg tablet, 1000mg q6h, #80 [x] Ibuprofen 400mg tablet, 400mg q6h, #40 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #15 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #20
Thyroidectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, #50 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #5 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #10
Parathyroidectomy	[x] Acetaminophen 500mg tablet, 1000mg q6h, #50 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #5 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #10
Open ventral hernia repair	[x] Acetaminophen 500mg tablet, 1000mg q6h, #60 [x] Ibuprofen 400mg tablet, 400mg q6h, #30 [x] Oxycodone 5mg tablet, 5mg q6h PRN pain, #10 [x] Ondansetron 4mg ODT, 4mg q8h PRN nausea, #10 [x] Polyethylene glycol 17g powder, 17g daily, hold for loose stool, #255g [x] Senna 8.6mg tablet, 8.6mg daily PRN constipation, #20

Figure 1. Mockup of intervention in order sets seen by providers



4.2 Outcomes

Primary outcome:

Difference between the two study arms in mean total opioid amount, measured in morphine milligram equivalents, in the postoperative discharge prescription for the index surgical encounter.

Secondary outcomes:

- Difference between the two study arms in the mean total amount of any additional opioids prescribed, measured in morphine milligram equivalents, after and within 30 days of discharge from the index encounter.
- Difference between the two study arms in the proportion with a documented phone call to surgical clinics or services at the study sites after and within 30 days of discharge from the index encounter.
- Difference between the two study arms in the proportion with an emergency department visit at the study sites after and within 30 days of discharge from the index encounter.

- Difference between the two study arms in the proportion with a readmission to a surgical service at the study sites after and within 30 days of discharge from the index encounter.

4.3 Study Schedule

Providers will be randomized just prior to study initiation. During the study, eligible patients (patient-encounter events) will undergo their usual operative and perioperative care. They will be identified subsequently via querying the EMR, with outcomes defined at baseline – the time of discharge from the index encounter – and during the follow-up period – after and within 30 days of discharge as specified above – for each patient-encounter (Table 2).

Table 2. Study Timepoints

Item	**Baseline**	**Follow-up (after and within 30 days of discharge)**
Data source: EMR, to be queried monthly during the study period		
Demographic information	x	
Clinical characteristics	x	
Primary outcome	x	
Secondary outcomes		x

5.0 Data Management and Information Security

Data management will be the responsibility of the study investigators. Hospital IT will assist with data abstraction from the hospital EMR based on pre-specified data collection fields from the study investigators. IT will create an electronic study database to be stored on a dedicated, secure, HIPAA-compliant, institutional Microsoft Teams group with access limited to the study team.

Data quality review will be conducted by the study investigators, including quality assurance checks during the study database creation process. The review will include enrollment, reasons for exclusion, patient demographics, and discharge medication prescription identification and categorization.

6.0 Statistical Analysis Plan

6.1 Randomization Overview

This is a single-center, cluster-randomized superiority trial, with two parallel groups. Randomization will be performed at the provider level, and analysis will be conducted at the patient-encounter level.

Surgical providers including resident physicians and advanced practice providers at the study sites will be randomly assigned to either the control or intervention group with a 1:1 simple randomization as per a computerized random number generator.

For those providers allocated to the intervention arm, hospital IT will alter their EMR interface such that the intervention version of the discharge ordersets would be displayed to them. For those providers allocated to the control arm, the usual care version of the ordersets would be displayed. During data collection and analysis, those patient-encounters with discharge orders written by providers in the intervention arm will be classified as the intervention group, and those with discharge orders written by providers in the control arm will be classified as the control group.

Due to the nature of the intervention and study design, neither clinical providers nor study staff can be blinded to allocation.

6.2 General Analytic Strategy

The primary analysis will compare the EMR intervention to usual care, aiming to assess whether the opioid amount prescribed at postoperative discharge at the index encounter is significantly different. The analytic strategy aims to account for the cluster-randomized design and potential clustering of opioid prescribing by providers.

