STUDY PROTOCOL

The Protocol of the Application of Economics & Social Psychology to Improve Opioid Prescribing Safety Trial 2 (AESOPS-2): Availability of Opioid Harm

Principal Investigator:

Jason N. Doctor, Ph.D., Associate Professor, University of Southern California
Mark Sullivan, Professor, University of Washington

Supported by:

The National Institute on Aging
R33AG057395

Version date: September 18, 2025

A. Background and Status of the Problem

The objective of this study is to evaluate an extension to an existing quality improvement program in Los Angeles County addressing opioid stewardship. Much of the increase in opioid prescribing rates from 1999 until the past decade was driven by the liberal attitudes toward prescribing opioids for non-cancer pain [1, 2]. Opioids carry significant risks of overdose and addiction, and there is evidence that non-opioid alternatives are safer and as effective [3]. The greater availability of prescription opioids has been accompanied by an alarming rise in the negative consequences related to opioid use. In 2017, there were 17,029 prescription opioid overdose deaths in the US [4]. The costs of prescription opioid adverse outcomes are staggering. Aggregate costs for prescription opioid harms are estimated at over $78.5 billion (in 2013 USD), and almost 25% of the aggregate economic burden is publicly funded (for instance, through Medicaid, Medicare, and veterans' programs) [5].

In 2016, the United States Centers for Disease Control and Prevention (CDC) issued the "CDC Guideline for Prescribing Opioids for Chronic Pain" which encourages the use of alternatives to opioids and other practices that minimize harm to patients [6]. Despite the introduction of this guideline, primary care clinicians, who prescribe 45% of all opioid prescriptions in the US, report practical challenges in implementing these recommendations [7]. The dynamics of opioid use make following guidelines difficult. Since opioid analgesia from a given dose declines with chronic use due to tolerance, doses end up increasing the chance of harm. Over time, the primary benefit of opioids for many patients is the avoidance of withdrawal. As patients become dependent on opioids, they may misconstrue the easing of withdrawal hyperalgesia that occurs with the consumption of opioids as ongoing effectiveness, and they may become reluctant to stop opioids [8]. More cautious opioid prescribing (including fewer new starts, avoidance of high doses, and slow, collaborative tapers for those already on high dose long-term therapy) may improve the balance of benefits and harms for patients with chronic pain. To become a more cautious prescriber, a clinician may need to be informed that opioid risks are present and relevant to his or her own patients.

A prior quality assurance study found that clinicians judge risk to patients as greater after information about a patient's fatal overdose is available to them [9]. Of course, not all clinicians prescribe to patients who suffer a fatal overdose, so the question remains whether providing feedback concerning non-fatal overdoses will have a similar impact on prescribing clinicians. Thus, the Application of Economics & Social psychology to improve Opioid Prescribing Safety (AESOPS) Availability of Harm trial will test whether or not providing feedback to clinicians on both fatal and non-fatal overdoses results in more judicious prescribing of opioids. The objective of the AESOPS Availability of Harm trial is to dampen the intensity and frequency of opioid prescribing in accordance with the Centers for Disease Control and Prevention recommendation to "go low and slow". We

aim to accomplish this by increasing the mental availability of risks associated with opioid use by notifying clinicians of harmful patient outcomes.

B. Method of Study in Detail

a) Purpose and hypotheses to be tested:

Study Synopsis

Application of Economics & Social psychology to improve Opioid Prescribing Safety (AESOPS) Trial 2 is a multi-site randomized trial that takes place among a clinic organization in Los Angeles, California (AltaMed Health Services) and one in Chicago, Illinois (Northwestern University). Participants in the trial are clinicians. Observations are visits where opioids are prescribed. Clinicians are randomized to receive either: 1) guidelines on opioid prescribing, or 2) information on an opioid harm experienced by one of their patients (non-fatal or fatal overdose). In Los Angeles, fatal overdose letters are already required by the County, therefore, only non-fatal overdose letters will be sent to clinicians in Los Angeles. These will be signed by the County Public Health Officer. In Chicago, Illinois, both types of letters will be sent. Outcomes are milligram morphine equivalents ordered by each participating clinician per week. A secondary outcome is referrals to medication assisted treatment. These data are collected from the electronic health record systems at AltaMed and Northwestern Medical Center. Determining overdoses involves connecting data on overdoses between hospital systems, or in the case of Illinois, state vital records. More specifically, non-fatal overdoses in Los Angeles connect opioid prescribing at AltaMed with Los Angeles County emergency department data (See Appendix 1, Figure 1a), non-fatal overdoses at Chicago's Northwestern University involve a search of the internal database that connects that University's outpatient clinic data with emergency department data (See Appendix 1, Figure 1b), and fatal overdoses among patients at Northwestern connect data from that institution with Illinois State Vital records (Illinois Department of Public Health (IDPH); See Appendix 1, Figure 1c). A pilot study was originally approved for the data exchange in Figure 1c and the secure data sharing exercise was successful.

The goal of the project is to dampen the intensity and frequency of opioid prescribing and to increase awareness and use of medication assisted therapy for persons with opioid use disorder through a cluster randomized trial. Overdose notification letters (See Appendix 2 and 3) will be sent to primary care clinicians randomized to the experimental study arm and meeting inclusion criteria at AltaMed Health Services or Northwestern Medicine. Both letters will include "if/when/then" language which advises the clinician to keep the letter's recommendations close when their next patient presents with pain. Clinicians notified of their patient's overdose will be compared to a control group receiving guideline education and no notification of their patient's overdose (Appendix 6). To quantify the effect of the notification letter, we will measure the change in clinician weekly milligram morphine equivalent (MME) prescribed to all of their patients in 6-month periods before and after receiving overdose feedback letters. The secondary outcomes include the change in proportion of patients prescribed at least 50 daily MME, buprenorphine referrals for medication assisted therapy, and access rates for referral links included in the letter.

Because the letters include patient identifying information linked to outpatient prescribing records, we requested a HIPAA waiver of authorization to match outpatient records to mortality and non-fatal overdose records. The research could not feasibly be conducted if research participants' authorization were required. AltaMed will release information under the auspices of a waiver of HIPAA authorization. USC and AltaMed have a fully executed Business Associates Agreement, Memorandum of Understanding and Data Use Agreement; Northwestern and IDPH and USC and Northwestern have a fully executed Data Use Agreement. AltaMed and Northwestern will cede to the County IRB as the IRB of record for this study.

To create the list of overdose patients for whom opioids were prescribed, outpatient records will be linked to the emergency department and, in the case of Northwestern patients, IDPH death records. Overdose data will be linked with outpatient records using matching software that complies with institutional security and privacy standards at IDPH and Los Angeles County. Where an existing direct link code is available (e.g. MRN), we will use the code.

