Rhode Island Prescription and Illicit Drug Study (RAPIDS)
Data & Safety Monitoring Board Charter
Appendix D - Statistical Analysis Plan

1. Data Acquisition and Transmission

The primary source of data will be survey responses, including self-reported behaviors. Surveys will be conducted on touch-screen tablets using REDCap™ (Research Electronic Data Capture) software, which allows for direct, secure, and remote data entry. Similar to other studies, we have found the combined computer-assisted personal interview and computer-assisted self-interview (CAPI/CASI), conducted by trained, in-person interviewers, acceptable to the study population and efficient to administer. These procedures will protect against loss of confidentiality, improve reporting of sensitive behaviors, and reduce participant burden.

A second source of data will be datasets owned by the Rhode Island Department of Health (RIDOH). Specifically, outcomes will include fatal and nonfatal overdose events among participants during the study period, as determined through linkage to administrative records. All fatal overdose events occurring in the state are certified and investigated by the Rhode Island Office of State Medical Examiners. Nonfatal opioid overdose events will be ascertained from the Rhode Island Emergency Medical Services (EMS) database, using a case definition for suspected opioid overdose developed by RIDOH,[1] and from emergency department encounters for overdose from the RIDOH Hospital Discharge Data (HDD) system.[2] These administrative records are reviewed regularly as part of ongoing surveillance efforts and represent comprehensive sources regarding overdose events occurring in Rhode Island. We will adhere to strict data security and confidentiality protocols when accessing administrative datasets, as outlined in our existing DUA with RIDOH and as approved by the Brown IRB.

There are three major assessment points: baseline, acute outcome (6 months post-randomization), and longer-term outcomes measured at 12 months. At baseline, after reviewing the study protocols and undergoing informed consent, all participants will complete an assessment battery and will then be randomized to one of the two study conditions. At all assessment visits, we will use computer-assisted personal interviewing (CAPI) to conduct participant interviews, which will include a computer-assisted self-interview (CASI) component for the collection of sensitive or stigmatizing information (e.g., injection drug use).

[1] https://cdn.ymaws.com/www.cste.org/resource/resmgr/ps/ps2022/Recommendations_for_EMS_NFOO.pdf
[2] https://health.ri.gov/data/hospitalization/discharge/

Stronghold computing environment: We will obtain a central storage service hosted by Brown University's Computing & Information Services (CIS) Stronghold project. Stronghold is a HIPAA-aligned (Health Insurance Portability and Accountability Act), secure computing environment developed for housing, sharing, and analyzing sensitive data. The project's Biostatistician will oversee the database architecture, dataset storage, and all input/output (i.e., RIDOH data transfer) regulations. Stronghold is a highly secure computer and storage Windows-exclusive environment for research needs that involve very sensitive data needing special handling, data usage agreements, etc. See section F1 (Trial Safety) for additional information about Stronghold security.

<u>All Stronghold users must:</u>

- Be approved by the Principal Investigator (PI), authorized in writing to Brown University Computing &
- Information Services (CIS);
- 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; and
- Complete an on-boarding process led by the PI or Senior Research Assistant, which includes a review of data security protocols and a guided walkthrough of accessing the Stronghold virtual environment.

<u>Data Transfers</u> – there are select methods to import data, including but not limited to:

- Select Rhode Island state agencies and other offices using a secure VPN tunnel
- Encrypted USB drives
- Secure transfer through firewall exception
- Import and export servers

For the proposed project, the Data Manager will conduct and automate secure data transfer of administrative overdose records with RIDOH. He/she will also manage the REDCap™ database architecture, dataset storage, and all input/output (i.e., data transfer) regulations.

2. Data Entry Methods

Survey data will be collected on password-protected tablets and computers within the Center for Epidemiologic Research (CER) at the Brown University School of Public Health. The REDCap™ platform exceeds patient confidentiality and data security requirements for clinical trials and are both HIPAA compliant and fully validated for FDA 21 CFR Part 11.

