PROVIDENT

The Preventing Overdose Using Information and Data From the Environment (PROVIDENT) Study

STATISTICAL ANALYSIS PLAN

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Official Study Title:

Reducing Drug-Related Mortality Using Predictive Analytics: A Randomized, Statewide, Community Intervention Trial

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PROVIDENT Data and Safety Monitoring Plan

Study Title: Reducing Overdose Mortality Using Predictive Analytics: A Randomized, Statewide, Community Intervention Trial

A. Summary of the Protocol

Study Design

This randomized, community-level intervention trial aims to develop a predictive analytics model that forecasts future overdose mortality. This tool, called **PROVIDENT (Preventing Overdose using Information and Data from the Environment)**, will be used to identify neighborhoods at high risk of future overdose outbreaks. The study will use a randomized design to inform a community-level overdose prevention approach in neighborhoods at high risk of overdose outbreaks.

This study will be conducted in two phases. In phase I (Specific Aim 1), we will develop a predictive analytics model to forecast future overdose mortality at the neighborhood level, defined as census block groups. There are 809 populated census block groups in Rhode Island, grouped in 39 cities/towns. We will use a spatiotemporal machine learning approach, in which the outputs of multiple classification and spatial-temporal machine learning prediction models are combined based on minimizing cross-validated risk.

In phase II (Specific Aim 2), we will conduct a randomized, statewide, policy intervention trial to evaluate whether prioritizing interventions to neighborhoods identified by the PROVIDENT model as being at highest risk of overdoses is more effective at reducing city-level overdose burden than a non-prioritized intervention approach. The primary outcome of the PROVIDENT trial will be city/town-level fatal and non-fatal overdose rates, measured from six months after the interventions have been implemented. Therefore, the trial will be randomized at the level of the city/town, rather than at the level of the individual.

Primary and Secondary Outcome Measures

We will evaluate, at the city/town level, whether prioritized intervention deployment to neighborhoods at high risk of future overdose reduces population-level overdose morbidity and mortality. The primary outcome of the trial will be the cumulative incidence of fatal and non-fatal overdose at the city/town level during the study period. While the PROVIDENT model only forecasts future overdose deaths, we will include a composite measure of municipal-level fatal and non-fatal overdose events as the primary end-point in the trial to ensure adequate power. We will compare fatal and non-fatal overdose rates in the treatment and control municipalities, allowing for a 6-month ramp-up period to allow time for the targeted interventions to be implemented.

Fatal overdoses will be defined as drug-related deaths deemed unintentional by the state medical examiner. Specifically, we will include all deaths that: (1) occur in a Rhode Island municipality; (2) the final manner of death was deemed an accident; and (3) a drug is listed on the death certificate as the primary cause of death or a significant contributing factor. The state-wide nature of Rhode Island's centralized medical examiner system means that all accidental deaths are investigated in a similar and consistent manner (including robust toxicological analyses, death scene investigation, and autopsy by a medical professional); all deaths are certified by the chief medical examiner, resulting in a highly reliable reporting system.

Non-fatal overdoses will be defined as emergency medical services (EMS) runs for suspected non-fatal opioid overdoses identified and classified using the Rhode Island Department of Health-modified Council of State and Territorial Epidemiologists (CSTE) case definition. These data are captured in the Rhode Island Emergency Medical Services Information System (RI-EMSIS) and validated by the Rhode Island Department of Health (RIDOH). The 2022 CSTE guidance identifies suspected nonfatal opioid overdoses when an EMS run meets any of 4 criteria: (1) the provider's primary impression or provider's secondary impression is opioid overdose-related, OR (2) the primary symptom or other associated symptoms is opioid overdose-related, OR (3) medication administered is naloxone and response to medication administered is improved, OR (4) the

patient care report narrative contains (a) at least 1 opioid-related keyword and (b) at least 2 overdose-related keywords. Based on this new standard guidance, in 2023, RIDOH updated its existing criteria for suspected nonfatal opioid overdose-related EMS case definition to align with CSTE guidance. The RIDOH-modified CSTE case definition uses five criteria to classify a nonfatal opioid overdose-related EMS run, where EMS records are flagged if any of the following criteria were met: (1) Primary/secondary impressions of the patient are opioid-related, and Narcan was given, OR (2) Primary/secondary impressions of the patient are opioid-related and mention Narcan or unresponsive term in the narrative report, OR (3) Narcan was given, and patient condition improved, OR (4) Mention of Narcan and at least two overdose-related keywords in the narrative report, OR (5) Narcan was given to the patient prior to EMS arrival. This RIDOH-modified CSTE case definition has been validated against the RIDOH original definition and CSTE-guided definition, and the modified case definition had a positive predictive value of 91.5% in identifying nonfatal opioid overdose-related EMS incidents (Enhanced Emergency Medical Services Case Definition to Identify Suspected Nonfatal Opioid Overdose–Related Incidents in Rhode Island). *Data from 2016 to the present have been updated by RIDOH with the new case definition, ensuring consistency, fidelity, and reliability of this case definition for the primary outcome measure.*