Primary hypotheses:

1. Clinicians randomized to the overdose notification group will exhibit a greater reduction in weekly MME from the pre- to post-period compared to clinicians randomized to the control group for fatal and non-fatal overdoses.
2. Among the clinicians who prescribed at least one opioid in the study period, those randomized to the overdose notification group will exhibit a greater reduction in the proportion of a clinician's patients prescribed at least 50 daily MME from the pre- to post-period compared to clinicians randomized to the control group for fatal and non-fatal overdoses.

b) Number of subjects:

AltaMed Health Services is a private health system in Los Angeles, California. AltaMed has 35 clinics with 134 clinicians with 17,674 such patients. Clinicians meeting inclusion criteria will be enrolled in the study. Northwestern Medicine is a regional health system affiliated with an academic medical center located in the Chicago region of Illinois and includes 60 primary care clinics that contain 387 clinicians with 12,552 patients using chronic opioid therapy for noncancer pain—on opioids for greater than three months.

c) Mechanism for subject selection or exclusion:

Eligible physicians and patients will be identified using outpatient opioid prescribing data

from electronic medical records. A clinician is eligible for inclusion if: 1) s/he prescribed a qualifying scheduled drug to a patient in the 12 months prior to their fatal or non-fatal overdose 2) the patient is 18 years old or older at the time of the overdose, 3) s/he practices within a health system enrolled in the study, and 4) the overdose occurs during the 12-month observation period.

A patient is eligible for identification in a physician notification if s/he (a) has been prescribed an opioid by an eligible clinician (b) has a documented overdose event in EHR or mortality data. Patients without overdose events will be excluded. Patients with fatal overdoses in Los Angeles County will be excluded to avoid redundancy with existing notification practices.

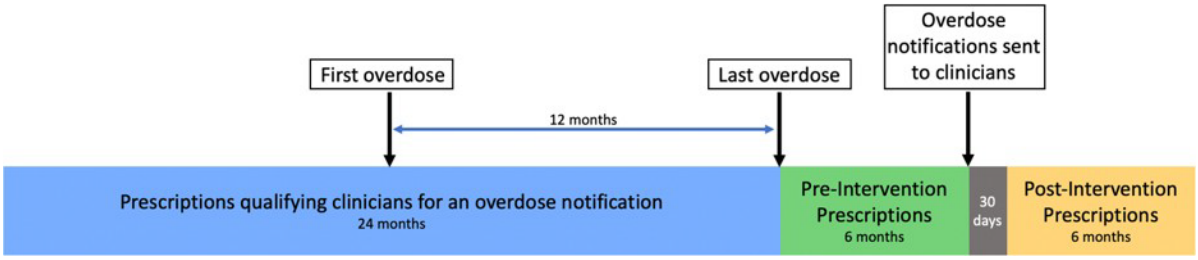
d) Duration of intervention:

The duration of the overdose notification intervention is one day.

e) Total duration which study will be performed (data collection, intervention, and analysis period):

The total duration of the study is 37 months, with 3 months devoted to data analysis, including a total of 40 months. We will look back 24 months for qualifying prescriptions. The pre-intervention period begins after the 12-month observation period and consists of the 6 months before the date on which the letter is sent. The post-intervention period consists of the 6 months following the 30-day washout period after the date on which the letter is sent. The 30-day washout period is used to account for differential time until receipt and opening of the notification envelope. See timeline below.

Figure 2. Study Timeline



f) Frequency, character, amount and types of collections:

This study will also collect primary data from the medical examiner's office, state vital records, emergency departments, and insurance claims.

List of Patients and Providers with Outpatient Opioid Prescriptions. We will use outpatient EHR data from Northwestern and Altamed to identify patients with opioid prescriptions and prescribing clinicians.

Non-Fatal Overdose Records: Los Angeles. AltaMed will securely transfer a list of providers and patients with opioid prescriptions and unique study identifiers to the Los Angeles County Department of Health Services. This list will be compared to Los Angeles County emergency department records for non-fatal overdose. Identifying non- fatal overdose events will involve non-fatal overdose diagnoses (ICD-10 codes; See Appendix 4), diagnosis codes for falls, and evidence of naloxone administration. Patient identifiers will be matched using LACDHS identity management software based on name, birthdate, and address information. Data from patients without overdose events will be destroyed. To avoid redundant messaging with existing LAC notifications of fatal overdoses, fatal overdoses will not be included. The list of AltaMed prescribers and patients with overdose events will be delivered to the Los Angeles County Department of Public Health to prepare notification letters.

Non-Fatal Overdose Records: Northwestern University. A one time data extract will be generated at the beginning of the study, looking back 24 months to identify clinicians who prescribed a qualifying scheduled drug to a patient in the 12 months prior to their non-fatal overdose. The list of patients with outpatient opioid prescriptions will be used to retrieve overdose records that occur within the 12 month observation period. Emergency department and outpatient records at Northwestern are secured in the same EHR. The list will be delivered to Northwestern study staff to prepare notification letters.

Quarterly Fatal Overdose Records. Opioid-related death data will be gathered from the Illinois Department of Public Health (IDPH). Each quarter, Northwestern study personnel will securely transfer IDPH a list of identifiers for patients who received an opioid prescription at a participating clinic. IDPH will use this information to identify if the patient is deceased. If so, IDPH will send back the date of death, cause of death, and whether the death was opioid-related via a secure file transfer process to Northwestern Medicine. IDPH will not send back information if a patient is not deceased. Analysts at Northwestern Medicine will link opioid-related decedents to identify opioid prescriptions and prescribers. The list of patients with fatal overdose will be returned to Northwestern Medicine for preparation of notification letters.

As described above, each system's enterprise software and identifiers will be employed to match patients and their providers across settings.

Allocation Data Set and Study Identifiers. Each patient and prescriber will be assigned a unique study identifier based on outpatient data before overdose data is added. The

randomization and allocation procedure described in Experimental Procedures (below) will be applied by the Los Angeles Department of Health Services and Northwestern Study Staff to create the final list of notifications.

HIPAA Limited Data Set. At the conclusion of the study period, each health system will prepare a HIPAA limited data set for analysis. The data set will include dates of overdose events, post-intervention opioid prescribing, and unique study identifiers. Study assignment, physician notification information, and overdose data from Los Angeles County Department of Public Health will be de-identified retaining unique study identifiers. Data will be transferred to USC Schaeffer Center HIPAA data enclave for analysis. No USC study personnel will have access to any patient identifying information. Links between identified data and study identifiers will be destroyed at the conclusion of the analysis.

