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Reducing the default dispense quantity for new opioid analgesic prescriptions: study protocol for a cluster randomized controlled trial

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Abstract (word limit = 300)

Introduction

As opioid analgesic consumption has grown, so have opioid use disorder and opioid-related overdoses. Reducing the quantity of opioid analgesics prescribed for acute non-cancer pain can potentially reduce risks to the individual receiving the prescription and to others who might unintentionally or intentionally consume any leftover tablets. Reducing the default dispense quantity for new opioid analgesic prescriptions in the electronic health record (EHR) is a promising intervention to reduce prescribing.

Methods and analysis

This study is a prospective cluster randomized controlled trial with two parallel arms. Primary care sites (n=32) and emergency departments (n=4) will be randomized in matched pairs to either a modification of the EHR so that new opioid analgesic prescriptions default to a dispense quantity of 10 tablets (intervention) or to no EHR change (control). The dispense quantity will remain fully modifiable by providers in both arms. From 6 months pre-intervention to 18 months post-intervention, patient-level data will be analyzed (i.e., the patient is the unit of inference). Patient eligibility criteria are: a) received a new opioid analgesic prescription, defined as no other opioid analgesic prescription in the prior 6 months; b) age ≥ 18 years; and c) no cancer diagnosis within 1 year prior to the new opioid analgesic prescription. The primary outcome will be the quantity of opioid analgesics prescribed in the initial prescription. Secondary outcomes will include opioid analgesic re-orders and health service utilization within 30 days after the initial prescription. Outcomes will be compared between study arms using a difference-in-differences analysis.

Ethics and dissemination

This study has been approved by the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board with a waiver of informed consent (2016-6036) and is registered on ClinicalTrials.gov (NCT03003832, 6 December 2016). Findings will be disseminated through publication, conferences, and meetings with health system leaders.

Strengths and limitations of this study: (1-5 points)

1. Reducing the default dispense quantity for new opioid analgesic prescriptions in the electronic health record is a novel intervention with the potential for widespread implementation and scale-up
2. A cluster randomized controlled trial will provide rigorous evidence for or against efficacy
3. Consideration of unintended consequences such as prescription re-orders and increased health service utilization will provide additional information on the impact of the intervention
4. The setting of the trial (a single urban medical center, with multiple, diverse clinics) may limit generalizability
5. Lack of access to data (i.e., prescriptions and visits) at outside institutions may lead to measurement error for some outcomes

Introduction

In the United States, opioid consumption, opioid use disorder, and fatal overdoses involving opioids have increased dramatically. Between 1999 and 2015, sales of opioid analgesics tripled.[1] In 2015, 33,091 individuals died of a drug overdose involving opioids.[2] Beyond the human cost, the economic cost of opioid use disorder and overdose is estimated to be almost $80 billion (2015 USD) annually.[3]

While most research aiming to reduce morbidity and mortality from opioid analgesics focuses on people with chronic pain, opioid analgesics for acute non-cancer pain are also associated with significant personal and public health risk. Fatal and non-fatal overdoses occur among people with new or short-term opioid analgesic prescriptions.[4,5] Furthermore, up to 72% of people prescribed opioid analgesics have tablets left over, and most plan to keep them.[6-8] Leftover tablets are often misused, diverted, or accidentally ingested by household members (e.g., children) and are a contributor to overdose mortality beyond the index patient/prescription.[9-13] Previous interventions to reduce opioid analgesic prescribing for acute pain have included provider education or promulgation of guidelines; however, these interventions can be labor-intensive and may only have short-lived effects.

Environmental or structural interventions, such as modifying default prescribing options, have the potential to change provider behavior. Defaults can have powerful effects, including in health care settings.[14] For opioid analgesic prescriptions, this would take the form of reducing the default dispense quantity (i.e., the default number of tablets to dispense) for all new prescriptions. While providers can modify the number of tablets actually prescribed, default options can alter practice. For example, within the electronic health record (EHR), changing prescription defaults from brand name to generic increased generic prescribing significantly.[15] In one recent study involving opioid analgesics, *removing* the existing default dispense quantity for two types of opioid analgesics was associated with a modestly higher mean number of tablets dispensed and an increase in the variability of prescriptions, relative to pre-intervention.[16] While these studies suggest that defaults can alter opioid analgesic prescribing behavior,

the impact of reducing the default dispense quantity to encourage reductions in opioid analgesic prescribing has not been rigorously studied.

While reducing the default dispense quantity for new opioid analgesic prescriptions has the potential to reduce the quantity prescribed for acute pain, any reduction may be offset, at least in part, by the potential for unintended consequences. These can include an increased need for prescription re-orders, medical visits due to inadequately treated pain, or both. However, the large proportion of patients with leftover opioid analgesic tablets suggests that reductions in the quantity prescribed will simply move toward aligning prescriptions with what patients actually take for the acute episode of pain.[6-8]

The goal of this study is to investigate the impact of a uniform, reduced, default dispense quantity for new opioid analgesic prescriptions on the quantity prescribed for acute pain. We will test this intervention in a cluster randomized controlled trial in 32 primary care sites and 4 EDs, responsible for over 19,000 new opioid analgesic prescriptions annually. We hypothesize that, compared to control, reducing the default dispense quantity will lead to a higher percentage of prescriptions written for the new, reduced default number of tablets or fewer. In addition, compared to control, we hypothesize that reducing the default dispense quantity will not lead to a significant increase in opioid analgesic prescription re-orders or primary care visits, ED visits, or hospitalizations.