In exploratory analyses, we will examine the effect of the intervention on overdose fatalities and non-fatal overdoses separately to determine whether the intervention produced similar changes in rates of each outcome, and/or produced shifts in the distribution of fatal and non-fatal events without affecting the overall incidence rate. We will also examine the effect of the intervention on overdose fatalities and non-fatal overdoses separately and as a composite using the location of residence of the individual who overdosed rather than the incident location.

Study Sample

This trial will not enroll individual participants. Randomization and assessment of study outcomes will occur at the municipal level, and all study outcomes will be assessed at this same level. However, during the study period, all persons who reside in Rhode Island or who experience a qualifying event—defined as a fatal or non-fatal overdose captured by the state's multicomponent overdose surveillance system—may contribute data to either the PROVIDENT model or the study outcomes.

Based on 2016 data, we expect to observe approximately 1,800 events of fatal or non-fatal overdoses per year (see Table S1 below), which will be analyzed to evaluate the effects of the community-level intervention. Since all 39 cities/towns in Rhode Island will participate in the intervention trial, and due to the population-based nature of the fatal and non-fatal overdose surveillance system, every Rhode Island city and town may be eligible for inclusion in this study.

Inclusion/Exclusion Criteria

There are no exclusion criteria related to this study. The demographic breakdown of the participants representing these outcome events will most likely be similar to that of the available underlying epidemiology of the overdose epidemic in Rhode Island from 2014-2016 data, with approximately 72% male and 80% white.

Target population distribution (e.g., women, minorities, etc.)

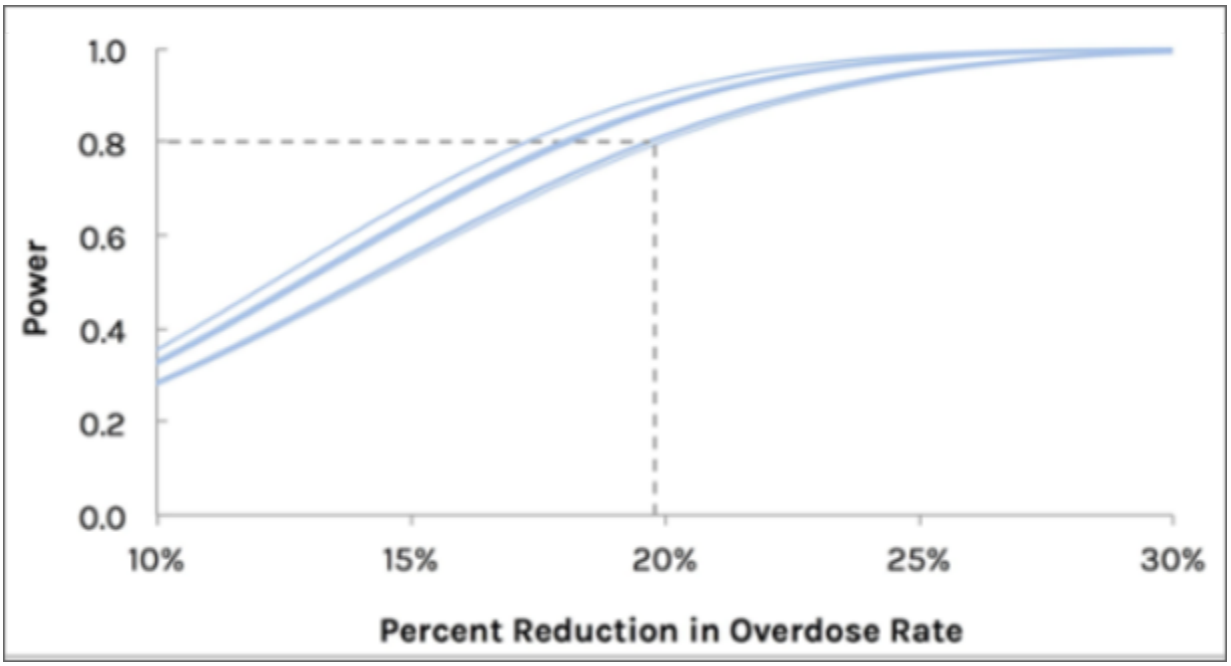
The target population for this project will be all persons residing in the State of Rhode Island. We anticipate the actual enrollment distribution for qualifying data events will be similar to the underlying epidemiological trends for overdose observed in the state. Currently, fatal and nonfatal overdose events affect all cities and towns across Rhode Island (see Table S1). We expect the demographic breakdown of the participants representing the overdose-related events will be similar to that of the available underlying epidemiology of the overdose epidemic in Rhode Island from 2014-2016 data, with approximately 72% male and 80% white.

