Roybal Pilot 1: Comparative Effectiveness of Two Letters to Encourage Judicious Prescribing of Opioids: A County-wide Project in Los Angeles

National Clinical Trial (NCT) Identified Number: NCT03856593

Principal Investigator: Jason Doctor, PhD

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the waiver of consent must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: April 1, 2019

Name*: Jason Doctor

Title*: Professor

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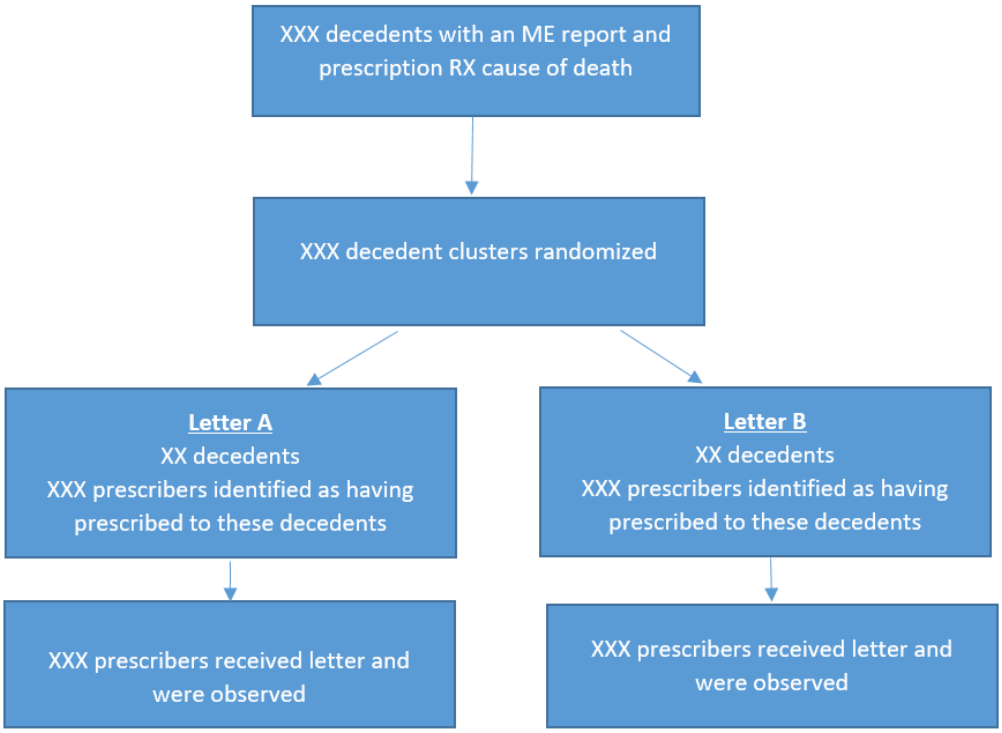
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Comparative Effectiveness of Two Letters to Encourage Judicious Prescribing of Opioids: A County-wide Project in Los Angeles
Grant Number:	P30AG024968
Study Description:	In collaboration with the Los Angeles County Medical Examiner's Office and the State of California's controlled Substance Utilization Review and Evaluation System (CURES), the investigators propose to review opioid poisonings over 12 months and send letters to prescribers in California when at least one of the provider's prescription(s) was filled by a patient who died of an opioid poisoning in Los Angeles County. The letters will be non-judgmental and factual, explaining that a patient of the provider who was being treated with prescription narcotics died of an opioid poisoning. The letters will also encourage judicious prescribing including use of the CURES system before prescribing. The investigators will evaluate physician prescribing practices over 24 months (12 months pre- and 12 months post-letter) using data from the CURES database. The hypothesis is that letters will make the risk of opioids more cognitively available and that physicians will respond by prescribing opioids more carefully, resulting in fewer deaths due to misuse and more frequent use of the CURES system.
Objectives*:	1) To conduct a randomized trial comparing two versions of a letter sent to prescribers in Los Angeles County notifying them that one of their prescriptions was filled by a patient who died of an opioid poisoning, and 2) Evaluate the effects of the randomized trial and identify factors that predict intervention effectiveness.
Endpoints*:	1) Average change over time in Milligram Morphine Equivalents (MME) dispensed 2) Average change over time in Benzodiazepine Equivalents (BE) dispensed
Study Population:	Los Angeles County prescribers
Phase* or Stage:	IV
Description of Sites/Facilities Enrolling Participants:	Los Angeles County Medical Examiner’s Office

