

Pre-Analysis Plan for:

Emails to Nudge Safer and Better-Informed Prescribing of Risky Drugs

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Abstract: Drug overdose deaths have skyrocketed in recent years, and many overdoses continue to involve prescribed medications like opioids and stimulants. At the same time, state prescription drug monitoring programs (PDMPs), which help clinicians prescribe these medications safely, remain underused. In Minnesota, 32% of opioid prescriptions are written by clinicians who do not use the PDMP. In many states, including Minnesota, policymakers have limited tools to raise PDMP use even though its use often required under state law. To address this policy dilemma, we will test e-mails designed to encourage PDMP use and evaluate their effects on PDMP use and controlled substance prescribing. Our work will include a projected 7,126 physician and physician assistant prescribers of opioids and other controlled substances who lack active PDMP accounts, never query the PDMP, or query the PDMP infrequently relative to their prescribing volume. We will randomly assign these prescribers to be sent (1) emails focusing on the legal requirements to use the PDMP, (2) emails focusing on the clinical benefits of the PDMP or (3) no emails. Our work will generate evidence on low-cost approaches to encourage PDMP use and safer controlled substance prescribing.

1. Introduction

This document details an analysis plan for measuring the impact of emails sent to Minnesota physicians and physician assistants who are not following the state's requirements to engage with the state's prescription drug monitoring program (PDMP). At the time of writing, we have seen only the original pre-intervention search, account, and query data from the PDMP which was used to create a list of clinicians to deliver the intervention to. We may perform additional analyses in the course of the study in addition to those specified below; if analyses are not pre-specified in this document we will make note of that fact when sharing results.

1.1. *Intervention*

Clinicians are included in this study if they prescribe controlled substances but either lack a PDMP account or have an inactive account; prescribe opioids but do not search the PDMP at all; or prescribe opioids but search infrequently relative to their prescribing. Based on an analysis of 2023 PDMP data, we anticipate that 7,126 clinicians meet these criteria and will be enrolled in the study.

Clinicians will be randomized at 1:1:1 ratio to two treatment arms or an “as usual” control arm. One treatment arm will be sent e-mails highlighting the state's legal requirements for prescribers to use the PDMP. The other treatment arm will be sent emails highlighting the clinical benefits of having access to the PDMP, particularly before prescribing opioids. Both treatment arms are sent an initial email and a follow-up email one month later. Clinicians in the control arms will not be sent any emails from this experiment but, like clinicians in the treatment arms, may get other emails from the PDMP. The e-mails will be sent via the e-mail platform GovDelivery.

1.2. *Primary outcome overview*

The goal of this study is to understand whether e-mails to prescribers with low or no PDMP engagement can increase PDMP use and thereby encourage safer prescribing. This study's two **primary outcomes** measure PDMP engagement and rates of potentially guideline-discordant opioid prescribing. They are described later in the analysis plan. For hypothesis testing, we will use multiple testing adjustment to control the family-wise error rate to 5%.

1.3. Secondary outcome overview

Secondary outcomes will be measured both within 2-months of the initial email as well as at other intervals. We will also consider as secondary outcomes the components of our primary endpoints as well as our primary outcomes measured at other time intervals. These outcomes will be treated as exploratory and so we will not use multiple testing adjustments when reporting their p-values.

1.4. Data

The trial will use search, account, and prescribing data from the PDMP as well as e-mail data from GovDelivery.

2. Analysis Overview

2.1. Regressions

We begin by pooling the two intervention arms and estimating the regression model:

$$Y_i = \alpha + \beta \cdot EMAIL_i + \delta X_i + \gamma Z_i + \varepsilon_i, \quad (1)$$

where i indexes participants, Y_i is the outcome, $EMAIL_i$ is an indicator for being assigned to either interventional arm, X_i is a vector of controls, and Z_i is a vector of strata indicators. To raise statistical power, we will include in X_i the lagged (pre-e-mail) dependent variable and controls for specialization.

To distinguish between effects of each letter, we will also include indicators for each arm separately:

$$Y_i = \alpha + \beta_1 \cdot MANDATE_i + \beta_2 \cdot CLINICAL_i + \delta X_i + \gamma Z_i + \varepsilon_i. \quad (2)$$

2.2. Controls

The main controls we will use are lagged (pre-e-mail) dependent variables and fixed effects for provider specialization.