Methods: Participants, interventions, and outcomes

Study Setting

Montefiore Medical Center (Montefiore) is the largest health care system in The Bronx (a borough of New York City) and provides comprehensive primary, specialty, surgical, and emergency care at 4 hospitals, 4 EDs, and over 40 ambulatory clinics, with over 3 million patient visits annually. Montefiore is also a major integrated health care delivery system, administering federal (i.e., managed Medicaid and

Medicare) and private insurance plans and coordinating care for approximately 225,000 individuals. For this study, we have selected the ambulatory settings in which opioid analgesic prescribing is common: primary care practices and EDs.

Eligibility criteria

Primary care and ED sites. We will include all primary care and ED sites within Montefiore. Primary care sites can be designated as internal medicine, family medicine, or urgent care.

Provider participants. As the intervention is a modification to the EHR, the primary participants are Montefiore providers. Eligible providers will include those who provide adult primary care or ED care.

Patient participants. We will analyze outcomes for patients that: a) received a *new* opioid analgesic prescription, defined as no other opioid analgesic prescription in the preceding 6 months (a definition used in previous cohort studies);[17,18] b) age ≥ 18 years; and c) no cancer diagnosis within 1 year prior to the new opioid analgesic prescription.

Intervention and control conditions

The intervention condition is a site-level change to the EHR to implement a uniform, reduced, default dispense quantity for new opioid analgesic prescriptions. The number of tablets actually prescribed will be *fully modifiable* by providers who can tailor the prescription based on clinical factors. The intervention will include all short-acting opioid analgesics commonly used to treat acute pain: immediate-release oxycodone, immediate-release hydrocodone, tramadol, and codeine. We will include all brand and generic formulations and all tablet strengths and co-formulations with acetaminophen.

We have chosen 10 tablets as the default dispense quantity for all medication products included in the intervention condition. For opioid analgesics, there are no specific studies addressing the optimal quantity that minimizes the risks of harms while adequately treating pain. Generally, guidelines recommend a limited duration with early re-assessment.[19-21] While medications included in the intervention are typically

written for a range of between 1 to 2 tablets every 4 to 6 hours, as needed, patients may only take between 1 and 3 tablets per day total.[22-24] We chose a default of 10 tablets because we believe it represents at least a 3- to 5-day supply for most patients.

The usual EHR will serve as the control condition. Depending on the exact medication product, the pre-existing default number of tablets is typically 30 or blank, with several outliers (Table). These pre-existing defaults are a mixture of those pre-loaded in the base installation of our EHR and those created by our institution when generating defaults for commonly-prescribed medications. While most products have a pre-existing default, some do not (i.e., the "quantity dispensed" field is blank). Therefore, while the intervention will reduce the default dispense quantity for most products, it will create a default dispense quantity for some.

Outcomes

To determine the impact of the intervention, we will analyze patient-level outcomes. Therefore, the unit of inference is the patient. We will collect outcome data from 6 months prior to intervention implementation to 18 months after implementation.

Primary outcome: Quantity of opioid analgesics. This outcome refers to the quantity prescribed in each new opioid analgesic prescription. We will use three measures of the primary outcome:

1. *≤ 10 tablets (primary measure, dichotomous).* We will classify all prescriptions as greater than or less than/equal to 10 tablets (the default). This outcome is relevant specifically to the impact of the intervention.
2. *Number of tablets to dispense (continuous).* This outcome is relevant to accidental ingestion and diversion (i.e., the number of tablets available for consumption).
3. *Total morphine milligram equivalents (MME) to dispense (continuous).* The use of MME standardizes comparisons between different types of opioid analgesics with different strengths

and potencies.[25] Overdose risk increases with increasing MME[4,26,27] so this measure is relevant to overdose risk.

Secondary outcomes:

1. *Opioid analgesic prescription re-orders within 30 days of the initial prescription.* Such re-orders can occur if patients do not receive an adequate supply of opioid analgesics to treat their pain in the initial prescription and contact their providers to obtain more. Measured as: a) any re-order (*y/n*); b) number of tablets; and c) MME.
2. *Health service utilization within 30 days of the initial prescription*. Medical visits can occur if patients experience an opioid-related adverse event (e.g., delirium) or intractable pain (e.g., from not enough medication). We will analyze the number of primary care visits, ED visits, and hospitalizations.

Provider and patient characteristics (covariates)

In addition to primary and secondary outcomes, we will collect additional data on providers and patients. We have selected variables that are likely to be confounders. For providers, we will collect sex and years since graduation from medical school. For patients, we will collect demographic information (age, sex, and race/ethnicity as recorded in the EHR). We will also collect the pain diagnosis at the visit where the initial opioid analgesic was prescribed (i.e., the indication for the opioid analgesic)[17] in addition to the presence or absence of a history of psychiatric illness and a history of substance use disorder within the 1 year preceding the initial opioid analgesic prescription.

Methods: assignment of interventions

Randomization

The unit of randomization will be the site (i.e., cluster randomization). We chose site-level randomization

instead of provider-level randomization to reduce contamination and to potentially increase the intervention's effectiveness via peer effects.[28,29] At Montefiore, virtually all providers only practice at one site. In addition, technical limitations of Montefiore's EHR (Epic) render provider-level randomization less feasible.

Study sites differ greatly in visit volume and characteristics; therefore, we will randomize in matched pairs to avoid a major imbalance which could threaten study validity. For primary care sites, within strata of specialty (i.e., internal medicine and family medicine) and whether the site is a training site for resident physicians (yes/no), we will use optimal non-bipartite matching to pair sites based on the number of new opioid analgesic prescriptions, the number of visits, and the percentage of patients with commercial insurance.[30] For ED sites, given the very large differences in visit volume, we will divide the 4 sites into a "pair" consisting of the largest ED versus the 3 other smaller EDs combined.

Blinding

Randomization of sites within pairs will be conducted by the study statistician and provided directly to the health information technology department. Other study investigators will therefore be blind to randomization assignment.