Description of Study Intervention/Experimental Manipulation:	We will conduct a randomized trial to test the two versions of a letter signed by the Chief Medical Examiner-Coroner and County Health Officer of Los Angeles County to notify prescribers of the death in their practice. Each letter version includes the decedent's name, date of birth and date of death, and outlines the annual number and types of prescription drug deaths seen by the medical examiner, discusses the value of and way to access the State's prescription drug monitoring program and includes five CDC guideline-recommended safe prescribing strategies: 1) Avoid co-prescribing of opioids with benzodiazepines, 2) prescribe minimal dose necessary for acute pain, 3) consider slow tapers with pauses to below 50 MME per day, 4) avoid prescriptions lasting greater than 3-months for pain, and 5) prescribe naloxone in conjunction with opioids for patients taking > 50 MME per day. Each letter also states that CURES review is required by law as of October 2, 2018.
Study Duration*:	24 months
Participant Duration:	24 months

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

Assessment	Enrollment	Randomization	Baseline	Intervention Period	Observation Period	Follow-up Period
	January 2019 to July 2020	Monthly: April 2019 to July 2020	12 months prior to decedent date of death (DOD)	1-6 months after DOD	2-13 months after Letter is sent	> 13 months after letter is sent
Data attainment on demographics	X	X	X			
Inclusion/ Exclusion Criteria	X					
Data attainment on controlled substances			X	X	X	
Data analysis						X

2 INTRODUCTION

2.1 STUDY RATIONALE

One promising strategy for changing physician behavior is through use of “nudges”. The term “nudge” identifies a set of social and cognitive devices that persuade decisions in subtle ways while preserving choice. When prescribing narcotics, physicians may not have recent experiences that come to mind as to why these drugs are dangerous, making risks seem remote. They may also not consult data on a patient’s other narcotic prescriptions in their State’s pharmaceutical drug monitoring program. One useful nudge capitalizes on a finding called “Availability”. Availability is the notion that people rely upon knowledge that is salient, recent and readily available to them to evaluate risks and make decisions. If a physician issued a prescription for a narcotic that resulted in a recent opioid poisoning, providing that physician with this feedback may make the physician more likely to consult a pharmaceutical drug monitoring program database and also prescribe more judiciously.

We published a randomized trial in the journal *Science* demonstrating that carefully crafted letters, supportive in tone and designed to increase the availability of patient harms, are effective in reducing opioid prescribing among high risk prescribers (i.e., those with a death in their practice).[9] Milligram morphine equivalents in prescriptions filled daily by patients of letter recipients compared to controls decreased by 9.7% (95% confidence interval: 6.2 to 13.2%; $p < 0.001$) over a 3-month period following intervention (Figure 2). We also observed both fewer high dose prescriptions and new patients started on opioids among letter recipients. Learning of a patient's fatal overdose may instill safe opioid prescribing habits in physicians.

Figure 2. Adjusted milligram morphine equivalent prescriptions

Parameter	Randomization group	
	Letter	Control
Prescribers followed	388	438
Preintervention	72.5 (71.3 to 73.7)	71.6 (70.3 to 72.8)
Postintervention	65.7 (63.8 to 67.5)	71.7 (70.0 to 73.5)
Increment (pre- to post-)	−6.8 (−9.9 to −3.8)	0.1 (−2.8 to 3.2)
Difference in increment	−6.9 (−13.1 to −1.0)	
P value	0.001	

2.2 BACKGROUND

Much of the increase in opioid prescribing rates from 1999 until the past decade has been driven by an increase in the use of prescription opioids to treat non-cancer pain *(Guy et al. 2017; Boudreau et al. 2009)*. Although opioids carry significant risks of overdose and addiction, they are no more effective for treating chronic non-cancerous pain over a one year period than non-opioid alternatives *(Krebs et al. 2018)*. 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 *(Scholl 2019)*. 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 25% of the aggregate economic burden is publicly funded (i.e., Medicaid, Medicare, and veterans' programs) *(Florence et al. 2016)*.