1. Primary analysis, primary outcome –
   The total opioid amount, measured in morphine milligram equivalents, in the postoperative discharge prescription for the index encounter will be assessed using Generalized Estimating Equations (GEE) with a linear mean model and an exchangeable correlation structure, where the main exposure is an indicator of randomized treatment group assignment, adjusting for surgical procedure type out of consideration that this may be correlated with providers and with opioid amount prescribed at discharge. Cluster robust standard errors, clustered at the provider level, will be used. Statistical tests will be two-sided with alpha = 0.05.

2. Secondary analyses

a. Secondary outcome 1 – The total amount of any additional opioids prescribed, measured in morphine milligram equivalents, after and within 30 days of discharge from the index encounter will be similarly assessed using GEE with a linear mean model and an exchangeable correlation structure, where the main exposure is an indicator of randomized treatment group assignment, adjusting for surgical procedure type, with cluster robust standard errors, clustered at the provider level.
b. Secondary outcome 2 – The proportion of patient-encounters with a documented phone call to surgical clinics or services after and within 30 days of discharge from the index encounter will be assessed using GEE with a logistic model and an exchangeable correlation structure, where the main exposure is an indicator of randomized treatment group assignment, adjusting for surgical procedure type, with cluster robust standard errors, clustered at the provider level.
c. Secondary outcome 3 – The proportion of patient-encounters with an emergency department visit after and within 30 days of discharge from the index encounter will be assessed using GEE with a logistic model and an exchangeable correlation structure, where the main exposure is an indicator of randomized treatment group assignment, adjusting for surgical procedure type, with cluster robust standard errors, clustered at the provider level.
d. Secondary outcome 4 – The proportion of patient-encounters with a readmission to a surgical service after and within 30 days of discharge from the index encounter will be assessed using GEE with a logistic model and an exchangeable correlation structure, where the main exposure is an indicator of randomized treatment group assignment, adjusting for surgical procedure type, with cluster robust standard errors, clustered at the provider level.

6.3 Sample Size and Statistical Power

Using historic data from 2016-2020 from the study sites, estimations of statistical power and sample size were conducted.

From these data, postoperative opioid prescriptions at discharge for the included surgical procedure types in this trial had a baseline mean opioid MME of 171. There are 118 surgical providers who commonly discharge patients after these procedures, and an estimated surgical volume of 485 cases total of the included procedure types in a 6-month period.

Numeric Results for a Test of Mean Difference

Test Statistic: T-Test with DF based on number of subjects
Hypotheses: H0: $\delta = 0$ vs. Ha: $\delta \neq 0$

Power	Subj Cnt Gr 1 N1	Subj Cnt Gr 2 N2	Clus Cnt Gr 1 K1	Clus Cnt Gr 2 K2	Clus Size Gr 1 M1	Clus Size Gr 2 M2	COV Clus Sizes COV	Diff μ1-μ2 δ	Std Dev σ	ICC ρ	Alpha
0.20498	242	242	59	59	4.1	4.1	0.53	0.10	0.66	0.33	0.05
0.39709	242	242	59	59	4.1	4.1	0.53	0.15	0.66	0.33	0.05
0.61984	242	242	59	59	4.1	4.1	0.53	0.20	0.66	0.33	0.05
0.80819	242	242	59	59	4.1	4.1	0.53	0.25	0.66	0.33	0.05
0.92471	242	242	59	59	4.1	4.1	0.53	0.30	0.66	0.33	0.05

Report Definitions
Power is the probability of rejecting a false null hypothesis. It should be close to one.
N1 and N2 are the number of subjects in groups 1 and 2, respectively.
K1 and K2 are the number of clusters in groups 1 and 2, respectively.
M1 and M2 are the average number of items (subjects) per cluster in groups 1 and 2, respectively.
COV is the coefficient of variation of the cluster sizes.
δ is the mean difference (μ1 - μ2) in the response at which the power is calculated.
σ is the standard deviation of the subject responses.
ρ (ICC) is the intracluster correlation.
Alpha is the probability of rejecting a true null hypothesis, that is, rejecting when the means are actually equal.