Power Calculation and Sample Size

To ensure adequate power, we will consider as the primary endpoint both fatal and non-fatal overdoses occurring at the municipal level. These events will be defined as described in the Primary and Secondary

Outcomes Measures above. These data are captured in the Rhode Island Office of the State Medical Examiner's drug overdose death records database and the Rhode Island Emergency Medical Services Information System. To estimate the power to detect significant differences between overdose rates in treatment and control cities/towns, we examined 2016 municipal-level overdose data. We used a stratified randomization scheme to conduct power simulations. Power was calculated for relative reductions in combined fatal/nonfatal overdose rates ranging from 15 to 30 percent. We used data from 2016 to set the underlying statewide overdose rate. We simulated randomization of each city to treatment versus control, estimated the expected number of events for each city based on population size and treatment assignment, and then used standard calculations for two-sample comparisons of Poisson rates. Due to the finite sample of municipalities with widely varying population sizes, the person-time of exposure in the control and treatment groups will vary depending on how cities are randomized. We therefore calculated power for several simulated randomizations, with 10 randomly selected instances shown (Figure S1). As shown, we will have at least 95% power to detect a >25% reduction in the treatment arm compared to cities/towns assigned to the control arm. These estimates are conservative: we assumed only one year of post-intervention follow-up time, whereas we anticipate two years based on the project timeline.

Figure S1: Power curves for the PROVIDENT trial from simulated randomizations (ten randomly selected instances are shown).



Expected enrollment distribution for cities/towns in Rhode Island (Table S1)

Table S1: The target population for this grant will be secondary data events from overdose surveillance records in the State of Rhode Island, randomized at the level of the city/town (2016).

City/Town	Population	Non-Fatal ODs	All fatal ODs	Annual OD Rate (per 100,000)	Urbanicity	Strata
Barrington	16310	9	1	61.31	Non-Urban	Non-Urban-Low
Bristol	22954	15	3	78.42	Non-Urban	Non-Urban-Low
Burrillville	15955	6	1	43.87	Non-Urban	Non-Urban-Low
Central Falls	19376	26	5	159.99	Urban	Urban-Low
Charlestown	7827	12	2	178.87	Non-Urban	Non-Urban-High
Coventry	35014	35	6	117.10	Non-Urban	Non-Urban-High
Cranston	80387	141	16	195.31	Urban	Urban-High
Cumberland	33506	8	10	53.72	Non-Urban	Non-Urban-Low
East Greenwich	13146	7	1	60.86	Non-Urban	Non-Urban-Low
East Providence	47037	51	8	125.43	Urban	Urban-Low
Exeter	6425	7	0	108.95	Non-Urban	Non-Urban-High
Foster	4606	2	1	65.13	Non-Urban	Non-Urban-Low
Glocester	9746	0	2	20.52	Non-Urban	Non-Urban-Low
Hopkinton	8188	17	2	232.05	Non-Urban	Non-Urban-High
Jamestown	5405	1	0	18.50	Non-Urban	Non-Urban-Low
Johnston	28769	42	14	194.65	Non-Urban	Non-Urban-High
Lincoln	21105	17	1	85.29	Non-Urban	Non-Urban-High
Little Compton	3492	1	1	57.27	Non-Urban	Non-Urban-Low
Middletown	16150	10	3	80.50	Non-Urban	Non-Urban-High
Narragansett	15868	11	3	88.23	Non-Urban	Non-Urban-High
New Shoreham	1051	0	2	190.30	Non-Urban	Non-Urban-High
Newport	24672	29	3	129.70	Urban	Urban-Low
North Kingstown	26486	15	7	83.06	Non-Urban	Non-Urban-High
North Providence	32078	39	13	162.10	Urban	Urban-Low
North Smithfield	11967	2	1	25.07	Non-Urban	Non-Urban-Low
Pawtucket	71148	129	29	222.07	Urban	Urban-High
Portsmouth	17389	12	7	109.26	Non-Urban	Non-Urban-High
Providence	178042	449	92	303.86	Urban	Urban-High
Richmond	7708	4	2	77.84	Non-Urban	Non-Urban-Low
Scituate	10329	4	5	87.13	Non-Urban	Non-Urban-High
Smithfield	21430	3	4	32.66	Non-Urban	Non-Urban-Low
South Kingstown	30639	17	2	62.01	Non-Urban	Non-Urban-Low
Tiverton	15780	3	2	31.69	Non-Urban	Non-Urban-Low
Warren	10611	13	2	141.36	Non-Urban	Non-Urban-High
Warwick	82672	132	25	189.91	Urban	Urban-High
West Greenwich	6135	4	1	81.50	Non-Urban	Non-Urban-High
West Warwick	29191	57	11	232.95	Urban	Urban-High
Westerly	22787	46	6	228.20	Non-Urban	Non-Urban-High
Woonsocket	41186	40	29	167.53	Urban	Urban-High
Total	1052567	1,461	336			