Methods: data collection, management and analysis

Data collection and management

We will obtain provider data from our institution's internal provider directory as well as publicly-accessible medical license data from New York State. We will obtain all patient data from Montefiore's EHR. Study data will be stored in an encrypted, password-protected database only accessible to study investigators.

Statistical analysis

We will conduct analyses at two time points, 6 months after intervention implementation and 18 months after intervention implementation. Using a difference-in-differences (DID) analysis, we will determine the impact of the intervention by comparing the change in outcomes in the intervention group to the change in outcomes in the control group.[31,32] For example, for the 6-month analysis, we will compare the change in the intervention group's outcomes from -6 months to +6 months to the change in the control group's outcomes from -6 months to +6 months.

A DID analysis has advantages. First, while we can include covariates to adjust for imbalance in site, provider, and patient characteristics between intervention and control groups, DID accounts for residual time-invariant group-level heterogeneity such as differences in baseline outcome levels and hard-to-measure factors like overall quality of care between intervention and control sites.[32] Second, DID will allow us to account for prescribing changes due to factors other than the intervention (e.g., state or city policies aimed at reducing prescribing).

We will conduct the DID analysis using generalized linear mixed regression models. We will include a variable indicating time (pre-intervention/post-intervention) and a variable indicating study allocation (intervention/control). In DID, the interaction of these two variables is the parameter of interest. We will include relevant site characteristics (number of new opioid analgesic prescriptions, the number of visits, and percentage of patients with commercial insurance), provider characteristics (sex and years since medical school graduation) and patient characteristics (age, sex, race/ethnicity, pain diagnosis, history of substance use disorder, history of psychiatric disorder) as covariates in all models. To account for the nesting of patients within providers and providers within sites, we will include random intercepts both at the provider level and at the matched site pair level. In addition to this specification, we will explore methods to allow for heterogeneity of the intervention's effect between matched pairs.

For each outcome, we will explore the distribution of the outcome variable and potential transformations to determine the appropriate regression models (e.g., binomial, linear, Poisson, or negative binomial). When analyzing the impact of the intervention at 18 months, we will identify any change in the intervention's impact after 6 months by using the 0 to 6 month post-intervention period as the referent.

In addition to the main analysis, we will conduct several exploratory sub-group analyses. We will analyze the impact of the intervention stratified by site type (i.e., primary care versus ED) and by medication type (e.g. Schedule II versus Schedule III and IV). We will also perform separate analyses on products where the pre-existing default was reduced and products where there was no pre-existing default (i.e., the pre-existing "quantity dispensed" field was blank).

Sample size

From preliminary data analyses, we estimate eligible providers (N=~17 per site) will write a total of 9,580 new opioid analgesic prescriptions (N=~15 prescriptions per provider) from the 36 sites during a six month post-intervention period. And, in the baseline period (i.e., 6 months prior), 32.7% of prescriptions will be for ≤ 10 tablets. From these parameters, we estimated the minimal detectable difference between study arms using a 3-level hierarchical model (i.e., patients clustered within providers who are clustered within matched site pairs). Because the intracluster correlation coefficient (ICC) is not known, we used a range of ICC from 0.01 to 0.1 at the patient level; only this level of ICC is needed for power analysis under our study design.[33] Within this range of ICC, alpha=0.05, power ≥ 80%, and assuming a 3% increase in prescriptions for ≤ 10 tablets in the control arm, this study will be powered to detect a change in the intervention arm of 6.8-7.1%. This is an increase in prescriptions ≤ 10 tablets from 32.7% pre-intervention to 39.5-39.8% post-intervention.

Methods: monitoring

The principal investigator (MAB) will oversee data and safety monitoring, including review of any protocol deviations (e.g., unplanned changes to the EHR) and submission of an annual progress report to the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board and the study funder (The National Institute on Drug Abuse of the National Institutes of Health). As this study evaluates an EHR modification using data collected directly from the EHR, study investigators will not have direct contact with any human subjects. Because of the low-risk nature of the intervention, we will not convene a formal Data Safety and Monitoring Board and will not conduct planned audits.

Ethics and dissemination

This trial was approved by the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board (IRB number: 2016-6036). This trial was also granted a waiver of informed consent, similar to previous studies of EHR-based provider interventions.[34,35] During data collection and analysis, all data collected for this study will be de-identified at the earliest possible opportunity and stored in an encrypted and password-protected database. At the conclusion of the trial, we will investigate the feasibility of depositing de-identified data in a publically-accessible repository that maintains confidentiality.

We will disseminate the results of this study through peer-reviewed publications, presentations at scientific conferences, and meetings with key stakeholders including health system leadership. Reporting of results will be in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension to cluster randomized trials.[36]

Limitations

This study has limitations. First, we will only able to obtain data from within our medical center, outside

prescriptions and visits will not be captured. Therefore, we may underestimate the number of opioid analgesic re-orders and the degree of health service utilization. Further, this may bias the study findings if patients in one arm are more likely to obtain follow-up care at Montefiore than patients in the other arm. Second, as our main data source is the EHR, we do not have information on whether prescriptions were actually dispensed and our outcome measures are limited to those recorded in the course of routine clinical care. To address this limitation, we are planning to conduct a telephone survey of patients to determine the impact of the intervention on patient-reported outcomes such as pain, functioning, and patient satisfaction.

Conclusion

Interventions to reduce the quantity of opioid analgesics prescribed for acute non-cancer pain are needed. Given widespread adoption of EHRs, reducing the default dispense quantity in the EHR to reduce opioid analgesic prescribing represents a scalable intervention with potential for broad impact. With almost 300 million opioid analgesic prescriptions written annually in the US, if reducing the default dispense quantity leads to a mean reduction of even 1 or 2 tablets per prescription, this intervention could potentially reduce the number of tablets dispensed annually by hundreds of millions. Decreases in supply may translate to downstream reductions in morbidity and mortality related to opioid analgesics.

