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Best Practice Alerts Informed by Inpatient Opioid Intake to Reduce Opioid Prescribing After Surgery (PRIOR) – A Cluster Randomized Multiple Crossover Trial

Megan L. Rolfzen, M.D.[a], **Abraham Wick, Pharm.D.**[b], **Edward J. Mascha, Ph.D.**[c,d], **Karan Shah, M.S.**[c,d], **Martin Krause, M.D.**[e], **Ana Fernandez-Bustamante, M.D., Ph.D.**[f], **Jean S. Kutner, M.D., M.S.P.H.**[g], **P. Michael Ho, M.D., Ph.D., FACC**[g], **Daniel I. Sessler, M.D.**[d,h], **Karsten Bartels, M.D., Ph.D., M.B.A.**[a,f,h]

[a]Department of Anesthesiology, University of Nebraska Medical Center, Omaha, NE, USA

[b]UCHealth, Pharmacy Analytics Core, Aurora, CO, USA

[c]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA

[d]Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

[e]Department of Anesthesiology, University of California San Diego, San Diego, CA, USA

[f]Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO, USA

[g]Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

[h]Outcomes Research Consortium, Cleveland, OH, USA

Abstract

Background: Over-prescription of opioids after surgery remains common. Residual and unnecessarily prescribed opioids can provide a reservoir for nonmedical use. We therefore tested the hypothesis that a decision-support tool embedded in electronic health records guides clinicians to prescribe fewer opioids at discharge after inpatient surgery.

Methods: We studied 21,689 surgical inpatient discharges in a cluster randomized multiple crossover trial from July 2020 to June 2021 in four Colorado hospitals. Hospital-level clusters were randomized to alternating eight-week periods during which an electronic decision-support tool recommended tailored discharge opioid prescriptions based on prior inpatient opioid intake. During active alert periods, the alert was displayed to clinicians when the proposed opioid prescription exceeded recommended amounts. No alerts were displayed during inactive periods. Carryover effects were mitigated by including 4-week washout periods. The primary outcome was oral morphine milligram equivalents prescribed at discharge. Secondary outcomes included combination opioid/non-opioid prescriptions and additional opioid prescriptions until day 28 after

Corresponding Author: Karsten Bartels, M.D., Ph.D., M.B.A., University of Nebraska Medical Center, 984455 Nebraska Medical Center, Omaha, NE 68198-4455, karbartels@unmc.edu, Phone: 402-559-4081.

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discharge. A vigorous state-wide opioid education and awareness campaign was in place during the trial.

Results: The total postdischarge opioid prescription was a median [quartiles] of 75 [0, 225] oral morphine milligram equivalents among 11,003 patients discharged when the alerts were active and 100 [0, 225] morphine milligram equivalents in 10,686 patients when the alerts were inactive, with an estimated ratio of geometric means of 0.95 (95% CI: 0.80, 1.13; P = 0.586). The alert was displayed in 28% (3,074/11,003) of the discharges during the active alert period. There was no relationship between the alert and prescribed opioid/non-opioid combination medications or additional opioid prescriptions written after discharge.

Conclusions: A decision-support tool incorporated into electronic medical records did not reduce discharge opioid prescribing for postoperative patients in the context of vigorous opioid education and awareness efforts. Opioid prescribing alerts might yet be valuable in other contexts.

Registered at ClinicalTrials.gov (NCT04446975).

Introduction

Although opioid-based therapy represents a cornerstone of pain management after surgery, unused postoperative opioids expand the reservoir available for nonmedical use.[1,2] Indeed, most opioids prescribed by surgeons are not used by patients, and the leftovers have the potential to contribute to the adverse effects of opioids on public health.[3–5] Despite decreases in opioid prescriptions in the United States since its peak in 2011, more than 11,000 deaths per month occurred from overdoses with natural and semisynthetic opioids (including oxycodone, hydrocodone, and morphine) in 2022.[6] Numerous initiatives have focused on procedure-specific prescribing recommendations, evidence-informed policies, and programs for safe opioid disposal.[7–9] But despite many federal, state, and local regulatory restrictions on prescribing, opioids remain the most commonly misused prescription drug in the United States.[10]

Because there is substantial variability in analgesic requirements, evidence-based optimization of opioid prescription at discharge is nuanced. The risks and benefits of opioids as part of an analgesic regimen for postoperative pain should be considered in the context of the surgical procedure, patient characteristics, and hospital course. Among other factors, in-hospital opioid intake before discharge is a reliable predictor for opioid intake after discharge.[11–14] The choice and dose of opioid prescriptions after surgery is nonetheless often driven by local practice conventions rather than patient-specific considerations.[4,12–14]

In an effort to change opioid prescribing practices at discharge to reflect anticipated individual needs, we embedded a decision-support tool into electronic health records. Specifically, we tested the hypothesis that a best-practice alert based on recorded inpatient opioid intake prior to discharge reduces the amount of opioids prescribed to surgical patients at discharge. Secondarily, we investigated the effects of the alert on the prescription of opioid/non-opioid combination medications and the need for additional opioid prescriptions during the initial 28 postdischarge days.