B. Analysis and Data Management

Analysis:

The analysis plan will be finalized and uploaded to the Open Science Framework (osf.io) before the start of the data analysis in accordance with the pre-specified analysis plan. We will employ standard methods for community intervention trials. The intervention effect will be quantified as a composite fatal and non-fatal overdose incidence rate ratio. We will have at least 5 years of data (from 2016 to 2020) to serve as the pre-intervention period. The trial formally began in November, 2021. We will exclude a six-month 'ramp up' period in all analyses to allow time for the targeted interventions to be deployed. We will have approximately two years of post-intervention data from May 15, 2022, to August 15, 2024.

We will use generalized linear mixed-effect modeling with Poisson or negative binomial link functions to estimate incidence rate ratios comparing overdose rates in treatment cities/towns to control cities/towns. Each municipality will have its own random intercept and slope to account for pre-intervention differences and time trends. Municipal population size will be incorporated as an offset, and 95% confidence intervals will be calculated using standard bootstrapping techniques to account for possible overdispersion of the data and the relatively small number of geographic units per arm. Although we will use stratified randomization to reduce pre-intervention differences in the treatment and control groups, potential biases from the imbalance can be corrected by including other covariates in the model. For example, measures of municipal-level racial/ethnic composition (e.g., percentage Hispanic/ Latino) will be included as covariates, given some evidence of imbalance in these variables between the two arms. Next, we will construct time-lagged regression models to consider the delayed impact of the interventions by staggering outcomes by zero to 6 months.

To account for Providence's significant contribution to nonfatal overdose events between 2016 and 2024, we will conduct several detailed analyses to assess the impact of the Providence Police Department protocol change (effective June 2023), which directed all overdose-related 911 calls in Providence to EMS. First, we will assess trends in EMS runs for suspected nonfatal opioid overdoses in Providence compared to other municipalities before and after the policy change. We will estimate the time-dependent effects of the protocol change on EMS runs for suspected nonfatal opioid overdose. To evaluate its impact on the trial's primary outcome, we will conduct sensitivity analyses by excluding Providence in one arm and a comparable municipality in the other.

Data acquisition and transmission:

Stronghold computing environment: The very nature of sensitive data requires a highly-protected data silo for it to be housed in. To achieve this objective, the Brown University School of Public Health (BUSPH) will purchase a central storage service hosted by Brown University's Computing & Information Services (CIS) Stronghold secure research computing environment. Stronghold is a HIPAA-compliant, secure computing environment developed for housing, sharing, and analyzing sensitive data. The Data Manager will oversee the database architecture, dataset storage, and all input/output (i.e., data transfer) regulations. Stronghold is a highly secure computer and storage Windows environment for research needs involving sensitive data needing special handling, data usage agreements, etc.

The PI is responsible for maintaining an up-to-date list of accounts that should be able to log into Stronghold, communicating this to the Stronghold Team through the Administrative Contact, and alerting the contact when a user should no longer be allowed access. Users that leave the university will have access terminated along with their Brown account, per CIS Policies: Computing Privileges: Access to Electronic Services.

All users must:

- Complete appropriate training for working with sensitive data (e.g., CITI training);
- Be in compliance with all relevant Institutional Review Board protocols;
- Be in compliance with any data use agreements or other agreements governing the use of the data stored on Stronghold.

Data Transfers – There are select methods to import data, including but not limited to:

- Select State offices use a VPN tunnel
- Encrypted USB drives
- Secure transfer through firewall exception
- Import and export servers

Termination of Service

Requests for termination of services should be made to the Administrative Contact. Services will be terminated by the next business day following the request. All data stored on Stronghold that is associated with the terminated account will be deleted upon termination of services.

Denial of Access

If a user fails to comply with the policies and procedures for accessing and using Stronghold, or in the case of a suspected or real security breach, CIS staff can temporarily deny access to Stronghold for the user and suspend all retrieval of information until approval is received from a designated authority.

Data Entry Methods

The project's Database Administrator will manage the database architecture, dataset storage, and all input/output (i.e., data transfer) regulations. The Research Assistant will conduct and automate secure data transfers with data-sharing partners across the state monthly, quarterly, or annually (depending on the Data Use Agreement with each data-sharing partner).

Data Analysis Plan

The quality of the data will be monitored semi-annually. The study's Data Analyst will analyze the data using SAS, R, ArcGIS, and Tableau software within the Stronghold computing environment.