While reducing the quantity of opioid analgesics prescribed for acute pain is appealing, any intervention must also take into account the potential for unintended consequences such as inadequately treated pain. To that end, we designed the current study to explicitly detect increases in opioid analgesic prescription re-orders and health service utilization. Further, our planned patient survey will help determine the intervention's impact on patient-reported outcomes.

In summary, reducing the default dispense quantity for new opioid analgesic prescriptions is a promising

intervention to reduce opioid analgesic prescribing for acute pain. We will test this intervention in a cluster randomized controlled trial, a design that will provide rigorous evidence. The results of this trial will contribute valuable information to future efforts to reduce morbidity and mortality from opioid analgesics.

Authors' contributions: MAB is principal investigator of this trial and led its conception and design. DN, MH, WS, and CC supervised the study design and all authors made substantial contributions to the conception and design of this work. MAB drafted the manuscript and all authors revised it for critically important intellectual content. All authors provided final approval of the manuscript.

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Competing interests: The authors declare that they have no competing interests

Table. Pre-existing default dispense quantity for short-acting opioid analgesics included in the intervention*

Opioid ingredient	Product name and strength	Primary care sites	Emergency department sites
Oxycodone	oxycodone 5 mg tablet	30	30
	oxycodone 5 mg capsule	30	30
	oxycodone 10 mg tablet	Blank	Blank
	oxycodone 15 mg tablet	30	30
	oxycodone 20 mg tablet	Blank	Blank
	oxycodone 30 mg tablet	30	30
	Roxicodone® 5mg tablet	20	20
	Roxicodone® 15 mg tablet	30	30
	Roxicodone® 30 mg tablet	30	30
	oxycodone-acetaminophen 2.5 mg-325 mg tablet	30	30
	oxycodone-acetaminophen 5 mg-325 mg tablet	Blank	Blank
	oxycodone-acetaminophen 7.5 mg-325 mg tablet	30	30
	oxycodone-acetaminophen 10 mg-325 mg tablet	30	30
	Percocet® 2.5 mg-325 mg tablet	30	30
	Percocet® 5 mg-325 mg tablet	Blank	Blank
	Percocet® 7.5 mg-325 mg tablet	20	20
	Percocet® 10 mg-325 mg tablet	20	20
	Endocet® 2.5 mg-325 mg tablet	30	30
	Endocet® 5 mg-325 mg tablet	Blank	Blank
	Endocet® 7.5 mg-325 mg tablet	30	30
	Endocet® 10 mg-325 mg tablet	30	30
Hydrocodone	hydrocodone-acetaminophen 5 mg-300 mg tablet	112	112
	hydrocodone-acetaminophen 5 mg-325 mg tablet	50	30
	hydrocodone-acetaminophen 7.5 mg-300 mg tablet	180	180
	hydrocodone-acetaminophen 7.5 mg-325 mg tablet	50	30
	hydrocodone-acetaminophen 10 mg-300 mg tablet	180	180
	hydrocodone-acetaminophen 10 mg-325 mg tablet	30	30
	Lortab® 5 mg-325 mg tablet	30	30
	Lortab® 7.5 mg-325 mg tablet	30	30
	Lortab® 10 mg-325 mg tablet	30	30
	Norco® 5 mg-325 mg tablet	30	30
	Norco® 7.5 mg-325 mg tablet	30	30
	Norco® 10 mg-325 mg tablet	30	30
Tramadol	Tramadol 50 mg tablet	Blank	Blank
	Ultram® 50 mg tablet	90	20
	Tramadol-acetaminophen 37.5 mg-325 mg tablet	30	30
	Ultracet® 37.5 mg -325 mg tablet	30	30
Codeine	codeine sulfate 15 mg tablet	30	30
	codeine sulfate 30 mg tablet	30	30
	acetaminophen-codeine 300-15mg tablet	30	30

acetaminophen-codeine 300-30mg tablet	Blank	15
acetaminophen-codeine 300-60mg tablet	30	30
Tylenol®/codeine #3 300-30 mg tablet	Blank	Blank
Tylenol®/codeine #4 300-60 mg tablet	30	30

*Pre-existing defaults are a mixture of those pre-loaded in the base installation of the electronic health record system and those created by our institution when generating defaults for commonly-prescribed medications

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	____1, 15_____
Protocol version	3	Date and version identifier	____12_____
Funding	4	Sources and types of financial, material, and other support	____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,15_____
	5b	Name and contact information for the trial sponsor	____15_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____15_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____12_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11,12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A, patients not directly recruited
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____9_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A, only investigators are blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____9_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A, outcomes collected directly from electronic health record
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____9_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____10,11_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____10,11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____10,11_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____11,12_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___11,12_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____11,12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____11,12_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___12_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___12_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___9_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A, this is a trial of an electronic health record modification
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____12_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___12_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A, trial has waiver of informed consent

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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Reducing the default dispense quantity for new opioid analgesic prescriptions: study protocol for a cluster randomized controlled trial

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Title: Reducing the default dispense quantity for new opioid analgesic prescriptions: study protocol for a cluster randomized controlled trial

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Abstract (word limit = 300)

Introduction

As opioid analgesic consumption has grown, so have opioid use disorder and opioid-related overdoses. Reducing the quantity of opioid analgesics prescribed for acute non-cancer pain can potentially reduce risks to the individual receiving the prescription and to others who might unintentionally or intentionally consume any leftover tablets. Reducing the default dispense quantity for new opioid analgesic prescriptions in the electronic health record (EHR) is a promising intervention to reduce prescribing.