C. List of Experimental Procedures to be Employed

a) List and detail risks:

- Mitigation of risk to participating physicians
    - Letters are a normal aspect of quality review. Letters notifying clinicians of a fatal overdose are mandated in Los Angeles County. [see LA County Board of Supervisors Meeting https://youtu.be/hBefHyAL5I8]. Therefore, risks faced by participants do not exceed that of normal clinical practice. We will take every precaution to mitigate risk to participating clinicians by keeping this disclosure private. All correspondence will be private and conducted through delivery using one of the following approaches: 1) US Postal Service, 2) institutional email, or 3) Epic inbox message, and will not be shared outside of the study.
- Mitigation of risk to patients
    - Risk of correspondence adds no additional risk compared to what is already being sent in the mail or by email (such as prior authorization letters by insurers or billing). Further, the HIPAA conduit exception allows HIPAA-covered entities to use the US Postal Service, institutional email, and Epic inbox messaging for the transmission of personal health information. US Letters and email are private and tampering with private mail is a federal offense.
    - The NIH has established a Data and Safety Monitoring Board for this study. The board consists of individuals with expertise in opioids, overprescribing, biostatistics or research methods. When notified of an unanticipated event following the intervention, the board will convene and make a decision as to whether the study should continue.
    - A potential risk is an adverse event, defined by the CDC as an abrupt

discontinuation of opioids for persons whose most recent prescription exceeds 49 MME daily dose; or as reported to study staff (10).

If there is a significant difference in the prevalence of these adverse events or overdoses between the treatment and control groups, the differences will be reported to the Data and Safety Monitoring Board and in the publication of the study results. *It is important to note that prior quality evaluations of these letters observed no additional risk of abrupt changes to opioid prescribing upon receipt of a letter (https://pubmed.ncbi.nlm.nih.gov/30093595/).*

- Management of overdose and prescribing data poses no more than minimal privacy risks. USC, health systems and IDPH comply with all local and federal security regulations protecting privacy. Identified patient data will be destroyed after the notifications have been prepared. A HIPAA Limited Data Set that includes outpatient prescribing records, overdose events, and notification status will be transferred to USC for data analysis in USC's HIPAA compliant enclave.

b) Experimental Procedures:

Randomization and Allocation. Overdose clusters are the units of randomization in this study. A cluster consists of all clinicians who prescribed one or more of the included scheduled drugs to the patient in the year prior to the overdose. Overdose clusters will be randomized to the overdose notification group or the control group, stratified by the health system which defines the cluster in the year prior to the overdose event. Allocation will be concealed until after the study groups are assigned. Clinicians who practice at multiple clinics will be assigned to the clinic at which the majority of their visits occurred in the year prior to the overdose event. If clinicians belong to more than one cluster (have multiple patients with opioid-related overdoses), they will be randomly assigned to one of those patients and placed in the corresponding study group. If clinicians belonging to more than one cluster are randomized to the intervention group, they will only receive an overdose notification regarding the one patient to whom they were randomly assigned.

Intervention. Clinicians in the intervention group receive a letter notifying them of their patient's fatal or non-fatal overdose. As described above, we will identify overdoses from electronic health record data from emergency departments and state vital records.

If randomized to the overdose notification group, physicians who prescribed a qualifying prescription to the deceased or surviving patient in the year prior to their overdose will be informed of the overdose via letter. The letters will alert prescribers to the patient's opioid-related overdose, recommend the use of their state's PDMP, and list evidence-based interventions to lower opioid-related overdoses (Appendix 2 and 3).

Controls. Clinicians in the control group will receive guideline education in the form of the CDC pocket guide and no notification of a patient overdose event (See Appendix 5). https://www.cdc.gov/drugoverdose/pdf/TurnTheTide_PocketGuide-a.pdf

D. Statistical Analysis Plan

Patients who experienced an opioid overdose will be randomized to either the letter intervention or control. We will analyze how the prescribing behavior of those patients' clinicians changed pre-to-post intervention. We will use means and medians for continuous measures for sample descriptive statistics, frequencies for count data and standard deviations, and interquartile ranges for variance. We will evaluate changes in opioid prescribing rates by group using an intent-to-treat difference-in-differences regression model on clinician hydrocodone morphine equivalent weekly dose. The coefficient for the group assignment, overdose type, and time interaction, also known as the difference-in-differences estimator, denotes the change over time in 5 MME hydrocodone pills for prescribers in the intervention group compared to prescribers in the control group for both fatal and nonfatal overdose victims. The use of a mixed-effects hierarchical knotted spline Poisson regression model offers a flexible way to accommodate non-linear trends in prescribing by group before and after introducing the intervention. This model places a knot at the intervention start date allowing slopes before and after the introduction of the intervention to vary for each group. Our primary outcome is the daily average number of 5 MME hydrocodone pills. If we have an excess of data clustering at zero, indicating weeks during which a physician wrote no opioid prescriptions, we will use a zero-inflated or left-censored regression. The regression model estimating the association between letter assignment and weekly 5 MME hydrocodone pills prescribed is shown in Eq. 1:

$$(pills)_{ijk}* = \beta_1 + \beta_2 \text{Time}_{ij} + \beta_3 (\text{Time}_{ij} - t*) + \beta_4 \text{Group}_i + \beta_5 \text{Overdose Type}_k + \beta_6 \text{Group}_i * \text{Overdose Type}_k + \beta_7 \text{Time}_{ij} * \text{Group}_i + \beta_8 (\text{Time}_{ij} - t*) * \text{Group}_i + \beta_9 \text{Time}_{ij} * \text{Overdose Type}_k + \beta_{10} (\text{Time}_{ij} - t*) * \text{Overdose Type}_k + \beta_{11} \text{Time}_{ij} * \text{Group}_i * \text{Overdose Type}_k + \beta_{12} (\text{Time}_{ij} - t*) * \text{Group}_i * \text{Overdose Type}_k + \eta + \delta_{i(k)} + \text{error}$$

where $(pills)_{ijk}*$ denotes the dependent variable for clinician i in week j, Time_{ij} is the study week indexed by j, t* is the spline knot for the start of the intervention, (Timeij - t*) is a truncated line function that is equal to (Time_{ij} - t*) when Time_{ij} > t* and 0 otherwise to allow for nonlinear trends in prescribing following the intervention, Group_i is dichotomous for the overdose notification intervention group, Overdose Type_k is dichotomous for a fatal overdose, η is the clinic random effect, and $\delta_{i(k)}$ is the random effect for each clinician i who prescribed to patient k who suffered an overdose.