C. Quality Assurance Plan

Database Management

The Data Manager and Stronghold staff will manage the database architecture, dataset storage, and all input/output (i.e., data transfer) regulations. The database will be maintained under several firewalls, with restricted access to the Internet, except for data imports and software installations. Control systems will be implemented to prevent data migration without authorization, complete with real-time notifications of breaches. Additionally, records pulled by approved BUSPH researchers will go through an automated de-identification process to ensure sensitive data cannot be unauthorizedly extracted from the secure server. The data will routinely undergo backup procedures to ensure that the data is recoverable in the event of system failure.

Data Quality and Data Protocol Monitoring

Periodic scanning of Stronghold servers will be done to identify potential security vulnerabilities. The Stronghold Team will attempt to make this service available as requested 24 x 7 x 365 at all times outside the planned maintenance window.

The Stronghold Team monitors and records all activity on the Stronghold system, including networking and access events, which may depend on the classification of the data and any applicable regulations. Project staff receive notification of any activity on the Stronghold system.

Protocol Deviations and Noncompliance Reporting

Protocol deviations and noncompliance reporting will be the responsibility of the Project Investigator and Project Director. Such issues will be monitored consistently, and if any deviations are found, they will be reported promptly to the Brown IRB.

D. Regulatory Issues

Reporting of Unanticipated Problems

The overall data and safety monitoring will be the responsibility of the co-Principal Investigator (PI), Dr. Brandon DL Marshall, PhD. The co-PI is also responsible for executing the Data and Safety Monitoring (DSM) plan and complying with the reporting requirements. The PI will summarize the DSM report to the National Institute on Drug Abuse (NIDA) annually as part of the progress report.

The PI will ensure that all study procedures are in place before initiating the protocol and that all study procedures and reporting of unanticipated problems are performed according to the protocol. Unanticipated events will be monitored by the investigative teams (at BUSPH and at the Rhode Island Department of Health). In addition, a Data Safety Monitoring Board (DSMB) will provide independent study monitoring, as described below.

The PI will monitor for unanticipated events that change the study risk level. If an unanticipated event occurs that changes the study risk level, the Study PI will immediately report this event to the IRB (Brown University), DSMB, and NIDA and will oversee the process of modifying the study as appropriate to address the change in risk. The PI will also provide annual reports summarizing unanticipated event data to the IRB.

Report of Changes or Amendments to the Protocol

All changes or amendments to the protocol will be submitted in writing and will receive prior approval from the Brown University IRB.

E. Trial Stopping Rules

The entire trial will stop if any investigator or a member of the DSMB judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, or good clinical practice. Once a concern of this proportion is raised, the decision to stop the trial will be made through immediate consultation with the IRB, the DSMB, and NIDA.

The trial may be stopped for the following reasons:

1. The occurrence of unanticipated events involving a loss of confidentiality or privacy (e.g., unintended or unauthorized access to the web tool housing model predictions or row-level data used as inputs for the predictive model).
2. The occurrence of unanticipated events involving a disruption to harm reduction service provision as a result of the study (e.g., diversion of resources away from cities/towns randomized to the control arm that would not have otherwise occurred if the study had not been taking place).
3. It becomes clear that successful completion of the study is not feasible due to logistical or administrative reasons (e.g., changes in leadership at the Rhode Island Department of Health, significant changes to the financial resources available to fund harm reduction service provision).
4. If factors external to the study fundamentally change the study's equipoise.
5. If the occurrence of an unanticipated event involves inappropriate access by criminal justice to the PROVIDENT model predictions or any information related to the trial that would not otherwise be granted.

Disclosure of any Conflict of Interest

All data-sharing partners and investigators will agree to specific terms of use for the data according to a signed Data Use Agreement, which includes a request to disclose any potential conflicts of interest.

Data Safety

This project will use Brown University's Stronghold secure computing environment. As described above, this computing environment is HIPAA compliant and has been developed for housing, sharing, and analyzing

sensitive data. Stronghold is customized to the security needs of each project's Data Use Agreements.

F. Trial Safety

Classification of Unanticipated Problems:

While the PROVIDENT trial does not involve direct interaction with individuals receiving harm reduction services, it does change the environment in which these services are provided. As such, changes in risk pertain to the overall safety of these environmental changes to ensure the safety of the individuals receiving these harm reduction services. Unanticipated problems associated with the PROVIDENT trial may be classified as one of the following categories:

1. Loss of Confidentiality

The intervention will use a web tool and interactive dashboard to visualize the neighborhood-level risk predictions from the PROVIDENT model. The PROVIDENT Web Tool has undergone a security review with Brown Computing and Information Services (CIS) and the Center for Computation and Visualization (CCV). Use of the Web Tool has been approved, and our team has worked carefully to ensure the protection of the model predictions.