Methods and analysis

This study is a prospective cluster randomized controlled trial with two parallel arms. Primary care sites (n=32) and emergency departments (n=4) will be randomized in matched pairs to either a modification of the EHR so that new opioid analgesic prescriptions default to a dispense quantity of 10 tablets (intervention) or to no EHR change (control). The dispense quantity will remain fully modifiable by providers in both arms. From 6 months pre-intervention to 18 months post-intervention, patient-level data will be analyzed (i.e., the patient is the unit of inference). Patient eligibility criteria are: a) received a new opioid analgesic prescription, defined as no other opioid analgesic prescription in the prior 6 months; b) age ≥ 18 years; and c) no cancer diagnosis within 1 year prior to the new opioid analgesic prescription. The primary outcome will be the quantity of opioid analgesics prescribed in the initial prescription. Secondary outcomes will include opioid analgesic re-orders and health service utilization within 30 days after the initial prescription. Outcomes will be compared between study arms using a difference-in-differences analysis.

Ethics and dissemination

This study has been approved by the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board with a waiver of informed consent (2016-6036) and is registered on ClinicalTrials.gov (NCT03003832, 6 December 2016). Findings will be disseminated through publication, conferences, and meetings with health system leaders.

Strengths and limitations of this study: (1-5 points)

1. Reducing the default dispense quantity for new opioid analgesic prescriptions in the electronic health record is a novel intervention with the potential for widespread implementation and scale-up
2. A cluster randomized controlled trial will provide rigorous evidence for or against efficacy
3. Consideration of unintended consequences such as prescription re-orders and increased health service utilization will provide additional information on the impact of the intervention
4. The setting of the trial (a single urban medical center, with multiple, diverse clinics) may limit generalizability
5. Lack of access to data (i.e., prescriptions and visits) at outside institutions may lead to measurement error for some outcomes

Introduction

In the United States, opioid consumption, opioid use disorder, and fatal overdoses involving opioids have increased dramatically. Between 1999 and 2015, sales of opioid analgesics tripled.[1] In 2015, 33,091 individuals died of a drug overdose involving opioids.[2] Beyond the human cost, the economic cost of opioid use disorder and overdose is estimated to be almost $80 billion (2015 USD) annually.[3]

While most research aiming to reduce morbidity and mortality from opioid analgesics focuses on people with chronic pain, opioid analgesics for acute non-cancer pain are also associated with significant personal and public health risk. Fatal and non-fatal overdoses occur among people with new or short-term opioid analgesic prescriptions.[4,5] Furthermore, up to 72% of people prescribed opioid analgesics have tablets left over, and most plan to keep them.[6-8] Leftover tablets are often misused, diverted, or accidentally ingested by household members (e.g., children) and are a contributor to overdose mortality beyond the index patient.[9-13] Previous interventions to reduce opioid analgesic prescribing for acute pain have included provider education or promulgation of guidelines; however, these interventions can be labor-intensive and may only have short-lived effects. In addition, as of December 2017, 24 states have passed laws setting limits on new opioid analgesic prescriptions;[14] however, enforcement mechanisms are often unclear and the impact of such laws on prescribing is not known.

Environmental or structural interventions, such as modifying default prescribing options, have the potential to change provider behavior. Defaults can have powerful effects, including in health care settings.[15] For opioid analgesic prescriptions, this would take the form of reducing the default dispense quantity (i.e., the default number of tablets to dispense) for all new prescriptions. While providers can modify the number of tablets actually prescribed, default options can alter practice. For example, within the electronic health record (EHR), changing prescription defaults from brand name to generic increased generic prescribing significantly.[16] In one recent study involving opioid analgesics, *removing* the existing default dispense quantity for two types of opioid analgesics was associated with a modestly higher mean

number of tablets dispensed and an increase in the variability of prescriptions, relative to pre-intervention.[17] While these studies suggest that defaults can alter opioid analgesic prescribing behavior, the impact of reducing the default dispense quantity to encourage reductions in opioid analgesic prescribing has not been rigorously studied.

While reducing the default dispense quantity for new opioid analgesic prescriptions has the potential to reduce the quantity prescribed for acute pain, any reduction may be offset, at least in part, by the potential for unintended consequences. These can include an increased need for prescription re-orders, medical visits due to inadequately treated pain, or both. However, the large proportion of patients with leftover opioid analgesic tablets suggests that reductions in the quantity prescribed will simply move toward aligning prescriptions with what patients actually take for the acute episode of pain.[6-8]

The goal of this study is to investigate the impact of a uniform, reduced, default dispense quantity for new opioid analgesic prescriptions on the quantity prescribed for acute pain. We will test this intervention in a cluster randomized controlled trial in 32 primary care sites and 4 EDs, responsible for over 19,000 new opioid analgesic prescriptions annually. We hypothesize that, compared to control, reducing the default dispense quantity will lead to a higher percentage of prescriptions written for the new, reduced default number of tablets or fewer. In addition, compared to control, we hypothesize that reducing the default dispense quantity will not lead to a significant increase in opioid analgesic prescription re-orders or primary care visits, ED visits, or hospitalizations.

Methods and analysis

Study Setting

Montefiore Medical Center (Montefiore) is the largest health care system in The Bronx (a borough of New York City) and provides comprehensive primary, specialty, surgical, and emergency care at 4 hospitals, 4 EDs, and over 40 ambulatory clinics, with over 3 million patient visits annually. Montefiore

is also a major integrated health care delivery system, administering federal (i.e., managed Medicaid and Medicare) and private insurance plans and coordinating care for approximately 225,000 individuals. For this study, we have selected the ambulatory settings in which opioid analgesic prescribing is common: primary care practices and EDs.