Materials and Methods

We conducted a cluster randomized multiple crossover trial[15] to evaluate a real-time best-practice alert embedded into electronic health records. The study design followed Pragmatic Explanatory Continuum Indicator Summary guidelines to maximize broad applicability and is reported according to Consolidated Standards of Reporting Trials Extension for Cluster Randomized Trials guidelines.[16,17] Institutional Review Board (IRB) approval was obtained prior to patient enrollment (single IRB of record: COMIRB, Protocol 19–3095). Patient and provider consent was waived because the alert supplemented the current standard of care, there was no requirement to respond, alerts were unlikely to be harmful, and might have proven beneficial. The trial was registered on June 25, 2020, at ClinicalTrials.gov (NCT04446975).

The clusters were an academic medical center and three community hospitals, all part of the UCHealth system, which serves both inner-city and rural populations across Colorado, Nebraska, Wyoming, and beyond. Primary study subjects were credentialed prescribers at each site. Eligible secondary study subjects were postsurgical hospital inpatients who were hospitalized at least one night before discharge. There were no exclusion criteria for the prescribing providers, but patients needed to be at least 18 years old.

Our prior work in three diverse samples of surgical procedures found that among available predictor variables that could be incorporated into an electronic decision-support tool, 24-hour pre-discharge opioid intake was most associated with patient-reported postdischarge opioid intake.[11–13] Consistent with these findings, guidelines recommend a tiered approach to opioid prescription by categorizing in-hospital opioid intake on the day prior to discharge: 1) no opioids, 2) more than zero to 22.5 milligram morphine equivalents (equivalent to three oxycodone 5 mg tablets), or 3) more than 22.5 milligram morphine equivalents.[18]

Centered on these findings and with local stakeholder input, we developed a best practice alert algorithm for commonly prescribed opioids based on prior day inpatient opioid intake (Table 1). Two conditions were required for the alert to be displayed to a provider: the prescription had to be written during an active alert period and the initial prescription attempt had to exceed the alert threshold. During the eight-week periods when prescriber alerts were active, providers who attempted to prescribe higher-than-recommended doses were automatically notified on the order screen with a suggestion for a reduced prescription. Within the alert, a suggestion to prescribe non-opioid adjuncts was also displayed. Final prescription decisions remained at the discretion of the provider.

The best practice alert was assessed over a 48-week period from July 2020 to June 2021 in all eligible patient discharges within the four hospitals. The four hospitals were randomized to the starting configuration (active alert or inactive alert) to control for potential period effects and avoid within-hospital contamination. The clusters alternated between active alert and inactive alert conditions for four eight-week periods, each separated by a four-week washout interval to minimize learning and augment masking (Figure 1). Randomization was implemented so investigators and data analysts remained masked to the condition designation. While alerts were displayed to providers during active periods if their

prescriptions were above the algorithm alert threshold, the schedule was not shared with providers or patients.

The primary outcome was the amount of opioids prescribed at discharge. Opioids prescribed were recorded by type and total amount dispensed in oral morphine milligram equivalents.[19] In 139 patients who had recorded medication names but no amounts recorded, we assumed that no medications were prescribed.

Secondary outcomes included opioid/non-opioid combination medications prescribed on the day of discharge and any additional opioid prescriptions written after discharge. Analgesic prescriptions were defined as a categorical outcome: opioids, combination opioid/non-opioid medications, or no opioid medications prescribed at discharge. To estimate the potential for under-prescribing, outpatient opioids prescribed days 1 to 28 postdischarge by any health system provider were reported dichotomously for every admission based on the discharge date.

Other study measurements obtained from electronic health records included demographic and clinical characteristics, hospitalization-specific variables, and perioperative information, including surgical subspecialty, in-hospital opioid intake, and ordering provider profession and ordering provider sex (Table 2). When a history of chronic pain was not recorded, we assumed that missing values represented not having chronic pain issues.