In 2016, the 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 *(Dowell et al. 2016)*. Despite the introduction of this guideline, primary care clinicians, who prescribe 45% of all opioid prescriptions in the US, report challenges in following these recommendations *(Kroenke et al. 2019)*. The dynamics of opioid use make following guidelines difficult. Since opioid analgesia from a given dose declines with chronic use due to opioid tolerance, doses increase and the chance of harm grows. Over time, the primary benefit of opioids for many patients becomes the avoidance of withdrawal. As patients become dependent on opioids, they may misconstrue the treatment of interdose withdrawal hyperalgesia as ongoing effectiveness and they may become reluctant to stop

opioids *(Juurlink 2017)*. 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) can improve the balance of benefits and harms for patients with chronic pain. To embrace more cautious prescribing, a clinician may need to be informed that opioid risks are present and relevant to his/her own patients.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is a small risk that people who are not connected with this study will learn a participant's identity or their personal information. Physicians may also experience some discomfort in learning that a patient that they prescribed to has died.

2.3.2 KNOWN POTENTIAL BENEFITS

Clinicians may benefit if the quality of care they provide their patients is improved by the intervention. They also may learn more about guidelines for appropriate prescribing.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

In sum, the risks of this study are small relative to the potential benefits in increased adoption of evidence-based practices, and improved patient outcomes through improved pain management and reduction in opioid use. Unfortunately, most people who develop opioid use disorder, use illicit opiates or synthetic opioids or who die of an opioid poisoning are introduced to these drugs medically. We hope that these pilot studies will have a number of benefits that will address the unmet needs of this important group of individuals. We anticipate that health care systems, government agencies and other policy makers will benefit from implementation of the interventions we develop. Even if the intervention(s) are not found to be beneficial, then the knowledge gained will hopefully lead to new insights that will result in successful redesign for future studies. Most importantly, we anticipate the approaches we are studying will lead to fewer opioid harms, fewer persons suffering from opioid use disorder and poisoning death and fewer tragedies for families of persons who find themselves misusing opioid medications.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Evaluate the effects of the randomized trial and identify factors that predict intervention effectiveness.	Average change over time in Milligram Morphine Equivalents (MME) dispensed Average change over time in Benzodiazepine Equivalents (BE) dispensed

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a decedent-cluster randomized field experiment; clusters of prescribers within each decedent will be randomly allocated to one of two letters interventions. This design avoids treatment contamination—clinicians prescribing to the same patient will be able to share information about the intervention without diluting its effect. If two or more decedents have the same prescriber, that prescriber will be assigned to one and only one of those decedent clusters by random draw. Two factors will serve as random strata: 1) whether the decedent received a prescription from a clinician with a single or multiple deaths, and 2) whether opioids only, opioids in combination with benzodiazepines, or benzodiazepines only were the cause of death. The first strata are designed to form equivalent groups on prescriber risk posture. The second strata equate preference for type of scheduled drug prescribed in practice. Strata will be crossed to form 2 x 3 = 6 randomization groups.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Given the recent results collected in San Diego County that were reported by our group in Science,[9] on August 14th, 2018 the Los Angeles County Board of Supervisors voted to explore the feasibility of sending letters to prescribers whose patients suffered a fatal overdose to encourage judicious prescribing. Dr. Doctor participated in these discussions and helped formulate along with the County Health Officer Muntu Davis, MD, MPH and the County Medical Examiner-Coroner, Jonathan Lucas, MD, two versions of the letter (described below). A report was submitted to the County in September on feasibility and a "make it so" Board motion on October 2, 2018 approved sending of the letters.

4.3 JUSTIFICATION FOR INTERVENTION

In 2016, the 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 *(Dowell* et al 2016). 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 (*Kroenke et al 2019]*. The dynamics of opioid use make following guidelines difficult. Since opioid analgesia from a given dose declines with chronic use due to opioid tolerance, doses increase and the chance of harm grows. Over time, the primary benefit of opioids for many patients becomes the avoidance of withdrawal. As patients become dependent on opioids, they may misconstrue the treatment of withdrawal hyperalgesia as ongoing effectiveness, and they may become reluctant to stop opioids (*Juurlink*, 2017*]*. 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) can improve the balance of benefits and harms for patients with chronic pain. To embrace more cautious prescribing, a clinician may need to be informed that opioid risks are present and relevant to his/her own patients.