Eligibility criteria

Primary care and ED sites. We will include all primary care (n=32) and (n=4) ED sites within Montefiore. Primary care sites can be designated as internal medicine, family medicine, or urgent care.

Provider participants. As the intervention is a modification to the EHR, the primary participants are Montefiore providers. Eligible providers will include those who provide adult primary care or ED care.

Patient participants. We will analyze outcomes for patients that: a) received a *new* opioid analgesic prescription, defined as no other opioid analgesic prescription of any type in the preceding 6 months (a definition used in previous cohort studies);[18,19] b) age ≥ 18 years; and c) no International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis code for cancer within 1 year prior to the new opioid analgesic prescription. For patients receiving more than one new opioid analgesic prescription during the study period, we will only include the first prescription.

Intervention and control conditions

The intervention condition is a site-level change to the EHR to implement a uniform, reduced, default dispense quantity for new opioid analgesic prescriptions. The number of tablets actually prescribed will be *fully modifiable* by providers who can tailor the prescription based on clinical factors. The intervention will include all short-acting opioid analgesics commonly used to treat acute pain: immediate-release oxycodone, immediate-release hydrocodone, tramadol, and codeine. We will include all brand and generic formulations and all tablet strengths and co-formulations with acetaminophen.

We have chosen 10 tablets as the default dispense quantity for all medication products included in the

intervention condition. For opioid analgesics, there are no specific studies addressing the optimal quantity that minimizes the risks of harms while adequately treating pain. Generally, guidelines recommend a limited duration with early re-assessment.[20-22] While medications included in the intervention are typically written for a range of between 1 to 2 tablets every 4 to 6 hours, as needed, patients may only take between 1 and 3 tablets per day total.[23-25] We chose a default of 10 tablets because we believe it represents at least a 3- to 5-day supply for most patients.

The usual EHR will serve as the control condition. Depending on the exact medication product, the pre-existing default number of tablets is typically 30 or blank, with several outliers (Table). These pre-existing defaults are a mixture of those pre-loaded in the base installation of our EHR and those created by our institution when generating defaults for commonly-prescribed medications. While most products have a pre-existing default, some do not (i.e., the "quantity dispensed" field is blank). Therefore, while the intervention will reduce the default dispense quantity for most products, it will create a default dispense quantity for some.

Outcomes

To determine the impact of the intervention, we will analyze patient-level outcomes. Therefore, the unit of inference is the patient. We will collect outcome data from 6 months prior to intervention implementation to 18 months after implementation.

Primary outcome: Quantity of opioid analgesics. This outcome refers to the quantity prescribed in each new opioid analgesic prescription. We will use three measures of the primary outcome:

1. *≤ 10 tablets (primary measure, dichotomous).* We will classify all prescriptions as greater than or less than/equal to 10 tablets (the default). This outcome is relevant specifically to the impact of the intervention.
2. *Number of tablets to dispense (continuous).* This outcome is relevant to accidental ingestion and

diversion (i.e., the number of tablets available for consumption).

3. *Total morphine milligram equivalents (MME) to dispense (continuous).* The use of MME standardizes comparisons between different types of opioid analgesics with different strengths and potencies.[26] Overdose risk increases with increasing MME[4,27,28] so this measure is relevant to overdose risk.

Secondary outcomes:

1. *Opioid analgesic prescription re-orders within 30 days of the initial prescription.* Such re-orders can occur if patients do not receive an adequate supply of opioid analgesics to treat their pain in the initial prescription and contact their providers to obtain more. Measured as: a) any re-order (*y/n*); b) number of tablets; and c) MME.
2. *Health service utilization within 30 days of the initial prescription*. Medical visits can occur if patients experience an opioid-related adverse event (e.g., delirium) or intractable pain (e.g., from not enough medication). We will analyze the number of primary care visits, ED visits, and hospitalizations for any reason.

Provider and patient characteristics (covariates)

In addition to primary and secondary outcomes, we will collect additional data on providers and patients. We have selected variables that are likely to be confounders. For providers, we will collect sex and years since graduation from medical school. For patients, we will collect demographic information (age, sex, and race/ethnicity as recorded in the EHR). We will also collect the pain diagnosis at the visit where the initial opioid analgesic was prescribed (i.e., the indication for the opioid analgesic) in addition to the presence or absence of a history of psychiatric illness and a history of substance use disorder within the 1 year preceding the initial opioid analgesic prescription. For pain diagnoses, we will group ICD-10-CM diagnosis codes into clinically meaningful categories based on the diagnostic categories outlined in the United States Department of Health and Human Services National Pain Strategy.[29] For history of

psychiatric illness and history of substance use disorder, we will use existing diagnosis code groupings produced by the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality of the United States Department of Health and Human Services.[30]

Randomization

The unit of randomization will be the site (i.e., cluster randomization). Compared to randomization at the level of the provider (i.e., individual-level randomization), randomization of sites would be expected to reduce statistical efficiency due to correlated outcomes within clusters.[31] However, we chose site-level randomization instead of provider-level randomization to reduce contamination and to potentially increase the intervention's effectiveness via peer effects.[32,33] At Montefiore, the vast majority of providers only practice at one site. In addition, technical limitations of Montefiore's EHR (Epic) render provider-level randomization less feasible.

Study sites differ greatly in visit volume and characteristics; therefore, we will randomize in matched pairs to avoid a major imbalance which could threaten study validity. For randomization, we will stratify sites by type (i.e., primary care versus emergency department). Further, within primary care sites, prescribing patterns and the intervention's impact may differ by specialty (i.e., internal medicine and family medicine) and whether the site is a training site for resident physicians. Therefore, we will stratify on these variables as well. Within strata, we will use optimal non-bipartite matching to pair sites based on the number of new opioid analgesic prescriptions, the number of visits, and the percentage of patients with commercial insurance.[34] For ED sites, given the very large differences in visit volume, we will divide the 4 sites into a "pair" consisting of the largest ED versus the 3 other smaller EDs combined.