Statistical Methods

Baseline balance on potential confounding factors was assessed using absolute standardized differences, calculated as the difference in means or proportions divided by the pooled standard deviation.[20] An absolute standardized difference > 0.1 was considered to indicate imbalance, and these variables were adjusted for all analyses.

Analysis was conducted at the individual patient level using a modified intention-to-treat strategy. Mixed (hierarchical) modeling procedures were utilized to account for the correlation within clusters and time and periods in the crossover cluster design.[21] Because the effect was estimated within hospital due to the crossover design, it was adequate to specify fixed effects of the hospital, alert condition, time periods, and surgical subspecialty grouped according to prior work.[22] We also included a random effect for cluster-periods to account for correlated observations within a cluster-period by assigning each cluster-period its own intercept.

The effect of the best practice alert on opioid prescription at discharge was evaluated using a linear regression model after log transforming the outcome. The treatment effect was reported as a ratio of geometric means (active alert/inactive alert) and the associated 95% confidence interval (95% CI). A geometric mean < 1.0 represents a decreased opioid prescription amount during the active alert condition relative to the inactive condition. Based on previous work,[12,13] we considered a one-third reduction in prescribed opioids to patients in the active alert period to be clinically meaningful.

The geometric mean and median are both appropriate summary measures for skewed data as they are robust to extreme values. Medians have the added advantage of a more intuitive

interpretation, but in practice, quantile regression models (used to estimate conditional medians) with complex mixed-model specifications are difficult to implement. Thus, we reported the unadjusted median in each treatment group to aid in interpretation, but the treatment effect was reported as the ratio of geometric means. We note that geometric means and medians are equal when data are lognormal data but can diverge in other situations — as it did for our results.

The effect of the best practice alert on additional prescriptions after discharge was evaluated using a log-binomial regression model, including the previously mentioned fixed effects. The random cluster-period effects were excluded as the mixed model failed to converge. The effect of the alert on the three-level analgesic categorical variable was assessed using a multinomial logistic regression model with a generalized logit link. Our pre-specified mixed-effects model with heterogeneous variances between the treatment groups on the cluster-period random effect and residual errors did not converge. We therefore report results from a simpler fixed-effects model.

We also conducted a post-hoc secondary analysis to evaluate whether a differential treatment effect existed for the subgroup of patients qualifying for an alert (i.e., the initially considered opioid dose exceeded the one recommended by our algorithm) compared to the subgroup of patients which did not. The analysis was conducted by fitting the primary outcome model with an additional interaction between the treatment group and an indicator of whether the patient qualified for an alert. The interaction was considered significant if $P < 0.15$. Additionally, as the primary outcome data was not log-normal, a sensitivity analysis was conducted using a quantile regression model (instead of linear regression) adjusting for the fixed effects.

All main effect analyses were conducted at $\alpha = 0.05$, two-tailed, and both *R 4.0.2* and *SAS 9.4* were used to conduct the analyses.

Sample Size Justification

We determined that it would be feasible to recruit 1,500 patients per cluster-period, across four hospitals for four time periods. Although we considered a 33% reduction in mean prescribed opioids to be a clinically meaningful difference, we used a smaller effect size (11%) for the power analysis to account for providers not following the suggested dose in some patients. We estimated that the trial would have > 99% power to detect a ratio of geometric means of 0.9 (active alert/inactive alert) for prescribed opioids, or a difference of −0.12 (active alert/inactive alert) on the log-scale, at the 0.05 significance level.

ClusterPower,[23] a flexible simulation-based package in R for estimating power and sample size in cluster randomized trials, was used. We randomly generated numerous datasets using a pre-specified effect size under the alternative hypothesis and then determined the empirical power based on how often the null hypothesis was rejected. Further detail regarding sample size derivation is available in the Supplemental Digital Content.

Results

A total of 21,864 patients from four hospitals were considered for inclusion in the analysis during the 48-week period from July 2020 to June 2021. One hundred seventy-five patients were excluded because they were less than 18 years old, yielding a final analysis sample size of 21,689 patients. Of these patients, 10,114 (47%) underwent general or orthopedic surgery. A total of 1,053 unique providers prescribed opioids to patients during the study period. Of these, 45% (472) were male, 41% (436) were attending physicians, 29% (309) were residents or fellows, and 29% (308) were in the non-physician category (physician assistants, nurse practitioners, clinical nurse specialists, or nurse midwives). There were no clinically important differences in potential confounding factors (i.e., all absolute standardized differences < 0.1) in providers and patients between the active alert period (N = 11,003) and inactive alert period (N = 10,686). However, some confounders had a high percentage of missing values, including 46% of discharge pain scores. Sample characteristics by hospital are displayed in Supplemental Digital Content.