The mixed logistic regression model for our secondary outcomes is shown in Eq. 2:

$$(high\ dose\ Rx)_{ijk} = \beta_1 + \beta_2 \text{Time}_{ij} + \beta_3 \text{Group}_i + \beta_4 \text{Overdose Type}_k + \beta_5 \text{Group}_i * \text{Overdose Type}_k + \beta_6 \text{Time}_{ij} * \text{Group}_i + \beta_7 \text{Time}_{ij} * \text{Overdose Type}_k + \beta_8 \text{Time}_{ij} * \text{Group}_i * \text{Overdose Type}_k + \eta + \delta_{i(k)} + \text{error}$$

where (*high dose Rx*)$_{ijk}$ is whether the visit had a high dose prescription of 50 MME or greater (yes vs. no) for clinician i, Time$_{ij}$ is the study period (pre- vs. post-intervention) indexed by j, Group$_i$ is dichotomous for the overdose notification intervention group, Overdose Type$_k$ is dichotomous for a fatal overdose, η is the clinic random effect, and $\delta_{i(k)}$ is the random effect for each clinician i who prescribed to patient k who suffered an overdose. We will compute the estimated pre- to post-intervention change in the mean proportion of high dose patient visits for each of the four intervention groups: nonfatal control, nonfatal letter, fatal control, fatal letter. The proportion will be calculated by dividing the total number of patient visits where an opioid of at least 50 MME was prescribed by the total number of opioid prescriptions.

E. Privacy of Individuals and Confidentiality of Data

We will utilize two types of data for this study:

Quality assurance program data: Data will include patient and physician identifiers. USC, health systems and IDPH comply with all local and federal security regulations protecting privacy. Identified patient data will be destroyed after the notifications have been prepared.

Program evaluation data. A HIPAA Limited Data Set that includes outpatient prescribing records, overdose, and notification status will be transferred to USC for data analysis in USC's HIPAA compliant enclave. Management of overdose and prescribing data poses no more than minimal privacy risks.

Waiver of Informed Consent. As our study design necessitates that physicians not be made aware they are participants in a research study, we are requesting a waiver of consent. We provide the following justification for this clinician waiver of consent: The Common Rule" (§46.116) specifies that informed consent can be waived when: "(1) The research involves no more than minimal risk to the subjects; (2) The research could not practicably be carried out without the requested waiver or alteration; (3) If the research involves using identifiable private information, the research could not be practicably carried out without the identifiable information; (4) The waiver or alteration will not adversely affect the rights and welfare of the subjects; [and] (5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation."

Debrief. We will have a participant debrief following completion of the study. Clinicians will be sent a debriefing statement (see Appendix 6) which contains the following information: a description of the nature and purpose of the study, specification of what data were collected about participants, and that the data will be aggregate and not linked back to individual providers or patients.

References:

1. G. P. Guy Jr *et al.*, "Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015," *MMWR Morb. Mortal. Wkly. Rep.*, vol. 66, no. 26, pp. 697–704, Jul. 2017.
2. D. Boudreau *et al.*, "Trends in long-term opioid therapy for chronic non- cancer pain," *Pharmacoepidemiol. Drug Saf.*, vol. 18, no. 12, pp. 1166–1175, 2009.
3. E. E. Krebs *et al.*, "Effect of Opioid vs Nonopioid Medications on Pain- Related

Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial," *JAMA*, vol. 319, no. 9, pp. 872–882, Mar. 2018.

4. L. Scholl, "Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017," *MMWR Morb. Mortal. Wkly. Rep.*, vol. 67, 2019, doi: 10.15585/mmwr.mm6751521e1.
5. C. S. Florence, C. Zhou, F. Luo, and L. Xu, "The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013," *Med. Care*, vol. 54, no. 10, pp. 901–906, Oct. 2016.
6. D. Dowell, T. M. Haegerich, and R. Chou, "CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016," *MMWR Recomm. Rep.*, vol. 65, no. 1, pp. 1–49, Mar. 2016.
7. K. Kroenke *et al.*, "Challenges with Implementing the Centers for Disease Control and Prevention Opioid Guideline: A Consensus Panel Report," *Pain Med.*, vol. 20, no. 4, pp. 724–735, Apr. 2019.
8. D. N. Juurlink, "Rethinking 'doing well' on chronic opioid therapy," *CMAJ*, vol. 189, no. 39, pp. E1222–E1223, Oct. 2017.
9. J. N. Doctor *et al.*, "Opioid prescribing decreases after learning of a patient's fatal overdose," *Science*, vol. 361, no. 6402, pp. 588–590, Aug. 2018.
10. D. Dowell, T. Haegerich, and R. Chou, "No Shortcuts to Safer Opioid Prescribing," *N. Engl. J. Med.*, vol. 380, no. 24, pp. 2285–2287, Jun. 2019.

F. Appendix

1. Figures 1a-1c
2. Fatal overdose notification letter
3. Nonfatal overdose notification letter
4. Nonfatal opioid overdose diagnosis codes
5. Guideline Education (Control) – CDC pocket card
6. Clinician Debrief letter

Appendix 1. Figures 1a-1c

Figure 1a. Schematic view of study procedures for communicating non-fatal overdose in Los Angeles. (Fatal overdose letters are mandated by Los Angeles County and are not part of the study).

