Analysis Plan

Project Name: Reducing Concurrent Opioid-Benzodiazepine Prescriptions through Provider Messaging

Project Code: 1725

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This document serves as a basis for distinguishing between planned (confirmatory) analysis and any unplanned (exploratory) analysis that might be conducted on project data. This is crucial to ensuring that results of statistical tests will be properly interpreted and reported. In order that the Analysis Plan fulfill this purpose, it is essential that it be finalized and date-stamped before we begin looking at the data — ideally, before we take possession of the data. Once this plan is finalized, a date is entered above, and the document is posted publicly on our team website.

Project Description

The purpose of this effort is to use low-cost informative e-mails to improve the process of prescribing of opioids and benzodiazepines within the National Capital Region/Military Health System (NCR/MHS), with the aim of decreasing concurrent opioid and benzodiazepine prescribing. Both the VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain (2017) and the CDC Guideline for Prescribing Opioids for Chronic Pain (2016) strongly recommend against the concurrent use of opioids and benzodiazepines. Taken together, these drugs could cause respiratory depression, enhanced sedation, and death. The intervention population will be prescribers and primary care managers associated with patients who have recently received concurrent prescriptions of opioids and benzodiazepines. Using a randomized approach, we will allocate the NCR/MHS providers associated with patients with concurrent prescriptions for opioids and benzodiazepines to one of two conditions:

1. E-mail alert — A messaging approach, in which we will send encrypted emails to the patient's opioid and benzodiazepine prescriber(s) and primary care manager that identify the concurrent prescriptions and detail the patient's prescription history, inform them of the VA/DoD guideline and risk to patient, and provide action steps and relevant resources. When multiple providers are involved, the email message will also encourage coordination across providers and provide relevant contact information

2. As-Usual — An as-usual approach, in which providers are not sent messages. These providers can access patient information through the MHS Opioid Registry as before.

Data and Data Structure

This section describes variables that will be analyzed, as well as changes that will be made to the raw data with respect to data structure and variables.

Raw Data

Description	Summary of Data Fields	Purpose
Enrollment tracker data (study enrollment table derived from Carepoint registry) *Source: tracker and detail tables*	Patient ID Provider ID Treatment arm Stratum Enrollment date	Denominator of study population Treatment assignment
Population summary data (general information about the patients – one record for each patient in the study) *Source: M2 (ACG, DEERS tables), saved registry data*	Patient ID Demographic information (age, race, sex) Risk score Historical utilization and diagnoses Historical enrollment DMIS Historical MHS coverage Date of death	Baseline patient characteristics
Prescription fill data (prescription drug fills associated with the patient population) *Source: M2 (PDTS table), ESSENCE*	Patient ID Date of service Prescriber ID NDC code Days supply and quantity dispensed Patient and total dollars paid	Prescribing outcomes
Professional provider encounter data (professional encounters for the patient population) *Source: M2 (CAPER, TED_NI tables)*	Patient ID Date of service Provider ID Place of service Type of service Diagnosis codes CPT codes Patient and total dollars paid	Professional provider utilization outcomes
Referral data (patient referrals to other providers) *Source: M2 (Referral table)*	Patient ID Referral date Referring provider ID Type of service referred Link to appointment/encounter record	Referral outcomes
Inpatient/ED provider encounter data (facility encounters for the patient population) *Source: M2 (CAPER, TED_NI, SIDR, TED_I tables)*	Patient ID Date of service Provider ID Provider type Diagnosis codes Procedure codes Patient and total dollars paid	Hospital utilization outcomes

Outcome Variables to Be Analyzed:

Primary Outcome

The primary outcome will consist of three component outcomes:

1. Opioid days
2. Benzodiazepine days

3. Days with overlapping opioids and benzodiazepines

Each component outcome will be measured at 90 days from the date the patient was enrolled. As we will describe later, the primary outcome will be adjusted for multiple testing.