The median opioid dose prescribed at discharge was 75 oral morphine milligram equivalents [Q1, Q3: 0, 225] when the alert was active versus 100 oral morphine milligram equivalents [Q1, Q3: 0, 225] when the alert was inactive. The ratio of geometric means (active alert/inactive alert) for opioids prescribed at discharge was estimated as 0.95 (95% CI: 0.80, 1.13; P = 0.586) using a linear mixed model with fixed effects for hospital, treatment, time period, surgical specialty, and random effects for the cluster-period (Table 3). Thus, the best practice alert did not significantly affect the amount of opioids prescribed at discharge.

The percentage of patients without prescribed opioids at discharge was 35% in both the active and inactive alert groups. The number of patients with prescriptions exceeding 225 oral morphine milligram equivalents (the maximum dose recommended by our algorithm) was 2,208 (20%) in the active alert group and 2,201 (21%) in the inactive alert group (Figure 2).

Opioids in the first 28 days after discharge were prescribed in 2,046 (19%) patients in the alert group and 1,870 (17%) patients in the non-alert group. Alerts were not found to affect postdischarge opioid prescriptions, with an estimated odds ratio of 1.06 (95% CI: 1.00, 1.12; P = 0.052). Furthermore, alert exposure was not found to affect the odds of being prescribed opioid/non-opioid combination preparations [odds ratio 0.94 (95% CI: 0.86, 1.03)] or of being prescribed opioids [odds ratio 1.00 (95% CI: 0.93, 1.06)] compared to receiving no opioid medications at discharge (Table 3).

During active periods, best practice alerts were shown to prescribers in 28% (N = 3,074) of the cases. During the inactive alert period, 30% (N = 3,182) of the patients qualified for an alert, although none was presented, as per the study protocol (Table 1). A total of 340 of the active alert patients qualified for an alert, yet an alert was not displayed. Whereas among inactive alert patients, 111 qualified for an alert, and the alert was displayed. In the post-hoc secondary analysis, we assessed whether a differential treatment effect existed for the subgroup of patients qualifying for an alert compared to the patients who did not. The median opioid doses prescribed at discharge in the subgroup qualifying for an alert were

201 oral morphine milligram equivalents [Q1, Q3: 75, 338] during active alert periods and 225 oral morphine milligram equivalents [Q1, Q3: 112, 338] during inactive alert periods. The treatment effect in the subgroup of patients eligible for alerts was an estimated ratio of geometric means of 0.89 (95% CI: 0.79, 0.99; P = 0.027). For the 71% of patients who did not qualify for an alert, the estimated ratio of geometric means was 1.02 (95% CI: 0.86, 1.22; P = 0.788). However, we did not find evidence for an interaction between whether patients qualified for an alert and the randomized treatment group (P = 0.822). Thus, displaying best-practice alerts did not appear to change prescriber behavior (Table 4).

In the sensitivity analysis to the primary outcome analysis, using quantile regression on all patients, the 50th percentile, 75th percentile, and 95th percentile difference in opioid prescription at discharge were all estimated to be 0 (P = 1.00), which is consistent with the results of our primary analysis.

Discussion

In this randomized multiple crossover cluster trial of 21,689 adult surgical patients, those discharged during the active best practice alert period received a median of 75 oral morphine milligram equivalents, while those discharged during the inactive alert period received a median of 100 oral morphine milligram equivalents (P = 0.586). The embedded clinical decision-support tool did not significantly or meaningfully change the amount of opioids prescribed at discharge. Nor did opioid-prescription guidance alter the prescription of combination opioid/non-opioid preparations, or the need for additional opioid prescriptions during the initial 28 days after discharge.

The national awareness of the opioid epidemic and its public health implications within the “opioid ecosystem”, especially in Colorado, are relevant to the context of this study.[24] General and colorectal surgery departments were among the first to adopt enhanced recovery after surgery protocols initially developed by European academic surgeons. The protocols included limiting long-acting opioids with additional emphasis on opioid-sparing multimodal analgesic approaches.[25] General surgeons were also the first to marshal enhanced recovery protocols within the UCHealth system,[26] and since 2018, new legislation, including Colorado Senate Bill 18–022, further limited prescription duration.[27] Although exceptions exist for acute postoperative surgical pain, the implementation of such policies may explain why 35% of patients were discharged without an opioid prescription, and only a quarter of the prescription attempts initially exceeded an opioid dose that our algorithm considered reasonable. In fact, even in the reference group, the median discharge prescription was only 100 morphine milligram equivalents, corresponding to about 13 oxycodone 5-milligram tablets. Although opioid prescription rates have dropped over the last decade in the United States, surgical opioid prescribing at discharge still vastly differs from international practices. In a recent eight-country, 4,690-patient study of surgical patients after three common general surgical procedures, U.S.-based patients were 18 times more likely to be prescribed opioids at discharge than those in other countries.[28]