Blinding

Randomization of sites within pairs will be conducted by the study statistician and provided directly to the health information technology department. Other study investigators will therefore be blind to

randomization assignment.

Data collection and management

We will obtain provider data from our institution's internal provider directory as well as publicly-accessible medical license data from New York State. We will obtain all patient data from Montefiore's EHR. Study data will be stored in an encrypted, password-protected database only accessible to study investigators.

Statistical analysis

We will conduct analyses at two time points, 6 months after intervention implementation and 18 months after intervention implementation. Using a difference-in-differences (DID) analysis, we will determine the impact of the intervention by comparing the change in outcomes in the intervention group to the change in outcomes in the control group.[35,36] For example, for the 6-month analysis, we will compare the change in the intervention group's outcomes from -6 months to +6 months to the change in the control group's outcomes from -6 months to +6 months.

A DID analysis has advantages. First, while we can include covariates to adjust for imbalance in site, provider, and patient characteristics between intervention and control groups, DID accounts for residual time-invariant group-level heterogeneity such as differences in baseline outcome levels and hard-to-measure factors like overall quality of care between intervention and control sites.[36] Second, DID will allow us to account for prescribing changes due to factors other than the intervention (e.g., state or city policies aimed at reducing prescribing). For example, in July 2016, New York State enacted a law limiting opioid analgesic prescriptions for acute pain to a 7-day supply.

A DID analysis also relies on several assumptions which we will examine.[36,37] First, we will assess whether trends in outcomes were parallel between the intervention and control sites prior to the

intervention. For this analysis, in the pre-intervention period, we will determine the significance of an interaction term between study allocation (intervention/control) and month. Second, to determine the composition of the intervention and the control sites, we will calculate and report descriptive statistics for both provider and patient characteristics, pre- and post-intervention. Finally, we will examine the potential for contamination of the arms. Although we expect the number of providers that write prescriptions at both an intervention and a control site will be low, we will determine the number of such providers and report it.

We will conduct the main DID analysis using generalized linear mixed regression models. We will include a variable indicating time (pre-intervention/post-intervention) and a variable indicating study allocation (intervention/control). In DID, the interaction of these two variables is the parameter of interest. To adjust for potential changes in composition over time, we will include relevant site characteristics (number of new opioid analgesic prescriptions, the number of visits, and percentage of patients with commercial insurance), provider characteristics (sex and years since medical school graduation) and patient characteristics (age, sex, race/ethnicity, pain diagnosis, history of substance use disorder, history of psychiatric disorder) as covariates in all models. To account for the nesting of patients within providers and providers within sites, we will include random intercepts both at the provider level and at the matched site pair level. For all estimates, we will calculate heteroscedasticity robust (empirical) standard errors.[38,39]

For each outcome, we will explore the distribution of the outcome variable and potential transformations to determine the appropriate regression models (e.g., binomial, linear, Poisson, or negative binomial). When analyzing the impact of the intervention at 18 months, we will identify any change in the intervention's impact after 6 months (i.e., whether it decays over time) by using the 0 to 6 month post-intervention period as the referent.

In addition to the main analysis, we will conduct several exploratory sub-group analyses. We will analyze the impact of the intervention stratified by site type (i.e., primary care versus ED) and by medication type (e.g. Schedule II versus Schedule III and IV). We will also perform separate analyses on products where the pre-existing default was reduced and products where there was no pre-existing default (i.e., the pre-existing "quantity dispensed" field was blank).

Finally, we intend to explore other analyses examining the precise timing of any changes in outcomes (e.g., immediate or delayed) and to characterize the heterogeneity of the intervention's effect between matched pairs. Such analyses will be defined post-hoc and are subject to availability of resources such as additional statistical support and technical considerations such as convergence of relevant statistical models.

Sample size

From preliminary data analyses, we estimate eligible providers (N=~17 per site) will write a total of approximately 7,000 new opioid analgesic prescriptions (N=~11 prescriptions per provider) from the 36 sites during a six month post-intervention period. And, in the baseline period (i.e., 6 months prior), 32.7% of prescriptions will be for ≤ 10 tablets. From these parameters, we estimated the minimal detectable difference between study arms using a 3-level hierarchical model (i.e., patients clustered within providers who are clustered within matched site pairs). Because the intracluster correlation coefficient (ICC) is not known, we used a range of ICC from 0.01 to 0.1 at the patient level; only this level of ICC is needed for power analysis under our study design.[40] Because any change in outcomes in the control arm is also unknown, we used a range of increases in the percentage of prescriptions for ≤ 10 tablets in the control arm of between 0 and 10 percentage points. Within this range of ICC, change in control arm outcomes, alpha=0.05, and power ≥ 80%, this study will be powered to detect a change in the intervention arm, over

and above any change in the control arm, of 4.4 to 4.7 percentage points.

Timeline and Monitoring

We randomized sites and implemented the new default dispense quantity for the intervention arm on 13 December 2016. Before this change, primary care sites had the same EHR for approximately 19 months. Two emergency department sites had the same EHR for 11 months and two emergency department sites had the same EHR system for 7 months (i.e., those sites implemented the current EHR just before start of the 6-month pre-intervention period).

The principal investigator (MAB) will oversee data and safety monitoring, including review of any protocol deviations (e.g., unplanned changes to the EHR) and submission of an annual progress report to the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board and the study funder (The National Institute on Drug Abuse of the National Institutes of Health). As this study evaluates an EHR modification using data collected directly from the EHR, study investigators will not have direct contact with any human subjects. Because of the low-risk nature of the intervention, we will not convene a formal Data Safety and Monitoring Board and will not conduct planned audits.