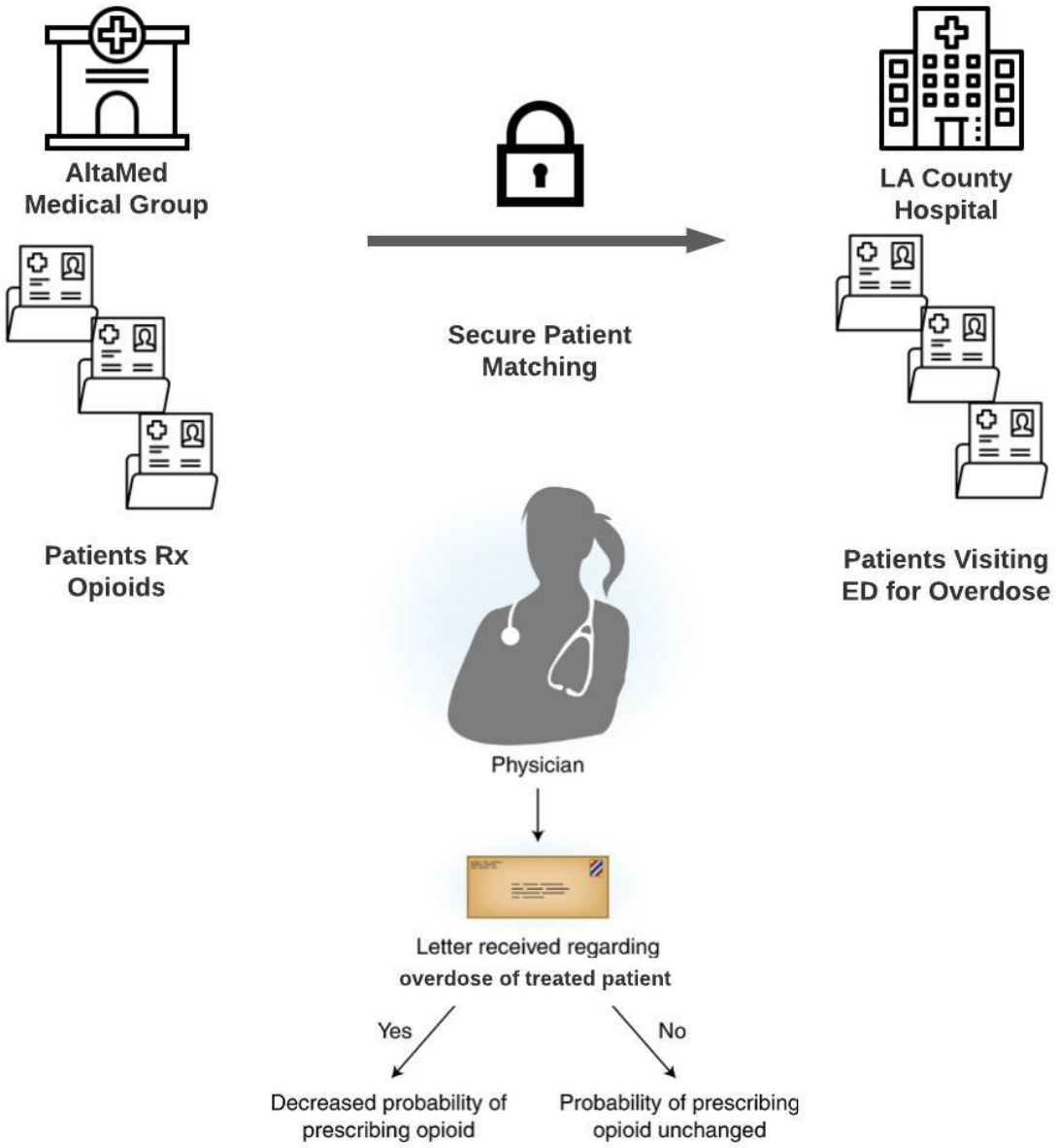


Figure 1b. Schematic view of study procedures for communicating non-fatal overdose in Chicago, Illinois.

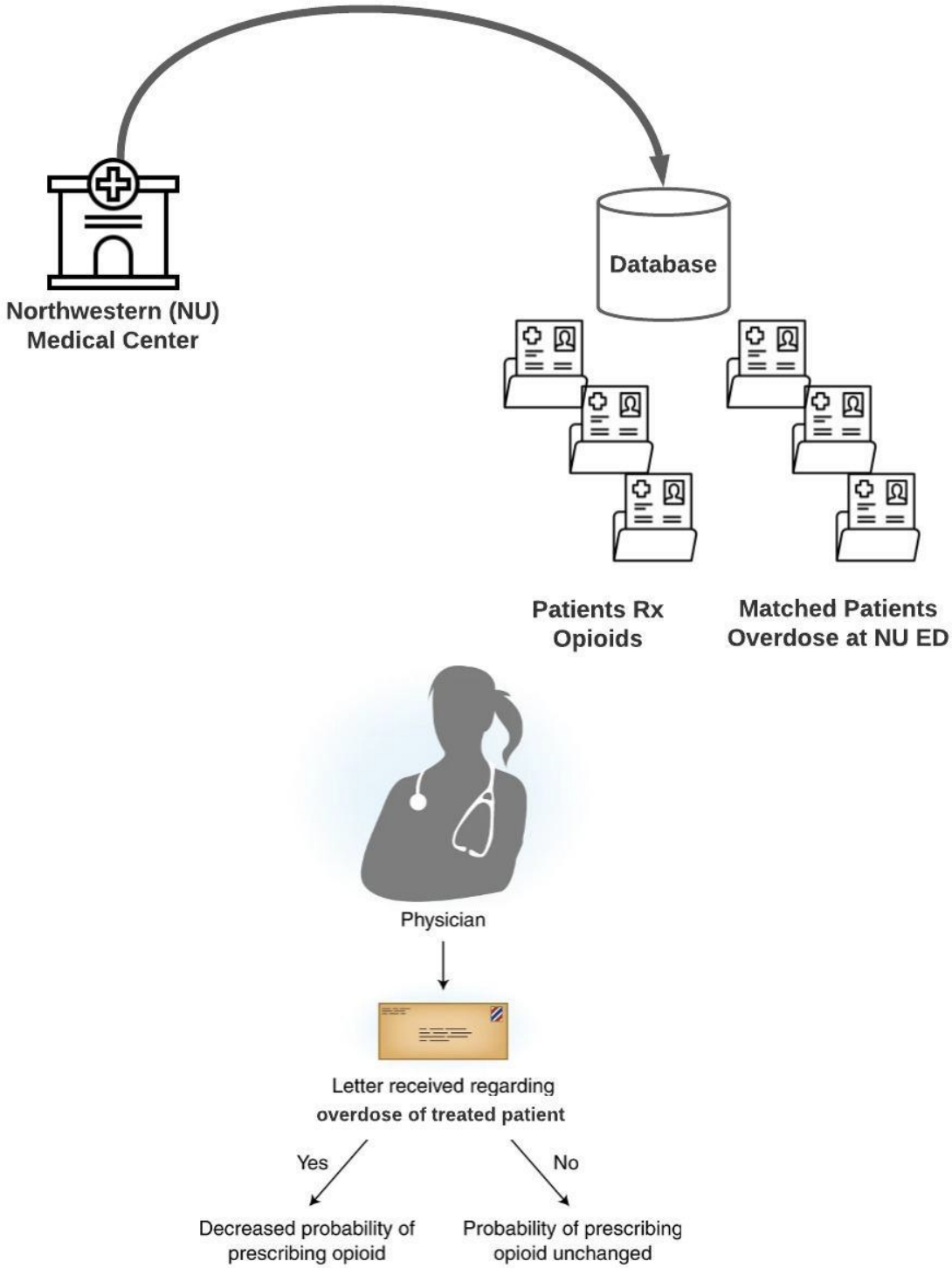
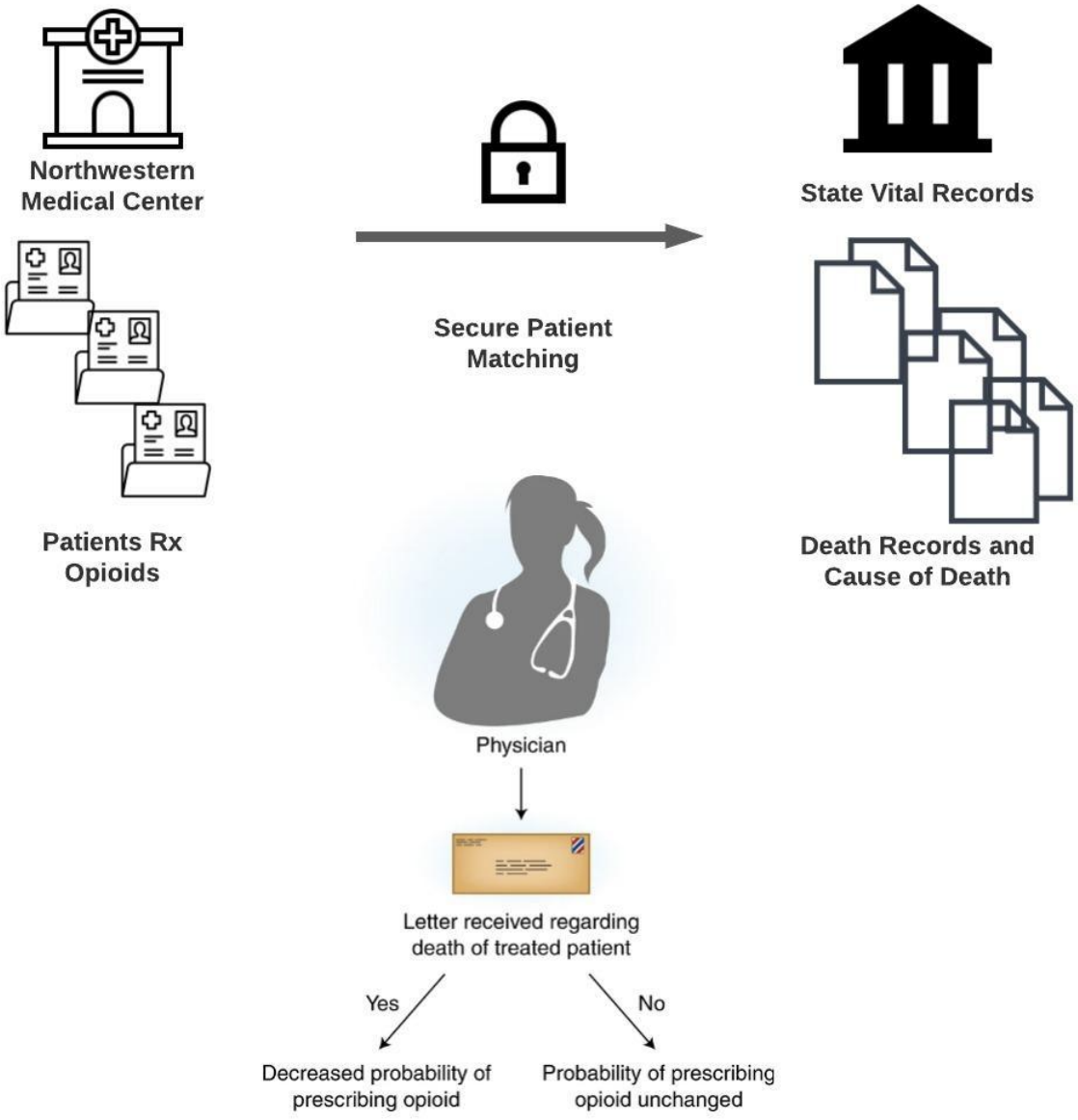