Clinical decision-support systems for computerized provider order entry have demonstrated reductions in adverse events from drug-drug interactions,[29] improvements in clinician

performance,[30] and lowering of pharmaceutical costs.[31] Historically, successful best practice alerts have integrated extensive education in tandem with an actionable alert feature.[32] Although our best practice alert was designed and executed with the best intention of adhering to the five “rights” of clinical decision-support (right information, to the right person, in the right format, through the right channel, at the right time), insufficient clinician engagement may have contributed to a lack of comprehension or awareness.[33] Moreover, we cannot presuppose that all incorporated electronic alerts will be advantageous or lead to positive change. There are several recent examples of innovative decision-support systems that did not garner expected user attention or anticipated clinical outcomes, whether due to alert fatigue or presumed user irrelevance.[34–36] A corollary is that novel decision-support systems should be formally tested and rigorously validated, just like other medical devices, as there may be unintended consequences if implemented without discretion.[37]

While emphasis has been placed on surgeon characteristics that predict differences in opioid prescribing after surgery,[38] we found that non-physician clinicians comprised 29% of the prescribing providers but were responsible for 53% of the discharge prescriptions. This potentially represents a shift in responsibility within care teams. Any successful system for limiting opioid prescribing will thus need to include both non-physician and physician prescriber buy-in. As physician anesthesiologists seek to add value to patient care, there is an opportunity in formulating perioperative multimodal plans and identifying high-risk individuals who would benefit from transitional pain management care.[24] National guidelines suggest non-opioid analgesics and non-pharmacologic modalities in addition to opioids as part of a balanced pain management plan in both surgical and nonsurgical settings.[39,40] In our study only 16% of discharges included prescriptions for combination medications, possibly reflecting current guidance to use over-the-counter analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs separately.

A limitation of conventional cluster randomized crossover trials is the possibility of systematic effects of period on the outcome, such as learning or overall care improvements. That risk was diminished by our alternating cluster trial design, which repeated the study unit four times to minimize time-dependent confounding from background improvements in healthcare and regression to the mean.[15] Carryover effects were minimized through the inclusion of four-week washout intervals.[41] Moreover, allowances were made to correlate outcomes within clusters and time periods. The Hawthorne effect was limited by continual observation throughout periods with and without intervention.[15]

Our study was limited to postsurgical inpatients. As such, our results should be cautiously extrapolated to ambulatory surgery or emergency departments. Prescribing clinicians were the primary subjects of the study, and, given the pragmatic trial design, we did not collect patient-reported outcomes such as self-reported opioid intake after discharge. While we achieved adequate balance (absolute standardized difference < 0.1) on all potential confounders, some categories had a high percentage of missing values, though none were part of the primary analysis and were not considered to affect power or efficiency of this study. Furthermore, analysis at the individual level was performed using a modified intention-to-treat strategy.

In summary, electronic opioid prescribing guidance embedded in an electronic ordering system did not significantly or meaningfully reduce discharge opioid prescribing for surgical inpatients. In the context of an analgesic education and awareness campaign, a clinical decision-support tool aimed at individualizing opioid prescribing at discharge did not lead to less opioid prescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing Interests:

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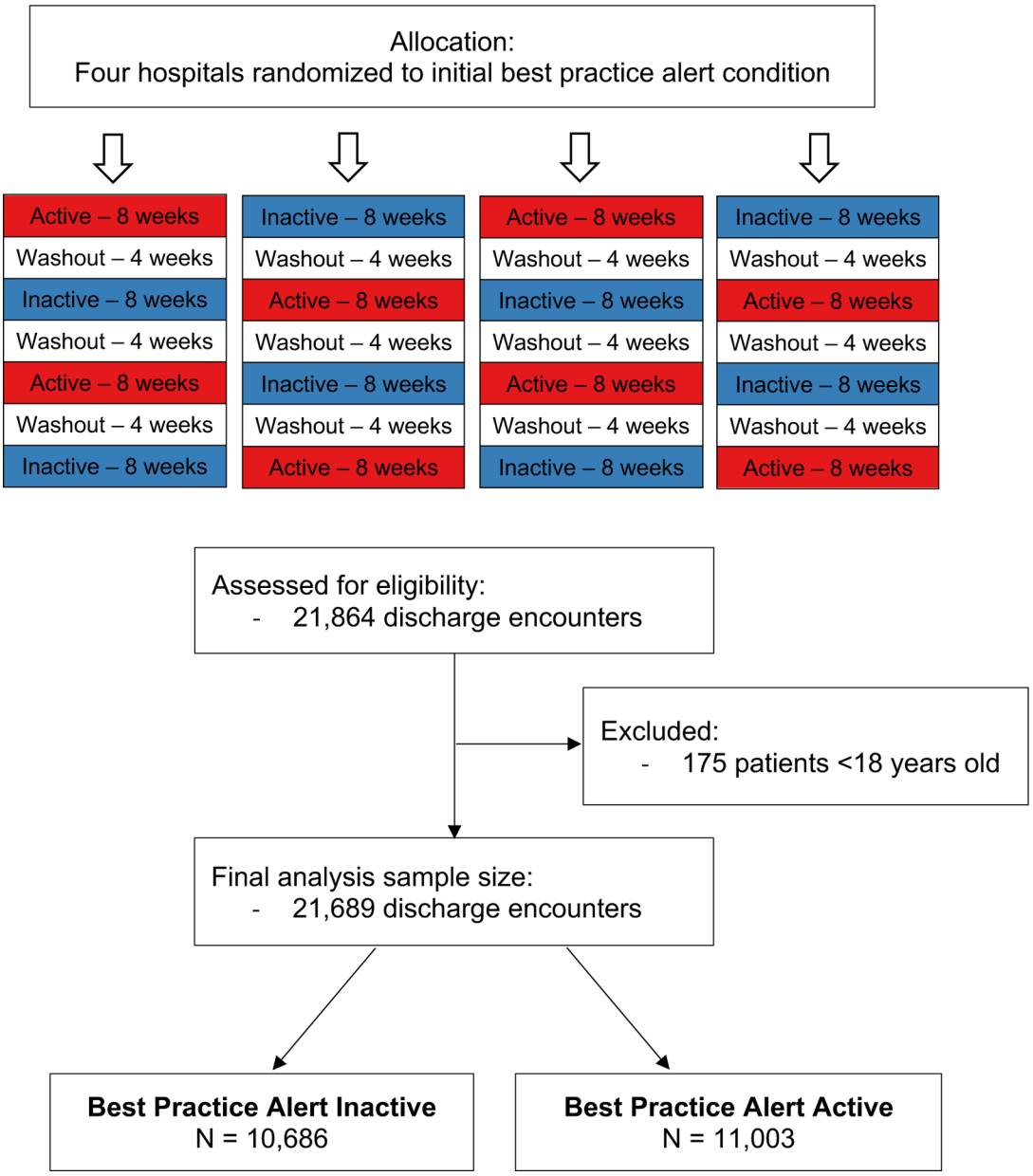

Figure 1: Consort flow diagram.

In this cluster randomized multiple crossover trial, each hospital was randomized to eight-week periods of the best practice alert being active versus inactive and four-week washout periods, which were based on the date of discharge.