We recognize that a loss of confidentiality through unauthorized access to the PROVIDENT Web Tool and model predictions may also result in psychological harm to individuals or in social harm. As such, the Center for Computation and Visualization personnel will be responsible for the system administration. Research staff will have logins to manage data and download data. Individuals accessing the web application will have access to only the required information and share only what is required. Additionally, only select analytic team members will have access to identifiable datasets. All data transfer procedures, analytic plans, and datasets will be approved by the Brown IRB, any additional institutional IRBs, and the DSMB.

PROVIDENT Web Tool Infrastructure: The web application is hosted in Firebase, and application data is stored in Firestore. The application is intended to be used exclusively by organizations' personnel (e.g., non-profits helping with opioid overdose prevention). Once an individual has been approved, they may create a username and password. Authentication is managed using Firebase native authentication.

Logged-in individuals interact with a series of surveys approved by Brown IRB that collect information about services and programs for opioid overdose prevention available in corresponding neighborhoods. Approved organizations will also have access to the PROVIDENT model predictions through the use of the web application. Approved Brown researchers will use the data collected to examine what and how many directed overdose prevention activities are driven in part by the PROVIDENT model to measure fidelity and penetration. Finally, using the surveys, we will regularly query organizations that are approved to use the Web Tool about unauthorized use in community settings (e.g., inadvertent sharing of PROVIDENT screenshots during a community meeting).

Data will be downloaded from Firebase to Brown University data servers through provided, secure APIs (including web). Firebase and Firestore encrypt data during transfer and at rest. Firebase is certified under major security and privacy standards. Privacy and security information in Firebase can be found here. Data protection is managed through security rules, which in this particular case are set to only allow write access to users that have passed the simple authentication mechanism.

Center for Computation and Visualization personnel will be responsible for system administration. People, Place, and Health Collective researchers will have logins to manage and download data.

2. Loss of Privacy

This project uses secondary data exclusively; therefore, the confidentiality of study data is paramount. Our research requires the use of existing surveillance records related to overdose, medical events, and prescribing

events. Access to such records for legitimate research purposes has been approved by our data-sharing partners (including the Rhode Island Department of Health and the Rhode Island Department of Corrections), and our team has worked carefully to ensure the protection of these data.

We recognize that a loss of privacy may also result in psychological harm to individuals or social harm. As such, the Project Investigator will use Brown's state-of-the-art Stronghold computing environment to transfer, analyze, and protect all research data. Data-sharing partners will share only the required datasets and variables. Additionally, only select analytic team members will have access to identifiable datasets. All data transfer procedures, analytic plans, and datasets will be approved by the Brown IRB, any additional institutional IRBs, and the DSMB.

Research Database Infrastructure: This project will benefit from and expand upon data security resources provided by the Brown University "Stronghold" computing system. Stronghold is a secure computing and storage environment that enables Brown researchers to analyze sensitive data while complying with regulatory or contractual requirements. Stronghold is currently self-certified to meet the security requirements and controls for HIPAA (Health Insurance Portability and Accountability Act) and is undergoing the certification process for FISMA (Federal Information Security Management Act) and CJIS (Criminal Justice Information Security). We will use the Stronghold secure computing environment to store, maintain, and transfer data between Brown University and data stakeholders, including RIDOH and other state agencies (e.g., Office of the State Medical Examiners, the Rhode Island Department of Corrections).

Stronghold is a secure virtual computing environment designed for remotely analyzing sensitive data. It uses encrypted SSH (Secure Shell) with two-factor authentication for remote access. Access to each virtual network is limited to a single PI and any additional students or staff the PI authorizes in writing to Brown University Computing & Information Services (CIS). The PI enters into a written agreement with CIS that authorized users must comply with all necessary training requirements. CIS staff with access to Stronghold have completed CITI course modules for working with human subjects data, as Brown's Office of Research Protection requires.

Stronghold is accessible only from within the Brown campus network and by Virtual Private Network connections (using two-factor authentication) outside the campus network. All network connections to Stronghold pass through at least two firewalls: a dedicated firewall on the Brown campus network and a host-based firewall in the Stronghold environment.

The Stronghold system is physically located in a locked rack in a CCV-monitored data center on the Brown campus. Only certain authorized CIS staff have access to this locked rack. Entry to the data center is limited to authorized Brown IT personnel and their guests, and all entries are logged.

This service is customized to the needs of individual users and their data use agreements. Each investigator is given a dedicated environment for their project to support their co-investigators, graduate students, research assistants, interviewers, and other collaborators. Access to the Internet is restricted except for required locations for data imports or necessary software downloads. Import and export controls are in place to limit who can perform data migration, where sensitive data can come from, and where desensitized or anonymized data can be moved. Sensitive data is subject to file system auditing, and real-time alerting is available at the request of the PI.