Notifying physicians via a letter of the death of their patient has been shown to significantly reduce opioid prescribing (Doctor et al. 2018). Two versions of a letter will be signed by the Chief Medical Examiner-Coroner and County Health Officer of Los Angeles County to notify prescribers of the death in their practice. Each letter version includes the decedent's name, date of birth and date of death, and outlines the annual number and types of prescription drug deaths seen by the medical examiner, discusses the value of and way to access the State's prescription drug monitoring program and includes five CDC guideline-recommended safe prescribing strategies: 1) Avoid co-prescribing of opioids with benzodiazepines, 2) prescribe minimal dose necessary for acute pain, 3) consider slow tapers with pauses to below 50 MME per day, 4) avoid prescriptions lasting greater than 3-months for pain, and 5) prescribe naloxone in conjunction with opioids for patients taking > 50 MME per day. Each letter also states that CURES review is required by law as of October 2, 2018.

Version B of the letter includes additional text involving an "if/when/then statement" along with an injunction to providers to share safety information with patients so that they identify as a "safe prescriber." The text reads as follows: *When your next patient presents with pain, keep the above 5 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 scheduled drugs may carry.* "If/when/then" is a form of "pre-suasion" that provides simple rules that tie goals to specific actions and has been used successfully to encourage behavior in many areas including medication adherence and drug abuse rehabilitation.[21] Letters will be signed and posted in the U.S. mail.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, received a letter, and been observed for >13 months following letter receipt.

The end of the study is defined as completion of the >13-month data observation period following receipt of letter shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

We will intervene on <u>all</u> clinicians and allied health professionals with prescribing privileges and at least one prescription drug death over the course of a year as part of a public health program to encourage safe prescribing in Los Angeles County. Informed consent of patients and clinicians is waived under HHS regulations at 45 CFR 46.116(c), as the study was evaluating a County public service safe prescribing program. As part of the County safe prescribing program, prescribers will be identified in the Controlled Substance Utilization Review and Evaluation System (CURES) system. All California pharmacies and clinics that dispense controlled substances must submit reports to CURES on a weekly basis. In consultation with the program manager of CURES, a letter notifying CURES administrators that prescriptions from these clinicians would be evaluated prospectively after the safe prescribing letters have been sent will be submitted to the CURES system.

5.1 INCLUSION CRITERIA

The inclusion criteria for clinicians are as follows: a) must be located in Los Angeles County, b) have scheduled drug prescribing privileges and, c) have prescribed a schedule II, III, or IV drug to a person in the 12 months prior to their opioid-related death.

5.2 EXCLUSION CRITERIA

Clinicians not meeting the inclusion criteria above will be excluded from the study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Not applicable

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will intervene on all clinicians and allied health professionals with prescribing privileges and at least one prescription drug death over the course of a year as part of a public health program to encourage safe prescribing in Los Angeles County. Informed consent of patients and clinicians is waived under HHS regulations at 45 CFR 46.116(c), as the study is evaluating a County public service safe prescribing program. We will utilize data from the County Medical Examiner's Office to identify opioid-related deaths and the state's prescription drug monitoring program (CURES) to identify prescribers to those decedents.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Two versions of a letter will be signed by the Chief Medical Examiner-Coroner and County Health Officer of Los Angeles County to notify prescribers of the death in their practice. Each letter version includes the decedent's name, date of birth and date of death, and outlines the annual number and types of prescription drug deaths seen by the medical examiner, discusses the value of and way to access the State's prescription drug monitoring program and includes five CDC guideline-recommended safe prescribing strategies: 1) Avoid co-prescribing of opioids with benzodiazepines, 2) prescribe minimal dose necessary for acute pain, 3) consider slow tapers with pauses to below 50 MME per day, 4) avoid prescriptions lasting greater than 3-months for pain, and 5) prescribe naloxone in conjunction with opioids for patients taking > 50 MME per day. Each letter also states that CURES review is required by law as of October 2, 2018.