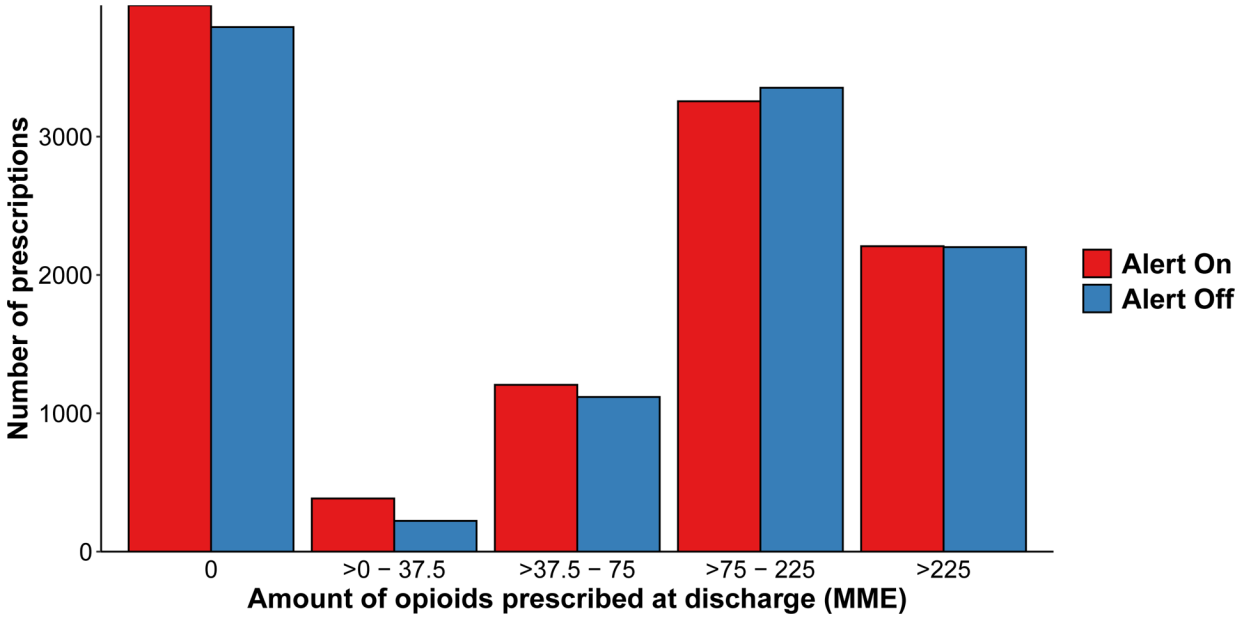

Figure 2: Opioid prescription amount at discharge by alert condition.
MME: morphine milligram equivalents.

Table 1.

Electronic provider-facing opioid prescription decision support tool (best practice alert) algorithm based on in-hospital opioid intake documented in electronic health records.

In-hospital opioid intake (oral morphine milligram equivalents)	Alert threshold (oral morphine milligram equivalents)	Best Practice Alert
0 / day	37.5 (5 oxycodone 5mg tablets)	• No prescription for opioids for use after discharge *OR* • Reduction of the total amount of opioids to 5 oxycodone 5mg tablets (37.5 morphine oral milligram equivalents)
> 0 < 22.5 / day	75 (10 oxycodone 5mg tablets)	• Reduction of the total amount of opioids prescribed to 10 oxycodone 5mg tablets total (75 oral morphine milligram equivalents)
>22.5 / day	225 (30 oxycodone 5mg tablets)	• Reduction of the total amount of opioids prescribed to 15 oxycodone 5mg tablets (112.5 oral morphine milligram equivalents) *OR* • Reduction of the total amount of opioids prescribed to 30 oxycodone 5mg tablets (225 oral morphine milligram equivalents)

Suggestions for lower oxycodone discharge prescriptions were electronically displayed within the order entry interface of the electronic health record only if a provider attempted to write a prescription above the alert threshold. For the 37.5 and 225 morphine milligram equivalent thresholds, clinicians were offered two dosing options to choose from; for the 75 morphine milligram equivalent threshold, only one option was suggested in the best practice alert. Final prescription decisions remained at the discretion of the provider. For hydrocodone prescriptions, a separate algorithm was used.

Table 2:

Patient and provider clinical and demographic characteristics.

	Missing (%)	Active Alert (N = 11,003)	Inactive Alert (N =10,686)	Absolute Standardized Difference
Age in years (mean (SD))	0	56 (18)	57 (18)	0.018
Male (%)	0	5,137 (47)	4,907 (46)	0.015
Ethnicity (%)	0			0.004
Hispanic		1,524 (14)	1,468 (14)	
Non-Hispanic		9,368 (85)	9,112 (85)	
Other		111 (1)	106 (1)	
Race (%)	0			0.052
American Indian and Alaska Native		93 (0.8)	81 (0.8)	
Asian		191 (2)	186 (2)	
Black or African American		696 (6)	632 (6)	
Native Hawaiian and Other Pacific Islander		30 (0.3)	25 (0.2)	
White or Caucasian		8,748 (80)	8,546 (80)	
Other		1,245 (11)	1,216 (11)	
Insurance (%)	0			0.026
Medicaid and indigent care		2,231 (20)	2,057 (19)	
Other		8,772 (80)	8,629 (81)	
Residence (%)	0			0.008
Urban		9,298 (85)	8,995 (84)	
Rural		1,703 (16)	1,684 (16)	
Surgical specialty (%)	0			0.055
General		2,559 (23)	2,524 (24)	
Cardiothoracic		799 (7)	803 (8)	
Obstetric or Gynecologic		1,296 (12)	1,258 (12)	
Neurological		853 (8)	916 (9)	
Orthopedic		2,641 (24)	2,390 (22)	
Urologic		699 (6)	720 (7)	
Vascular		276 (3)	284 (3)	
Otolaryngologic or Plastic Surgery		496 (5)	474 (4)	
Other		881 (8)	878 (8)	
Multiple		503 (5)	439 (4)	
Type of Hospital (%)	0			0.071
Academic Medical Center		5,134 (47)	4,609 (43)	
Community Hospital		5,869 (53)	6,077 (57)	
Chronic Pain (%)	0	674 (6)	625 (6)	0.012
Pain score at discharge (mean (SD))	46	4.8 (2.3)	4.6 (2.3)	0.050
Ordering Provider Profession (%) *				0.059
Non-physician		3,851 (54)	3,613 (52)	
Attending Physician		1,849 (26)	1,985 (29)	