Stronghold Data Security Policies for Investigators: The PI may impose additional requirements regarding credentials, connection methods, or clients based on the nature of the data. All systems (workstations, laptops, etc.) used to connect to Stronghold must have the following security precautions in place:

a. A password-protected lock-out screen that appears after inactivity of 5 minutes or less.
b. Up-to-date antivirus and malware installed.
c. An up-to-date operating system with all currently available updates installed.
d. Physical security (either card access or keyed locks) prevents unauthorized users from physically accessing the system while connected to Stronghold.
e. All connections to Stronghold will be made through a virtual private network (VPN). Currently, Stronghold supports the OpenVPN client.

f. Study reports, results, and published manuscripts will suppress all identifiable information and include only aggregated results.

3. Disruption to Service Provision

An unanticipated problem may occur if there is an occurrence of an unanticipated event involving a disruption to harm reduction service provision as a result of the study (e.g., diversion of resources away from cities/towns randomized to the control arm that would not have otherwise occurred if the study had not been taking place).

The randomized control trial evaluates whether cities and towns receiving the PROVIDENT model predictions will have a lower overdose rate than municipalities in an intervention arm. Municipalities assigned to the control condition should receive the same overall amount of resources and mix of interventions as the treatment arm communities in accordance with the state's overdose strategic plan but without prioritization of specific neighborhoods. While the PROVIDENT model predictions are intended for cities and towns to prioritize intervention deployment to neighborhoods at high risk of future overdose *within* a city or town in the treatment arm, the model predictions are not intended to prioritize intervention deployment to neighborhoods at high risk of future overdoses over neighborhoods in the control arm. Mitigating disruption to service provisions, such as inappropriate withholding of resources from municipalities assigned to the control condition, is imperative to maintaining safety and minimizing harm throughout the trial.

We anticipate disruption to service provisions may lead to physical or psychological harm to individuals or social harm. To minimize the potential for harm, interim analyses for safety will be conducted every six months to track resource allocation within each community organization throughout the study and identify any unanticipated events constituting a disruption of typical service provision. Interim safety analyses will include assessing information collected in survey forms completed by community organizations and information gathered during focus groups. We will ask organizations to complete the forms and regularly provide information about their services in each city and town.

4. Changes to Trial Logistics

An unanticipated event that changes trial logistics may constitute an unanticipated problem if it becomes clear that successful completion of the study is not feasible due to logistical or administrative reasons (e.g., changes in leadership at the Rhode Island Department of Health, significant changes to the financial resources available to fund harm reduction service provision). These changes will be monitored on an ongoing basis by the study teams at BUSPH and RIDOH and will be reported to the DSMB according to the reporting procedures described below.

5. Inappropriate Access by Criminal Justice

An unanticipated problem is considered if the occurrence of an unanticipated event involves criminal justice's inappropriate access to the PROVIDENT model predictions or any information related to the trial that would not otherwise be granted. For example, if a community organization details where they are targeting their efforts as a product of using the PROVIDENT predictions during the Governor's Overdose Task Force meeting and if a police officer is in attendance, this may inadvertently lead to an increase in policing in the specified locations.

We anticipate inappropriate access by criminal justice may lead to physical or psychological harm to individuals or social harm. To minimize the risk of harm, we will conduct safety analyses every six months to monitor municipal-level data on drug-related arrests and charges. Specifically, we will compare the intervention arm and the control arm to assess changes in drug and narcotic offenses in Rhode Island at the municipal/precinct level using the National Incident-Based Reporting System. We will also conduct analyses to identify changes in the demographics of arrestees. Finally, we will ask each community organization how they are using resources and if any results have been shared with non-participating parties on a six-month basis to identify changes in access.

Any changes identified will be followed until resolved or considered stable by the Co-PIs and reported to the DSMB according to the reporting procedures described below.

Reporting Procedures for Unanticipated Problems

Our research team will follow the guidelines described above and below for reporting unanticipated problems. The level of risk for the study and unanticipated problems will all be monitored and managed directly by the Project Investigator with support from the Project Director.

Consultation from the Brown IRB will be immediately available to the PI to address any required actions, investigations, or changes to the risk level of the study.

Events that satisfy any of the criteria for an unanticipated problem described above must be reported promptly to the Brown IRB and NIDA. Timelines for reporting unanticipated problems depend on the unanticipated problem category. Unanticipated problems that involve the loss of privacy or the loss of confidentiality will be reported to the IRB and NIDA within one business day of discovery. Unanticipated service disruption problems must be reported to the IRB and NIDA within 30 days of discovery. Unanticipated problems that involve changes to trial logistics must be reported to the IRB and NIDA within six months of discovery if the unanticipated problem is unresolved after three months of discovery. Unanticipated problems involving inappropriate access by criminal justice must be reported to the IRB within six months of discovery if the unanticipated problem is unresolved after three months.