Limitation

This study has limitations. First, we will only able to obtain data from within our medical center, outside prescriptions and visits will not be captured. Therefore, we may underestimate the number of opioid analgesic re-orders and the degree of health service utilization. Further, this may bias the study findings if patients in one arm are more likely to obtain follow-up care at Montefiore than patients in the other arm. Second, as our main data source is the EHR, we do not have information on whether prescriptions were actually dispensed and our outcome measures are limited to those recorded in the course of routine clinical care. To address this limitation, we are planning to conduct a telephone survey of patients to determine the impact of the intervention on patient-reported outcomes such as pain, functioning, and

patient satisfaction.

Ethics and dissemination

This trial was approved by the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board (IRB number: 2016-6036). This trial was also granted a waiver of informed consent, similar to previous studies of EHR-based provider interventions.[41,42] During data collection and analysis, all data collected for this study will be de-identified at the earliest possible opportunity and stored in an encrypted and password-protected database. At the conclusion of the trial, we will investigate the feasibility of depositing de-identified data in a publically-accessible repository that maintains confidentiality.

We will disseminate the results of this study through peer-reviewed publications, presentations at scientific conferences, and meetings with key stakeholders including health system leadership. Reporting of results will be in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension to cluster randomized trials.[43]

Authors' contributions: MBa is principal investigator of this trial and led its conception and design. DN, MH, WS, and CC supervised the study design and all authors (MBa, DN, MH, WS, MS, MBe, and CC) made substantial contributions to the conception and design of this work. MBa drafted the manuscript and all authors (MBa, DN, MH, WS, MS, MBe, and CC) revised it for critically important intellectual content. All authors (MBa, DN, MH, WS, MS, MBe, and CC) provided final approval of the manuscript.

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Competing interests: The authors declare that they have no competing interests

Table. Pre-existing default dispense quantity for short-acting opioid analgesics included in the intervention*

Opioid ingredient	Product name and strength	Primary care sites	Emergency department sites
Oxycodone	oxycodone 5 mg tablet	30	30
	oxycodone 5 mg capsule	30	30
	oxycodone 10 mg tablet	Blank	Blank
	oxycodone 15 mg tablet	30	30
	oxycodone 20 mg tablet	Blank	Blank
	oxycodone 30 mg tablet	30	30
	Roxicodone® 5mg tablet	20	20
	Roxicodone® 15 mg tablet	30	30
	Roxicodone® 30 mg tablet	30	30
	oxycodone-acetaminophen 2.5 mg-325 mg tablet	30	30
	oxycodone-acetaminophen 5 mg-325 mg tablet	Blank	Blank
	oxycodone-acetaminophen 7.5 mg-325 mg tablet	30	30
	oxycodone-acetaminophen 10 mg-325 mg tablet	30	30
	Percocet® 2.5 mg-325 mg tablet	30	30
	Percocet® 5 mg-325 mg tablet	Blank	Blank
	Percocet® 7.5 mg-325 mg tablet	20	20
	Percocet® 10 mg-325 mg tablet	20	20
	Endocet® 2.5 mg-325 mg tablet	30	30
	Endocet® 5 mg-325 mg tablet	Blank	Blank
	Endocet® 7.5 mg-325 mg tablet	30	30
	Endocet® 10 mg-325 mg tablet	30	30
Hydrocodone	hydrocodone-acetaminophen 5 mg-300 mg tablet	112	112
	hydrocodone-acetaminophen 5 mg-325 mg tablet	50	30
	hydrocodone-acetaminophen 7.5 mg-300 mg tablet	180	180
	hydrocodone-acetaminophen 7.5 mg-325 mg tablet	50	30
	hydrocodone-acetaminophen 10 mg-300 mg tablet	180	180
	hydrocodone-acetaminophen 10 mg-325 mg tablet	30	30
	Lortab® 5 mg-325 mg tablet	30	30
	Lortab® 7.5 mg-325 mg tablet	30	30
	Lortab® 10 mg-325 mg tablet	30	30
	Norco® 5 mg-325 mg tablet	30	30
	Norco® 7.5 mg-325 mg tablet	30	30
	Norco® 10 mg-325 mg tablet	30	30
Tramadol	Tramadol 50 mg tablet	Blank	Blank
	Ultram® 50 mg tablet	90	20
	Tramadol-acetaminophen 37.5 mg-325 mg tablet	30	30
	Ultracet® 37.5 mg -325 mg tablet	30	30
Codeine	codeine sulfate 15 mg tablet	30	30

codeine sulfate 30 mg tablet	30	30
acetaminophen-codeine 300-15mg tablet	30	30
acetaminophen-codeine 300-30mg tablet	Blank	15
acetaminophen-codeine 300-60mg tablet	30	30
Tylenol®/codeine #3 300-30 mg tablet	Blank	Blank
Tylenol®/codeine #4 300-60 mg tablet	30	30

*Pre-existing defaults are a mixture of those pre-loaded in the base installation of the electronic health record system and those created by our institution when generating defaults for commonly-prescribed medications

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	____1, 15_____
Protocol version	3	Date and version identifier	____12_____
Funding	4	Sources and types of financial, material, and other support	____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,15_____
	5b	Name and contact information for the trial sponsor	____15_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____15_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____12_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11,12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A, patients not directly recruited
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____9_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A, only investigators are blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____9_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A, outcomes collected directly from electronic health record
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____9_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____10,11_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____10,11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____10,11_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____11,12_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___11,12_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____11,12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____11,12_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___12_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___12_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___9_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A, this is a trial of an electronic health record modification
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____12_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___12_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A, trial has waiver of informed consent

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.