Version B of the letter includes additional text involving an "if/when/then statement" along with an injunction to providers to share safety information with patients so that they identify as a "safe prescriber." The text reads as follows: *When your next patient presents with pain, keep the above 5 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 scheduled drugs may carry.* "If/when/then" is a form of "pre-suasion" that provides simple rules that tie goals to specific actions and has been used successfully to encourage behavior in many areas including medication adherence and drug abuse rehabilitation. Letters will be signed and posted in the U.S. mail.

6.1.2 ADMINISTRATION AND/OR DOSING

Not applicable

6.2 FIDELITY

No text is to be entered in this section; rather it should be included under the relevant subheadings below. This section refers to efforts made to confirm that the intervention is appropriately conducted by the interventionist(s). It is distinct from the content of ***Section 6.4****,* ***Study Intervention Adherence****, which is intended to capture a study participant's adherence to an intervention.*

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

It is the primary role of the data analysts (Marcella Kelley and Emily Stewart) to: 1) determine the appropriate number of eligible providers to reach sufficient statistical power, 2) record provider information in a secure, password protected database located at LA County Medical Examiner-Coroner's office and, 3) track enrolled providers in regards to their intervention status and progress.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For randomization, two decedent lists will be generated from the crossed strata levels. Using random.org's sequence generator, two true random integer sequences derived from atmospheric noise will determine decedent order in each list. For each ordered list, prescribers to decedents in the first half will receive Letter A, the second half of the list will receive Letter B.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Not applicable

6.5 CONCOMITANT THERAPY

Not applicable

6.5.1 RESCUE THERAPY

Not applicable

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Not applicable

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Not applicable

7.3 LOST TO FOLLOW-UP

Not applicable

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Data will be obtained by providing CURES with a list of prescriber names, alongside randomized digit IDs to anonymize human subjects. The list will include the date range for retrieving all schedule II, III, and IV drugs written by the prescriber in that time. These dates will be based on the decedent date of death and letter sent date for each prescriber - 12 months before the decedent date of death and 13 months after the letter was sent, which includes a one-month wash out period. Based on the earliest decedent date of death and latest letter sent date, we will obtain data from October 1, 2017 to August 31, 2021. CURES will provide the data to USC researchers with the randomized digit IDs (i.e., omitting prescriber and patient names) to ensure the confidentiality and privacy of human subjects. All data will be transferred and reintegrated into LA Medical Examiner-Coroner's database using Secure File Transfer Protocol.

8.2 SAFETY ASSESSMENTS

Although we will be unable to determine if there are hospitalizations or ED visits for opioid withdrawal in patients of clinicians in the intervention group, we will monitor this potential safety issue by comparing clinicians who received a letter to controls to determine if there are any dramatic reductions (>20% from baseline) in opioid prescribing in the post-intervention period as a result of the letter. The U.S. does not have an integrated healthcare system with complete data on hospitalizations for all patients to evaluate induced withdrawal. However, it is possible for us to evaluate if providers induce withdrawal on patients by exhibiting high rates of MME reductions (see p. 589 Doctor et al., Science 361, 588–590 (2018). In our previous work, we demonstrated that for letters, there was no difference in the proportion of prescribers in the intervention or control group who made substantial (>20%)

reductions in opioid prescribing in the post-intervention period (z =1.279, P > 0.05). We will use this same outcome to evaluate potential harm to patients in this trial.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Not applicable

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

Although we will be unable to determine if there are hospitalizations or ED visits for opioid withdrawal in patients of clinicians in the intervention group, we will monitor this potential safety issue by comparing clinicians who received a letter to controls to determine if there are any dramatic reductions (>20% from baseline) in opioid prescribing in the post-intervention period as a result of the letter. The U.S. does not have an integrated healthcare system with complete data on hospitalizations for all patients to evaluate induced withdrawal. However, it is possible for us to evaluate if providers induce withdrawal in patients by exhibiting high rates of MME reductions (see p. 589 Doctor et al., Science 361, 588–590 (2018). In our previous work, we demonstrated that for letters, there was no difference in the proportion of prescribers in the intervention or control group who made substantial (>20%) reductions in opioid prescribing in the post-intervention period ($z = 1.279$, $P > 0.05$). We will use this same outcome to evaluate potential harm to patients in this trial.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

At any time, clinicians can report an adverse event or unanticipated problem potentially related to the letters to the medical examiner's office or the County or City public health officer who co-signs the letter and provides contact information.