2.3. Strata

Using historical PDMP data, we estimate the relationship between baseline covariates and the primary prescribing outcome. When the actual list of clinicians in the trial is confirmed, we will use these estimates to predict each clinician's primary prescribing outcome and stratify on the predictions in blocks of three. This stratification method was employed successfully in our previous trial.

2.4. Duration

Our primary outcomes are measured during the 2-month period after the first e-mail is sent.

We will also measure outcomes at shorter and longer durations. Specifically, to look for evidence on the timing and persistence of impacts, we will consider outcomes by month for up to nine months after emails are sent.

3. Effects on PDMP Engagement

The PDMP engagement primary outcome is an indicator of PDMP engagement during the 2-month period after the first e-mail is sent. This will indicate whether the clinician's level of engagement rose, relative to the criteria for inclusion in the study. The outcome will be defined as follows:

- Account creation for clinicians enrolled because they lacked one
- Reactivating an account for clinicians enrolled because their account was inactive
- Any search for clinicians enrolled because they never searched
- Increased search rates for clinicians enrolled because they infrequently searched¹

3.1. Secondary outcomes related to engagement

Secondary outcomes related to PDMP engagement include the components of the primary endpoint measured separately (account creation, account reactivation, any search, and above-threshold search rate) as well as our primary outcome measured at alternative intervals, total search query volume, creation of delegate users,² and average characteristics of patients searched by clinicians, described below.

We construct the average characteristics of patients searched by the clinician to assess the targeting of PDMP searches. Average characteristics include prior prescription drug receipt and prior receipt of risky prescription medication interactions. We compare characteristics of the marginal patient searched due to the intervention compared to the infra-marginal patient (see Gruber et al., 1999).

4. Effects on Prescribing

The prescribing primary outcome is a composite measure of several guideline-discordant opioid prescribing behaviors is created to assess guideline-discordant prescribing within 2 months of email deployment. The components of this measure are:

- Opioid co-prescriptions with other opioids
- Co-prescriptions of opioids with benzodiazepines
- Co-prescriptions of opioids with gabapentinoids
- High daily opioid doses (morphine-equivalent daily dose >90)
- Long-duration opioid prescriptions (>7 days) to opioid-naive individuals

The components will each be standardized to have mean 0 and standard deviation 1. Then, the standardized components will be averaged together to create the composite primary endpoint.

4.1. Secondary outcomes related to prescribing endpoints

In addition to guideline-discordant opioid prescribing, we measure prescribing volume, including:

- Total days supplied of controlled substances
- Total days supplied of opioids
- Total days supplied of benzodiazepines
- Total days supplied of gabapentinoids
- Total days supplied of stimulants

¹ We define infrequent searching as a clinician whose search count is less than 1/3 their opioid fill count. Because clinicians can search before prescribing drugs other than opioids, this approach is, if anything, conservative.

² Delegate users are accounts that can check the PDMP on behalf of clinicians.

- Total opioid morphine milligram equivalents

We also include the components of our primary outcome measured separately as well as our primary outcome measured at alternative intervals.

5. Measuring Implementation

Measuring e-mail engagement assesses mechanisms driving PDMP engagement or guideline-discordant prescribing effects, or lack thereof. To understand the potential of our email communication, we will measure:

- Email open
- Click-through on e-mail links
- Email bounce

E-mail engagement is a secondary outcome and can be used to scale any effects to generate a “treatment on the treated” estimate.

6. Heterogeneous Effects

If emails are causing increased PDMP engagement or changes in prescribing endpoints, we will examine heterogeneity in effects across the following groups:

- Physicians (MD/DO) vs. physician assistants
- No active PDMP account at baseline vs. active PDMP account at baseline

7. References

Gruber, J., Levine, P., Staiger, D., 1999. Abortion Legalization and Child Living Circumstances: Who is the “Marginal Child”? *Q. J. Econ.* 114, 263–291. <https://doi.org/10.1162/003355399556007>

8. Appendix

8.1. Poisson Regression Specification

We may consider Poisson regressions because we are interested in percent changes in outcomes due to the emails. The Poisson regression will let us produce these statistics even if the outcome is sometimes zero.

The regressions will assume that the physician-level outcome takes the form:

$$y_i = \exp(\alpha + \beta * TREAT_i + \delta X_i + \gamma Z_i) + e_i$$

The coefficient of interest in the Poisson regressions is β . This coefficient can be interpreted as the percent change in y due to the email, analogous to an OLS regression with $\ln(y)$ on the left-hand side.