<u>Secondary Outcomes</u>

We will also analyze a host of secondary outcomes. These outcomes fit into eight classes:

1. Robustness of primary outcomes to alternative definitions
   - Measuring each component at 30 days duration rather than 90 days
   - Measuring each component at 180 days duration rather than 90 days
   - Opioid MME (morphine milligram equivalent)
   - Benzodiazepine DME (diazepam milligram equivalent)
   - Opioid fills (rather than days supply of the fills)
   - Benzodiazepine fills (rather than days supply of the fills)
   - Indicator for having any opioid fill
   - Indicator for having any benzodiazepine fill
   - Opioid cost ($)
   - Benzodiazepine cost ($)
2. Prescribing of risk mitigation and use disorder treatment medications
   - Naloxone fills
   - Use disorder treatment medication (methadone, buprenorphine, XR naltrexone) days
3. Prescribing of alternative psychoactive medications
   - Non-BZD sleep aid days
   - Gabapentinoid days
   - Muscle relaxant days
   - Antipsychotic days
4. Prescribing of non-opioid pain relievers
   - NSAID days
5. Adverse changes in prescribing
   - Rapid opioid taper
   - Rapid benzodiazepine taper
6. Office visits with physicians, nurse practitioners, and physician assistants
   - Visits with the patient's prescriber(s) and/or PCM (as identified upon QI enrollment)
   - Visits with all physicians, nurse practitioners, and physician assistants
7. Use of pain management, mental, and behavioral health services
   - Visits with pain management physicians
   - Visits to pain management specialists or clinics (including physicians)
   - Visits with psychiatrists
   - Visits to mental or behavioral health specialists or clinics (including psychiatrists)
8. Referrals to pain management, mental, and behavioral health services

- Referrals to pain management specialists or clinics (including physicians)
- Referrals to mental or behavioral health specialists or clinics (including psychiatrists)
9. Use of the hospital (inpatient and emergency department)
   - Visits to the hospital
   - Visits for mental health reasons
   - Visits for overdoses
   - Visits for use disorders

All prescribing and utilization outcomes will be created by transformations from the raw data described previously. All measurements are at 90 days duration unless otherwise stated.

Transformations of Variables:

Prescribing outcomes

The primary outcomes will come from raw, prescription drug fill level data with dates of service during the outcome period. We will identify opioid and benzodiazepine drug fills by matching the National Drug Code (NDC) on the fill to the CDC directory of select controlled substances (https://www.cdc.gov/drugoverdose/resources/data.html).

To construct overlapping days, we will assume that each drug is active starting from its date of service and ending 'days supply'-1 days later. Then, we will calculate the number of days during which an opioid and a benzodiazepine were both active for the patient (Gellad et al. 2017, Sun et al. 2017).

Outcomes that state they will measure "days" will measure the "days supply" on prescription fills with dates of service during the outcome period. Outcomes that count fills will count the number of prescription drug fill records.

Outcomes using MME or DME will use equivalency tables to convert opioids and benzodiazepines of different strengths into common units: morphine equivalents for opioids and diazepam equivalents for benzodiazepines. The CDC data includes an equivalency table for opioids. Following other research on benzodiazepines, we will construct our own equivalency table for these drugs by referencing tables published in psychiatry, substance use, and addiction medicine textbooks . For each prescription drug fill, we will multiply its number of units (i.e. number of pills) by its strength per unit (available in the CDC data) and then by its MME/DME conversion factor to yield its MME/DME. Then we will sum the MME of all opioid fills to yield a total MME and we will sum the DME of the benzodiazepine fills to yield a total MDE.

Rapid opioid and benzodiazepine tapers will be defined based on clinical practice guidelines and recent literature.

Utilization outcomes

Other utilization outcomes involve counting physician / nurse practitioner / physician assistant, clinic, inpatient, and ED visits or referrals. These outcomes will be constructed by processing raw encounter-level or referral-level data. Because single encounters may generate multiple claims or records in the data, the records will be aggregated to the patient-provider-day level before counting the number of visits. That is, multiple records for the same patient and provider in one day will not be counted as more than one visit.

Imported Variables:

We will import data on pharmaceuticals from the CDC file: drug class, strength per unit, and MME conversion factor. We will construct our own table of MDE conversion factors. When processing other pharmaceuticals not included in the CDC file, we will use data from IBM Micromedex RED BOOK.

Transformations of Data Structure:

The prescribing data will initially be at the fill level, i.e. each record will represent one dispense of a particular drug by a pharmacy to a patient. We will transform the data by collapsing it to the patient level, aggregating the dispensing events together to produce the three primary outcomes. We will then join the collapsed prescribing file with the enrollment file.