We do not expect there to be adverse events directly influenced by the clinical guidance being delivered in this study. All study interventions encourage clinicians to follow well-established national guideline recommendations and known best practices. While the expectedness of adverse events is very low, we will investigate each and every numerator case identified in all safety measures described above. For cases identified by the safety monitoring measures, we will perform manual physician chart review to examine the clinical circumstances and to make a judgment (1) the expectedness of the event [unexpected, expected], (2) the likelihood that the safety event was study related [not related/possibly related/definitely related] and (3) judge the event's severity [abnormal clinical finding without symptoms/symptoms requiring clinical intervention/short term disability or hospitalization/death AND separately define the severity as mild, moderate, or severe].

These will be conducted only by authorized study personnel. Study personnel will interview clinicians treating patients when needed to obtain additional information. Each case identified will have a case report form with these variables and will be signed and dated by study staff completing the form. These forms will be stored in a locked office. Each adverse event will be given an identification number. If study personnel believe that a patient that experienced an adverse event would benefit from seeing or communicating with their clinician who previously received a letter, the PI will within 2 business days reach out to this clinician advising them to contact the patient as soon as possible.

We will within a business day report any clinician reported adverse events, safety analysis, or unanticipated problems to the USC IRB. Our report will include appropriate identifying information for the study, a detailed description of the adverse event, and a description of any changes to the protocol or other corrective actions that have been taken or are proposed. If an adverse event occurs, we will review relevant clinical decision support and ensure others are not at a greater risk of harm than was previously known or recognized. We will notify our NIA Program Officer of any serious adverse events.

Clinician participants are only receiving a letter informing them of a recent patient death due to opioid overdose. Additional patient deaths related to this study are not expected. However, should we identify a patient death in safety measures described above we will report the death to the NIA Program Officer and the USC IRB within 24 hours of our knowledge of the death.

The seriousness of the adverse event will be documented on the case report form. We will categorize all of the following as serious adverse events: patient death, life-threatening event, hospitalization-initial or prolonged, disability/incapacity, and events that required intervention to prevent permanent impairment. The clinician reviewing the event will determine the seriousness of the event. If it is an event other than those listed above that the reviewing clinician feels is an 'other' serious event, it will be discussed with another clinical study team member to reach consensus. All details will be documented on a case report form.

8.3.5 ADVERSE EVENT REPORTING

See 8.3.4.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

See 8.3.4.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Unanticipated Problems that are unexpected, related or possibly related to this research (including anywhere there is a reasonable possibility that the incident or outcome may have been caused or associated with the study) and that suggests that the research places clinicians or patients at greater risk of harm than was previously known or recognized will be thoroughly and promptly investigated. The Unanticipated Problem will be investigated, formally written down with a corrective plan and measures to prevent reoccurrence. This report will be shared with the NIA Program Officer and Safety Officer within 48 hours of study's knowledge of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Milligram morphine equivalents in prescriptions filled daily by patients of letter recipients will decrease following receipt of letter as compared to baseline.

9.2 SAMPLE SIZE DETERMINATION

We calculated the sample size needed to detect an effect of the letter intervention using standard formulas for power analysis in cluster randomized trials and the 'clusterPower' package in R statistical computing language. For this calculation we used data on decedents and prescribers at the San Diego County Medical Examiner between January 1 and December 31, 2013 published in Lev et al. 2016 and Doctor et al. 2018. We assume a two tailed test with a 5% Type I error rate and an 80% chance to detect an effect. Doctor et al. (2018) found mean of 5.5 prescribers for each decedent. Coefficient of variation we assume to be 1.22, which implies that 99% of decedents had 20 or fewer prescribers in the year before their death. We assume a 50% reduction in mean difference as compared to the effect reported in Doctor et al. 2018 and a standard deviation of +140 daily MME within cluster. Most clinician clusters for process measures have intracluster correlations that fall between 0.05 and 0.15. We assume a more conservative intracluster correlation of 0.2; in our design we randomized by decedent to reduce intracluster correlation. We utilized the Taylor method for calculating variance inflation due to unequal cluster sizes. Under these assumptions, we would need 103 decedents per study arm; given annual opioid overdose frequency in Los Angeles, we expect to have 192 per arm. We have ample power to detect an effect.