Figure 1c. Schematic view of study procedures for communicating fatal overdose in Chicago, Illinois. A pilot project has already been completed.



Appendix 2. Fatal Overdose Notification Letter to Clinician

Dear *(Name of Prescriber)*,

This letter is to inform you that your patient, {Name, Date of Birth}, died on {Date}. Prescription opioid overdose was either the primary cause of death or contributed to the death.

Northwestern Medicine is tracking outcomes for patients on opioids and other scheduled drugs. A significant proportion of overdoses are due to the combination of opioids with a sedative medication. Patients may obtain legitimate prescriptions for opioids, benzodiazepines, muscle relaxants, and sleep aids from more than one prescriber. When taken in any combination, these medications put patients at greater risk of overdose and death. Many fatal and non-fatal overdoses are a result of long-term therapeutic prescribing or of combined prescription medications with drugs obtained from other sources.

Our aim is to alert clinicians to the potential dangers of opioid medications and how common death from misuse of these medications is in Chicago and throughout Illinois.

Northwestern Medical Group would like to remind you that Illinois has a prescription drug monitoring program called the Illinois Prescription Monitoring Program (ILPMP) which *helps prescribers avoid prescribing controlled substances when they are likely to do more harm than good.*

ILPMP contains information about whether and when other clinicians have prescribed controlled substances to your patient within the last 12 months. With few exceptions, prescribers are required by state law to check the ILPMP when prescribing opioids. **Review of the ILPMP could alert you to problematic medication usage, potential addiction or diversion, and help inform safe medication prescribing and monitoring.**

This information is available through Epic and at https://www.ilpmp.org/CDC/login.php.

You may show your commitment to being a safe prescriber by using the following evidence-based interventions to lower overdose rates:

1. **Avoid co-prescribing** an opioid and a benzodiazepine. Opioids and benzodiazepines can have additive central nervous system depressant effects.

2. **Avoid opioid prescribing for chronic pain and avoid/minimize opioid prescribing for acute pain.** According to the Centers for Disease Control and Prevention (CDC), clinicians should avoid opioids for chronic pain, and when necessary for acute pain, start with the lowest effective dose of immediate-release opioids. Three days or less is often sufficient to address acute pain. Opioids should not be considered first-line

or routine therapy for chronic pain.

3. **Taper opioids to safer doses.** The CDC recommends that for patients already on long-term high-dose opioid therapy, taper to a dose that is lower than 50 morphine milligram equivalents (MME) and consider slow opioid tapers as well as pauses in the taper if needed for long-term users.

4. **Avoid "the 90-day cliff."** One California study found that nearly 70% of patients who died of prescription-related overdoses were prescribed scheduled drugs for 3 consecutive months. [i] The CDC recommends opioids should be discontinued if benefits do not outweigh risks (if realistic goals for pain and function have not been met).

5. **The CDC recommends prescribing naloxone** to patients on higher than 50 MME of opioids per day.