	Missing (%)	Active Alert (N = 11,003)	Inactive Alert (N =10,686)	Absolute Standardized Difference
Resident or Fellow physician		1,411 (20)	1,333 (19)	
Ordering Provider Sex * Male (%)		3,351 (47)	3,279 (47)	0.004

* The data does not reflect information about unique providers. As every provider handled multiple cases, these are characteristics for each prescription written. The number of unique providers was 1,053. Percentages presented are based on non-missing data only.

Absolute standardized difference was calculated by dividing the difference in means by standard deviation. Absolute standardized difference > 0.10 was considered to indicate imbalance. Pain score was calculated using the visual analog scale. The non-physician provider category includes nurse midwives, nurse practitioners, and physician assistants. For ethnicity and race, the other category includes unknown and patient refusal classifications.

Table 3.

Treatment effect on the primary and secondary outcomes.

Outcome	Active Alert (N = 11,003)	Inactive Alert (N = 10,686)	Treatment effect (95% CI)	P-value
Primary	*Median [Q1, Q3]*		*Ratio of geometric means*	
Oral morphine milligram equivalents prescribed at discharge	75 [0, 225]	100 [0, 225]	0.95 (0.80, 1.13)	0.586[a]
Secondary	*Frequency (%)*		*Odds ratio*	
Additional opioid prescriptions	2,046 (19)	1,870 (17)	1.06 (1.00, 1.12)	0.052[b]
Pain medication category				
Opioid/Non-opioid combination	1,687 (15)	1,758 (16)	0.94 (0.86, 1.03)	0.333[c]
Opioid	5,455 (50)	5,202 (49)	1.00 (0.93, 1.06)	
No opioid medication	3,861 (35)	3,726 (35)	-	

[a] P-value obtained from a linear mixed model with fixed effects for hospital, treatment, time period,surgical specialty, and random effects for the cluster-period.

[b] P-value obtained from a log-binomial mixed model with fixed effects for hospital, treatment, time period, surgical specialty, and random effects for the cluster-period.

[c] P-value obtained from a multinomial logistic model with fixed effects for hospital, treatment, time period, and surgical specialty.

Table 4.

Post-hoc subgroup analysis.

	Subgroup: Qualified for Alert			**P-value**
	Active Alert	***Inactive Alert***	**Treatment effect (95% CI)**	
	N = 3,074	**N = 3,182**		
	Median [Q1, Q3]		***Ratio of geometric means***	
Oral morphine milligram equivalents prescribed at discharge	201 [75, 338]	225 [112, 338]	0.89 (0.79, 0.99)	0.027[a]
	Subgroup: Not qualified for Alert			**P-value**
	Active Alert	***Inactive Alert***	**Treatment effect (95% CI)**	
	N = 7,929	**N = 7,504**		
	Median [Q1, Q3]		***Ratio of geometric means***	
Oral morphine milligram equivalents prescribed at discharge	50 [0, 150]	48 [0, 150]	1.02 (0.86, 1.22)	0.788[b]
Overall interaction p-value = 0.822 [c]				

Results for the post hoc analysis comparing the group of patients qualifying for alerts to the group of patients not qualifying for alerts. If patients' prescriptions qualified for an alert, the alerts were displayed to providers in the active alert group but not in the inactive alert group.

[a]P-value obtained from a linear mixed model with fixed effects for hospital, treatment, time period and surgical specialty, and random effects for the cluster-period, after stratifying on patients who qualified for an alert.

[b]P-value obtained from a linear mixed model with fixed effects for hospital, treatment, time period and surgical specialty, and random effects for the cluster-period, after stratifying on patients who did not qualify for an alert.

[c]P-value for the interaction between alert group and patients qualifying for an alert was obtained from a linear mixed model with fixed effects for hospital, treatment, time period and surgical specialty, and random effects for the cluster-period.