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Population (i.e., all randomized participants)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will convert opioids to milligram morphine equivalents (MME) using formulas published by the CDC.[29] Descriptive and inferential statistics will be carried out in STATA (Version 14.0; Stata Corporation, College Station, TX). The *cmp* command in STATA will be used to compute a difference in differences estimator within a mixed-model censored linear regression.[30] The difference in differences estimator compares the average change over time in MME dispensed for prescribers in the group receiving letter version A, compared to the average change over time for those prescribers in receiving version B. To ensure normally distributed data, we evaluate the natural log of MME. Censored regression has a continuous component and a discrete one. The natural log MME doses estimated over days where opioids were dispensed in the name of a prescriber represent the continuous part, and days with no opioids filled in that prescriber's

name represent the discrete part of the model. We denote estimation of the dependent variable as $log(\widehat{MME}) *$ to distinguish it from uncensored estimation. The analysis is represented by:

$$log(\widehat{MME})*_{ijk} = \beta_1 x_{1ij} + \beta_2 x_{2ij} + \beta_3 x_{3ij} + \delta_{i(k)} \quad [1]$$

where β_1, $\beta_2$and β_3 are fixed effects coefficients on time, x_1, intervention, x_2,and time by intervention interaction, x_3, respectively. Alphabetic subscripts describe the *i*th prescriber, *j*th prescription filled and *k*th decedent, the nested random intercept $\delta_{i(k)}$is normally distributed with mean zero and variance, $\sigma^2_{i(k)}$, for each *i* prescriber nested in (i.e., having prescribed to) decedent *k*, *i*(*k*). With natural log transformed data, the value 100·[*exp*{β_3} - 1] measures precisely the percentage change in MME attributable to the intervention when data are uncensored (see Woolridge (2008), pp. 212 and 410).

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Not applicable

9.4.4 SAFETY ANALYSES

Although we will be unable to determine if there are hospitalizations or ED visits for opioid withdrawal in patients of clinicians in the intervention group, we will monitor this potential safety issue by comparing clinicians who received a letter to controls to determine if there are any dramatic reductions (>20% from baseline) in opioid prescribing in the post-intervention period as a result of the letter. The U.S. does not have an integrated healthcare system with complete data on hospitalizations for all patients to evaluate induced withdrawal. However, it is possible for us to evaluate if providers induce withdrawal on patients by exhibiting high rates of MME reductions (see p. 589 Doctor et al., Science 361, 588–590 (2018). In our previous work, we demonstrated that for letters, there was no difference in the proportion of prescribers in the intervention or control group who made substantial (>20%) reductions in opioid prescribing in the post-intervention period (z =1.279, P > 0.05). We will use this same outcome to evaluate potential harm to patients in this trial.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

For sample (clinician and decedent) descriptive statistics, we will use means and medians for continuous measures, frequencies for count data, and standard deviations and interquartile ranges for variance.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

All providers meeting the study inclusion criteria will participate in the pilot study. We will not undersample or oversample clinicians who are women and/or members of minority racial and ethnic groups, so we expect to enroll them in proportion to their population prevalence. Although we can report on sex/gender and race/ethnicity of the decedents (if the information is available in the Medical Examiner's report), we will likely not have racial/ethnic information available for providers through CURES data. However, we will have access to the sex/gender of providers and will conduct analyses to investigate any differences between groups. Per the Frequently Asked Questions on NIH policy regarding Inclusion on the basis of Sex/Gender and Race/Ethnicity, if we are using previously collected data sets that do not conform to the current (1997) OMB standards and have no plans of collecting any new/additional data from the subjects, we will note this in the comments section of our Planned Enrollment Report.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable

9.4.9 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Informed consent of patients and clinicians is waived under HHS regulations at 45 CFR 46.116(c), as the study is evaluating a County public service safe prescribing program.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Not applicable

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Not applicable

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study

participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, or IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. All research activities will be conducted in as private a setting as possible.