6. **Prescribed medications for opioid use disorder.** Clinicians should offer medications for opioid use disorder, such as buprenorphine/naloxone, to their patients with opioid use disorder. Physicians, physician assistants, and advanced practice nurses can file a waiver to prescribe buprenorphine for the indication of opioid use disorder by visiting the SAMHSA website (http://www.samhsa.gov/medication-assisted-treatment/become-buprenorphine-waivered-practitioner) or by calling SAMHSA at 866-287-2728. On April 28, 2021, SAMHSA announced that it will waive the training requirement for physicians, physician assistants, and advanced practice nurses to become waivered to prescribe buprenorphine for the indication of opioid use disorder. Further, you can use the Epic Social Determinants of Health (at the bottom left of your Storyboard), click on "Select Community Resources", and find "Substance Use" resources.

When your next patient presents with pain, keep the above 6 recommendations close at hand to assist with their safe care. Also, be comfortable voicing your concern about prescribing safety with them so that they are also aware of the dangers associated with scheduled drugs. We also encourage you to routinely log into ILPMP and learn more about the prescriptions your patient received leading up to the death.

Again, this letter is meant to be informative only, is not affiliated with other initiatives, and there is no expectation of reply. We understand that learning of your patient's death can be difficult. We hope that you will take this as an opportunity to join us in preventing future deaths from drug overdose.

Sincerely,

[Medical Director or other similar role]

[1] Lev, R., Petro, S., Lee, O., Lucas, J., Stuck, A., Vilke, G. M., & Castillo, E. M. (2016). A description of Medical Examiner prescription-related deaths and prescription drug monitoring program data. *The American journal of emergency medicine*, *34*(3), 510–514. https://doi.org/10.1016/j.ajem.2015.12.023

Appendix 3. Nonfatal Overdose Notification Letter to Clinician

Dear (Name of Prescriber),

This is a courtesy notification to inform you that your patient, {Name, Date of Birth}, visited the Emergency department on {Date} with a nonfatal opioid overdose.

Northwestern Medicine is tracking outcomes for patients on opioids and other scheduled drugs.
A significant proportion of overdoses are due to the combination of opioids with a sedative medication. Patients may obtain legitimate prescriptions for opioids, benzodiazepines, muscle relaxants, and sleep aids from more than one prescriber. When taken in any combination, these medications put patients at greater risk of overdose and death. Many fatal and non-fatal overdoses are a result of long-term therapeutic prescribing or of combined prescription medications with drugs obtained from other sources.

Our aim is to alert clinicians to the potential dangers of opioid medications and how common death from misuse of these medications is in Chicago and throughout Illinois.

Northwestern Medical Group would like to remind you that Illinois has a prescription drug monitoring program called the Illinois Prescription Monitoring Program (ILPMP) which *helps prescribers avoid prescribing controlled substances when they are likely to do more harm than good.*

ILPMP contains information about whether and when other clinicians have prescribed controlled substances to your patient within the last 12 months. With few exceptions, prescribers are required by state law to check the ILPMP when prescribing opioids. **Review of the ILPMP could alert you to problematic medication usage, potential addiction or diversion, and help inform safe medication prescribing and monitoring.** This information is available through Epic and at https://www.ilpmp.org/CDC/login.php.

Emergency department visits for an overdose strongly suggest a diagnosis of opioid use disorder. The one-year mortality following an opioid overdose is high at 10%. If your patient's overdose was due to opioid use disorder, medications for opioid use disorder, such as buprenorphine/naloxone, can be safely prescribed in any setting of care and greatly reduce mortality risks through prevention of future overdose. Medications for opioid use disorder improve your patients' chances of recovery.

You may show your commitment to being a safe prescriber by using the following evidence-based interventions to lower overdose rates:

1. **Avoid co-prescribing** an opioid and a benzodiazepine. Opioids and benzodiazepines can have additive central nervous system depressant effects.

2. **Avoid opioid prescribing for chronic pain and avoid/minimize opioid prescribing for acute pain.** According to the Centers for Disease Control and Prevention (CDC), clinicians should avoid opioids for chronic pain, and when necessary for acute pain, start with the lowest effective dose of immediate-release opioids. Three days or less is often sufficient to address acute pain. Opioids should not be considered first-line or routine therapy for chronic pain.

3. **Taper opioids to safer doses.** The CDC recommends that for patients already on long-term high-dose opioid therapy, taper to a dose that is lower than 50 morphine milligram equivalents (MME) and consider slow opioid tapers as well as pauses in the taper if needed for long-term users.

4. **Avoid "the 90-day cliff."** One California study found that nearly 70% of patients who died of prescription-related overdoses were prescribed scheduled drugs for 3 consecutive months.[ii] The CDC recommends opioids should be discontinued if benefits do not outweigh risks (if realistic goals for pain and function have not been met).

5. **The CDC recommends prescribing naloxone** to patients on higher than 50 MME of opioids per day.

6. **Prescribed medications for opioid use disorder.** Clinicians should offer medications for opioid use disorder, such as buprenorphine/naloxone, to their patients with opioid use disorder. Physicians, physician assistants, and advanced practice nurses can file a waiver to prescribe buprenorphine for the indication of opioid use disorder by visiting the SAMHSA website (http://www.samhsa.gov/medication-assisted-treatment/become-buprenorphine-waivered-practitioner) or by calling SAMHSA at 866-287-2728. On April 28, 2021, SAMHSA announced that it will waive the training requirement for physicians, physician assistants, and advanced practice nurses to become waivered to prescribe buprenorphine for the indication of opioid use disorder. Further, you can use the Epic Social Determinants of Health (at the bottom left of the Storyboard), click on "Select Community Resources," and find "Substance Use" resources.

When your next patient presents with pain, keep the above 6 recommendations close at hand to assist with their safe care. Also, be comfortable voicing your concern about prescribing safety with them so that they are also aware of the dangers associated with scheduled drugs. We also encourage you to routinely log into ILPMP and learn more about the prescriptions your patient received leading up to the overdose.

This letter is meant to be informative only and there is no expectation of reply. We understand that learning of your patient's overdose can be difficult. We hope that you will join us in our effort to prevent future drug overdoses. Please take this as an opportunity to talk with your patient and perhaps other patients in your practice who may be at-risk.

Sincerely,

[Medical Director or similar role]

[i] Lev, R., Petro, S., Lee, O., Lucas, J., Stuck, A., Vilke, G. M., & Castillo, E. M. (2016). A description of Medical Examiner prescription-related deaths and prescription drug monitoring program data. *The American journal of emergency medicine*, *34*(3), 510–514. https://doi.org/10.1016/j.ajem.2015.12.023

TURN THE TIDE

PRESCRIBING OPIOIDS FOR CHRONIC PAIN

ADAPTED FROM CDC GUIDELINE

Opioids can provide short-term benefits for moderate to severe pain. Scientific evidence is lacking for the benefits to treat chronic pain.