The differences (δ) denote differences in log(MME) between providers exposed/not exposed to the intervention. The mean of log(MME) in the provided data was 4.91, with SD 0.66. These log-scale differences correspond to the following percentage changes in the geometric mean of MME on the linear scale. For example, a change from 4.91 to 4.81 (0.10) on the log scale would correspond to a change from 136 to 122.4 (10%) in the geometric mean of MME on the linear scale.

δ (difference in log MME)	% change in geometric mean MME
0.10	10%
0.15	14%
0.20	18%
0.25	22%
0.30	26%

Summary Statements

Sample sizes of 242 in group one and 242 in group two, which were obtained by sampling 59 clusters with an average of 4.1 subjects each in group one and 59 clusters with an average of 4.1 subjects each in group two, achieve 20% power to detect a difference between the group means of at least 0. The standard deviation of subjects is 0.66. The intracluster correlation coefficient is 0.33. The coefficient of variation of cluster sizes is 0.53. A two-sided t-test was used with a significance level of 0.05. This test used degrees of freedom based on the number of subjects.

7.0 Data and Safety Monitoring Plan (DSMP) and Study-Related SAEs and AEs

This study is low risk. While all EMR features and ordersets can potentially influence clinical decisions, these risks can be mitigated by clinical judgment and discretion by providers who remain fully able to not use or modify any suggested medication orders as part of the study. Both the need to know evidence-based recommendations and the need to modify from them when appropriate are existing risks in usual clinical care.

The primary risks of this study pertain to data confidentiality, to be addressed as below. Data confidentiality and security will be managed as delineated in section 5.0 Data Management and Information Security, including all existing institutional protections for electronic data security, and data storage only on a dedicated, secure, HIPAA-compliant, institutional Microsoft Teams group with access limited to the study team.

Oversight Responsibilities
Oversight of the trial will be provided by the study investigators.

Monitoring Procedures
Study data are accessible at all times for the study investigators to review. The investigators will review AEs and SAEs on a quarterly basis. The lead investigator ensures all protocol deviations, AEs, and SAEs are reported to the steering committee and institutional review board according to the applicable regulatory requirements.

Collection and Reporting of SAEs and AEs
For this study, the following AE definitions are used:

Adverse event:

- Breach of confidentiality within the study data

Serious adverse event:

- Adverse event involving patients' protected health information or providers' prescribing records within the study data, presenting risks to patients and providers

AEs are graded according to the following scale:

> Mild: An experience that is transient, & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
>
> Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

AEs relating to data confidentiality for the study data are assessed through existing monitoring measures by hospital IT.

8.0 Protection of Human Participants

The risks and benefits for participants involved in this trial are appropriately balanced. All of the medications in the intervention orderset are recommendations based on evidence from literature and on current best practices within the institution. To further mitigate the potential risks to patients and providers, text will also be included with the intervention orderset to emphasize to providers the potential need to modify orders and to use their clinical judgment. Both the need to know evidence-based recommendations and the need to modify from them when appropriate are existing risks in usual clinical care. We think we can potentially reduce risks to patients and providers by distilling these issues into a single EMR feature with medication defaults and accompanying information.

Additionally, there is the potential risk of unauthorized access to patients' protected health information, including medical and surgical records as well as information on opioid and other prescription medication use. A confidentiality breach could also cause potential harm to providers' reputation and professional and financial standing. We will be taking appropriate and rigorous data security measures as described above.

Based on the study design and the low-risk nature of the study, consent was waived by the institutional review board for providers and patients. The waiver of consent will allow for minimization of the potential for bias in the results from individuals acting differently in either study arm because they know they are being observed (Hawthorne effect).

Participant confidentiality is strictly held in trust by the participating investigators and their staff.

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