The DSMB will be notified of any unanticipated problems and will be asked to convene at the earliest possible time to discuss, but no longer than 30 days after the unanticipated problem notification.

Plans for Interim Analysis of Efficacy Data

Since the study outcomes for non-fatal and fatal overdoses in part rely on mortality data from the Office of the State Medical Examiner (OSME) that is delayed by approximately five months, detection of a significant difference between the intervention arm and the control arm may be unlikely within a brief time period. As such, one interim analysis for efficacy will be conducted 18 months after the launch of the trial. The DSMB will review these results and may decide to continue or terminate the trial if there is evidence of efficacy at 18 months.

G. DSM Plan for Administration

Responsibility for Data and Safety Monitoring

The Principal Investigator, Brandon DL Marshall, PhD, is responsible for data safety and monitoring. This process will be monitored weekly by his team, including the Project Director, Data Analyst, and Research Assistant, with quarterly updates to the entire team of Co-Investigators. The project team will ensure that all policies and processes outlined in the Data Use Agreements are followed accordingly and that data are transferred and shared on the agreed-upon timeline using the IRB-approved data transfer methods. Additional data and safety monitoring reporting includes semi-annual updates to the DSMB and annual reports to the IRB and NIDA.

The content of the annual DSM report will include the following:

a. Brief description of the trial
b. Summary of qualifying data events observed during the annual period (i.e., fatal and nonfatal overdoses) by study arm
c. Regulatory issues
d. Unanticipated problems (as described above)
e. Efficacy of the trial interim analyses (conducted once at 18 months)

Data and Safety Monitoring Board (DSMB) Plan

Members and Affiliation, Conflict of Interest

A single Data and Safety Monitoring Board (DSMB) will be appointed to oversee this project. The DSMB will consist of members outside the research group conducting this study but may include individuals affiliated with one or more data-sharing partners who are not directly related to the project. The DSMB will include at least one individual with expertise in statistics or biostatistics. Any potential conflicts of interest must be disclosed during the application process. The Brown University IRB will ultimately approve the membership, meeting frequency, and Safety Monitoring Plan for the DSMB.

Frequency of Meetings & Protection of Confidentiality

The DSMB will meet semi-annually with the Co-PIs and project director to review DSMP protocol adherence. All Data Safety Monitoring Board members will receive a copy of the protocol. The protocol includes the data and safety monitoring plan, which will be used as a guide during the DSMB meetings. The DSMB will review any issues related to deviations from the protocol and reported unanticipated events. The DSMB will review and approve the study protocol before the start of the study and review major amendments to the protocol.

Monitoring Activities (initial and ongoing study review)

Monitoring activities and stopping rules are specific to the scope of the PROVIDENT trial. While the PROVIDENT trial does not involve direct interaction with individuals receiving harm reduction services, it does change the environment in which these services are provided. As such, responsibilities will include monitoring the overall safety of these environmental changes to ensure the safety of the individuals receiving these harm reduction services.

Activities will include monitoring unanticipated problems that are:

1. Unexpected given the study protocols;
2. Related (or possibly related) to participation in the study; and
3. Suggested that the research places subjects or others at greater risk of harm than was previously recognized.

The DSMB will be notified within 24 hrs. of unanticipated problems that involve loss of privacy or breach of confidentiality. Upon notification of any unanticipated problem, the DSMB will convene at the earliest possible time to discuss it, but no longer than 30 days from the time of the unanticipated event notification. At the end of each meeting, the DSMB will vote on the continuation of the study, particularly regarding safety and confidentiality issues. The DSMB will also provide written reports to be shared with the IRB, summarizing oversight activities, recommendations, and any concerns regarding study safety.

The DSMB will provide this recommendation to the Co-PIs and IRB through study comments. In addition, the DSMB will determine if there is sufficient concern to stop the trial.

Communication Plan to IRB, NIDA

The Principal Investigator and the Project Director will coordinate all communication and grant reporting to the necessary parties, with the goal of transparency across oversight boards (IRB, DSMB) and the funding institution. Examples of communication the PI shares include annual progress reports to NIDA, annual IRB protocol recertification, and semi-annual DSMB updates. Any unanticipated problems will be reported by the PI to the DSMB and IRB and, if required, the program officer at NIDA. The results of any DSMB or IRB comments will be shared as needed.

The DSMB will be asked to provide written documentation confirming a review of the protocol and agreement with the study design and the data safety monitoring plan (DSMP). The DSMB will ensure that all unanticipated problems are reported to the IRB by the Project Investigator according to policies and procedures.