Data for this project is extracted from Controlled Substance Utilization Review and Evaluation System CURES; https://oag.ca.gov/cures). Only designated members of the research team will have access to this data. Only data from eligible subjects will be analyzed. Marcella Kelley and Emily Stewart have been cleared and embedded as LA County volunteers and will collect all data on site at LA County Medical Examiner's office or from CURES Research Center. A data usage agreement has been put in place between LAC and USC to safely transfer de-identified data via a secure hard drive for analyses related to the evaluation. All data will be stored on password-protected computers and servers that are accessible only to study personnel with appropriate password authorization. These measures should be effective in minimizing breaches of confidentiality. Prior to study initiation, approval will be obtained from the Institutional Review Board at University of Southern California. This approval will be reevaluated each year as part of the Human Subjects Committee annual review process, paying particular attention to patient confidentiality and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

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

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the LA County Medical Examiners Office. After the study is completed, the de-identified, archived data will be transmitted to and stored at University of Southern California. Data may be made available through data use agreements among researchers interested in using the data, the Los Angeles County Medical Examiner's Office and the California State Department of Justice.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Independent Safety Monitor**
Jason Doctor, PhD	*Daniel Larach, MD*
University of Southern California	*University of Southern California*
635 Downey Way, Los Angeles, Ca	*1450 San Pablo St., Suite 3600, Los Angeles, Ca*
213.821.8142	*(410) 274-3034*
jdoctor@usc.edu	*daniel.larach@med.usc.edu*

This project is also governed by the Roybal Steering Committee consisting of the Roybal Center PIs and Co-Investigators.

10.1.6 SAFETY OVERSIGHT

For this single-site, single study arm, minimal risk intervention pilot study, the study staff and principal investigator will be responsible for ensuring participants' safety on a daily basis and for monitoring and responding to any adverse events or unanticipated problems and for reporting them to the IRB and the NIA Program Officer.

The presence of a DSMB is not requested or required by the NIA for this study. However, we have nominated a Safety Officer, Daniel Larach, MD.

In addition to the reporting to the IRB and NIA PO, we will report all adverse events that are both serious (SAE) and unexpected (i.e., have not been previously reported for the study's intervention) to the Safety Officer within 48 hours of the study's knowledge of SAE. The summary of all other SAEs will be reported to NIA PO and to the Safety Officer quarterly, unless otherwise requested by the Safety Officer.

10.1.7 CLINICAL MONITORING

Not applicable

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Not applicable. The USC IRB has issued a waiver of consent for participation in this study, but clinician participants who receive a letter will have the opportunity to ask questions and opt out of future mailings.

Source documents and the electronic data --- Data will be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

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

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Decedent data is collected from hard copies of death reports at the LA County office. Prescriber data is collected electronically from the CURES online portal, CURES Research Center, and the CA Department of Consumer Affairs (DCA) website. Patient and physician data are recorded in a secure, electronic database, and maintained by study analysts.

CURES provides records of opioids dispensed at California pharmacies attributable to each provider in our sample treating all civilian, non-Veteran's Administration and non-institutionalized patients. The Medical Examiner has authority to use CURES for the purpose of educating practitioners and others in lieu of disciplinary, civil, or criminal actions, in accordance with the California State's Health and Safety Code § 11165(c)(2). First name, last name, date of birth and address will identify each decedent in the medical examiner reports and CURES data. Drug Enforcement Agency (DEA) number will identify the prescribers in CURES data. Data from eligible clinicians will be extracted from CURES and kept onsite (Windows 10 OS) at the medical examiner's office for de-identified analytic file preparation. A file stripped of patient and clinician identifiers will be prepared and released for analysis on secure servers at the University of Southern California.

Data will be entered, tracked, edited, updated and reported by pre-approved analysts with the appropriate clearance.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after of study completion. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

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

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

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

There are restrictions with sharing this data. The data will be extracted from CURES 2.0 (Controlled Substance Utilization Review and Evaluation System), a database of Schedule II, III and IV controlled substance prescriptions dispensed in California serving the public health, regulatory oversight agencies,

and law enforcement. Data may be made available through data use agreements among researchers interested in using the data, the Los Angeles County Medical Examiner's Office and the California State Department of Justice.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CURES	Controlled Substance Utilization Review and Evaluation System
DSMB	Data Safety Monitoring Board
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MME	Milligram Morphine Equivalent
NCT	National Clinical Trial
NIH	National Institutes of Health
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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