We will perform analogous transformations of the prescribing, encounter, and referral data to construct the secondary outcomes.

Data Exclusion:

We do not anticipate making any data exclusions.

Treatment of Missing Data:

Because we will use 100% administrative data, we do not anticipate any missing data. Prescribing outcomes will consider prescriptions filled through the Military Health System (MHS). Study participants who exit the MHS will be analyzed with the data available on their health care encounters in the MHS.

Statistical Models & Hypothesis Tests

This section describes the statistical models and hypothesis tests that will make up the analysis — including any follow-ups on effects in the main statistical model and any exploratory analyses that can be anticipated prior to analysis.

Statistical Models:

We will estimate the following two linear regressions:

$$y_i = \alpha + \beta^y_{raw} * treat_i + Z_i\Theta + \varepsilon_i$$

$$y_i = \alpha + \beta^y_{adj} * treat_i + Z_i\Theta + X_i\Gamma + \varepsilon_i$$

Where i indexes patients; y_i is the outcome (e.g. overlapping days, MME, MDE, etc.); $treat_i$ is an indicator for for assignment to the treatment arm; Z_i are indicators for strata, and X_i are additional pre-specified control variables.

The former regression will yield "raw" or unadjusted estimates of the effect of the intervention. The latter regression will add control variables to raise statistical power and will produce adjusted estimates. All hypothesis tests for the primary outcomes will be based on the adjusted estimates.

The pre-specified control variables are:

- Lagged outcome i.e. the regression outcome defined over the time period immediately prior to study enrollment rather than after
- Lagged primary outcome components (opioid days, benzodiazepine days, and days with overlapping opioids and benzodiazepines) i.e. the vector of the three components defined over the 90 day period immediately prior to study enrollment rather than after
- Two-way interactions between the aforementioned variables

Hypothesis Tests

To maximize statistical power, we will assess the primary outcome using one-sided tests to establish whether the treatment is superior to the control. We will report the p-value of the following joint test of the three primary outcome components:

$$H_0 : \beta^{opioids}_{adj} = \beta^{BZDs}_{adj} = \beta^{overlap}_{adj} = 0$$
$$H_a : \beta^{opioids}_{adj} < 0 \text{ or } \beta^{BZDs}_{adj} < 0 \text{ or } \beta^{overlap}_{adj} < 0$$

In addition, to provide evidence on which endpoint, if any, was affected by the intervention, we will report for each: the point estimate, the p-value adjusted for multiple testing, and the p-value without adjustment for multiple testing.

Secondary outcomes will be assessed using two-sided tests:

$$H_0 : \beta^y_{adj} = 0$$
$$H_a : \beta^y_{adj} \neq 0$$

Inference Criteria, Including Any Adjustments for Multiple Comparisons:

For inference, we will report design-based standard errors for all estimates of treatment effects. All joint tests will use the design-based variance matrix estimates. In this context, "design-based" refers to the standard errors that would describe how our treatment effect estimates would vary

across multiple assignments of treatment following our design to the given experimental pool (i.e. HC2 standard errors).

For the primary outcome and primary outcome components, one-sided hypothesis tests with $P<0.05$ will be considered statistically significant. Multiple testing-adjusted p-values will be computed with the Westfall-Young algorithm.

The secondary endpoints will be assessed with two-sided hypothesis tests; $P<0.05$ will be considered statistically significant. These endpoints will be treated as exploratory and thus will not be adjusted for multiple testing.

Exploratory Analysis:

We expect to conduct a quasi-experimental analysis to look for spillovers on prescribing for patients outside the quality improvement intervention. This analysis will compare areas and/or prescribers in the quality improvement intervention to areas and/or prescribers that were not in the intervention.

References:

Gellad WF, Zhao X, Thorpe CT, et al. Overlapping buprenorphine, opioid, and benzodiazepine prescriptions among Veterans dually enrolled in VA and Medicare Part D. *Substance abuse.* 2017;38(1):22-25. doi:10.1080/08897077.2016.1267071.

Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *The BMJ.* 2017;356:j760. doi:10.1136/bmj.j760.