IN GENERAL, DO NOT PRESCRIBE OPIOIDS AS THE FIRST-LINE TREATMENT FOR CHRONIC PAIN (for adults 18+ with chronic pain > 3 months excluding active cancer, palliative, or end-of-life care).

BEFORE PRESCRIBING

1 ASSESS PAIN & FUNCTION

Use a validated pain scale. Example: PEG scale where the score = average 3 individual question scores (30% improvement from baseline is clinically meaningful).

Q1: What number from 0 – 10 best describes your PAIN in the past week? (0 = "no pain", 10 = "worst you can imagine")

Q2: What number from 0 – 10 describes how, during the past week, pain has interfered with your ENJOYMENT OF LIFE? (0 = "not at all", 10 = "complete interference")

Q3: What number from 0 – 10 describes how, during the past week, pain has interfered with your GENERAL ACTIVITY? (0 = "not at all", 10 = "complete interference")

2 CONSIDER IF NON-OPIOID THERAPIES ARE APPROPRIATE

Such as: NSAIDs, TCAs, SNRIs, anti-convulsants, exercise or physical therapy, cognitive behavioral therapy.

3 TALK TO PATIENTS ABOUT TREATMENT PLAN

- Set realistic goals for pain and function based on diagnosis.
- Discuss benefits, side effects, and risks (e.g., addiction, overdose).
- Set criteria for stopping or continuing opioid. Set criteria for regular progress assessment.
- Check patient understanding about treatment plan.

4 EVALUATE RISK OF HARM OR MISUSE. CHECK:

- Known risk factors: illegal drug use; prescription drug use for nonmedical reasons; history of substance use disorder or overdose; mental health conditions; sleep-disordered breathing.
- Prescription drug monitoring program data (if available) for opioids or benzodiazepines from other sources.
- Urine drug screen to confirm presence of prescribed substances and for undisclosed prescription drug or illicit substance use.
- Medication interactions. AVOID CONCURRENT OPIOID AND BENZODIAZEPINE USE WHENEVER POSSIBLE.

WHEN YOU PRESCRIBE

START LOW AND GO SLOW. IN GENERAL:

- Start with immediate-release (IR) opioids at the lowest dose for the shortest therapeutic duration. IR opioids are recommended over ER/LA products when starting opioids.
- Avoid ≥ 90 MME/day; consider specialist to support management of higher doses.
- If prescribing ≥ 50 MME/day, increase follow-up frequency; consider offering naloxone for overdose risk.
- For acute pain: prescribe < 3 day supply; more than 7 days will rarely be required.
- Counsel patients about safe storage and disposal of unused opioids.

See below for MME comparisons. For MME conversion factors and calulator, go to TurnTheTideRx.org/treatment.

50 MORPHINE MILLLIGRAM EQUIVALENTS (MME)/DAY:

- 50 mg of hydrocodone (10 tablets of hydrocodone/acetaminophen 5/300)
- 33 mg of oxycodone (~2 tablets of oxycodone sustained-release 15mg)

90 MORPHINE MILLLIGRAM EQUIVALENTS (MME)/DAY:

- 90 mg of hydrocodone (18 tablets of hydrocodone/acetaminophen 5/300)
- 60 mg of oxycodone (4 tablets of oxycodone sustained-release 15mg)

AFTER INITIATION OF OPIOID THERAPY

ASSESS, TAILOR & TAPER

- Reassess benefits/risks within 1-4 weeks after initial assessment.
- Assess pain and function and compare results to baseline. Schedule reassessment at regular intervals (≤ 3 months).
- Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm.
- If over-sedation or overdose risk, then taper. Example taper plan: 10% decrease in original dose per week or month. Consider psychosocial support.
- Tailor taper rates individually to patients and monitor for withdrawal symptoms.

TREATING OVERDOSE & ADDICTION

- Screen for opioid use disorder (e.g., difficulty controlling use; see DSM-5 criteria). If yes, treat with medication-assisted treatment (MAT). MAT combines behavioral therapy with medications like methadone, buprenorphine, and naltrexone. Refer to findtreatment.samhsa.gov. Additional resources at TurnTheTideRx.org/treatment and www.hhs.gov/opioids.
- Learn about medication-assisted treatment (MAT) and apply to be a MAT provider at www.samhsa.gov/medication-assisted-treatment.
- Consider offering naloxone if high risk for overdose: history of overdose or substance use disorder, higher opioid dosage (≥ 50 MME/day), concurrent benzodiazepine use.

ADDITIONAL RESOURCES

CDC GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN:
www.cdc.gov/drugoverdose/prescribing/guideline.html

SAMHSA POCKET GUIDE FOR MEDICATION-ASSISTED TREATMENT (MAT):
store.samhsa.gov/MATguide

NIDAMED: www.drugabuse.gov/nidamed-medical-health-professionals

ENROLL IN MEDICARE: go.cms.gov/pecos
Most prescribers will be required to enroll or validly opt out of Medicare for their prescriptions for Medicare patients to be covered. Delay may prevent patient access to medications.

JOIN THE MOVEMENT

of health care practitioners committed to ending the opioid crisis at TurnTheTideRx.org.

TURN THE TIDE

The Office of the Surgeon General

CDC

Appendix 6. Clinician debrief letter

Dear <name>:

Physicians in [institution name] are always looking for ways to prescribe more safely. We are interested in reducing unnecessary scheduled drug prescribing. This past [season], we evaluated whether providing clinical information to physicians led to more judicious scheduled drug prescribing. For some physicians, we connected different data sources to identify harmful events (fatal and nonfatal overdoses) among patients they treated with scheduled drugs. Those physicians for whom there were harmful events received a letter notifying them of their patient's clinical outcome. We did not identify harmful events for patients of other physicians and those physicians did not receive a letter. If you did not receive a letter, you were either in the control group or did not have any patients with harmful events that were identified. We want to know whether these letters had an impact on prescribing behavior compared to usual clinic operations that do not involve such notifications.

I am writing to let you know that data from visits at which you treated patients with scheduled drugs will be among the millions of records that will be combined to make this comparison. The comparison will be made without using your name or patient names or any identifying information other than date of service. This research study has been approved by the Los Angeles County Department of Public Health Institutional Review Board (IRB), University of Southern California IRB and Northwestern University IRB, which is the body that oversees human subjects research.

I hope you are as pleased as I am that you can play a role in helping us find better ways to encourage safe prescribing. I would be happy to answer any questions that you have.

Sincerely,

[Medical Director or similar role]