3. Data Analysis Plan

For all analyses, a series of routine procedures will first be conducted to ensure data accuracy/adequacy. Descriptive statistics will provide examination of the variables' distributional properties; if required, data will be transformed to achieve normality. For all analyses, we will adopt an intention-to-treat (ITT) approach to address potential problems inherent in following only intervention completers (e.g., self-selection effects, differential attrition across groups). However, we will conduct a modified ITT (mITT), excluding participants who were randomized but did not receive the intervention. For all analyses, the PI, senior biostatistician, and team of co-investigators/consultants will remain blinded to the assignment of study groups until after the statistical analyses are complete and finalized; however, the PI and Project Director receive unblinded information regarding the primary outcome as they were reported by participants, since it is considered a severe adverse event (SAE) and thus these cases are reported to members of the members of the data safety monitoring board (DSMB) and the institutional IRB.

Prior to conducting statistical analyses described below, we will create two baseline tables: 1) one that compares prognostic characteristics between treatment groups immediately after randomization; and 2) a second that compares prognostic baseline characteristics between treatment groups, stratified by whether they completed both outcome visits, a single outcome visit, or were lost to follow-up (i.e., did not complete either the six or 12 month study visit).

Assessing intervention efficacy in reducing fatal and nonfatal overdose (Aim 1, primary endpoint).

The primary outcome will be **non-fatal overdose**, defined as a composite outcome, consisting of one of the following:

1. A self-reported overdose ascertained at the six and/or 12 month follow-up visits;
2. A non-fatal opioid overdose identified in the Rhode Island EMS database, using a case definition for suspected overdose developed by RIDOH previously;
3. An emergency department encounter for an accidental drug overdose that did not result in death, using a case definition developed by the CDC;[3]

The primary analysis will be conducted using a survival framework, with time to *first* nonfatal overdose—identified through any of the data sources noted above—serving as the primary outcome. For self-reported data, event times will be estimated from SAE reports (in which participants are asked to estimate the date of their overdose). Participants will be right-censored as of the date of the first

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7948191/

outcome event or at the end of the follow-up period, defined as 15 months following the participant's baseline visit.

To account for potential imbalance and to improve statistical efficiency, we will adjust for known or anticipated prognostic variables measured at baseline. These variables will include sociodemographic characteristics (e.g., age, gender identity, race/ethnicity), recent criminal justice involvement, housing instability, and substance use patterns including injection drug use & history of overdose. Variables will be transformed or categorized as necessary to address skewed or imbalanced data. We will also adjust for pre-baseline EMS runs for suspected opioid overdoses and ED encounters for drug overdoses using the case definitions noted above, occurring up to six months prior to the date of the participant's baseline visit.

At the completion of the study, patterns of data missingness will be explored to determine the appropriate assumptions required for each affected variable. Missing covariate data considered to be missing completely at random (MCAR), missing at random (MAR) and/or missing not at random (MNAR) will be handled using multiple imputation in SAS (proc MI procedure). Performed in two stages using chained equations, the model will specify the conditional models for the missing outcome and covariates as "MCAR", "MAR", or "MNAR". First, missing patterns will be tested. Then, imputing procedures will be separated into an "imputation phase", "analysis phase" and a "pooling phase". Finally, models with complete case, available data, and fully imputed data will be compared based on their coefficients, standard errors (SE), and *p*-value for the covariates included in the model.

To examine the effect of missing self-reported outcome data on the results, we will first examine the concordance between the self-reported outcome and the primary endpoints relying on administrative data linkages. If a high degree of correlation is observed (e.g., $r > 0.80$), we will assume missing self-reported outcome information has a negligible impact on the results. If a lack of concordance is observed, we will conduct stratified analyses by number of completed outcome visits (e.g., zero, one, and two) and also employ imputation-based procedures as noted above.

Second, in an exploratory analysis, we will determine the effect of the intervention on the more severe overdose endpoints, defined as an EMS run for suspected overdose, an ED encounter for drug overdose, or drug overdose death. An unintentional fatal overdose (involving any substance) will be determined through linkage to the Office of the State Medical Examiner (OSME), which is responsible for investigating all accidental deaths. Specifically, as defined previously,[4] cases will be considered confirmed unintentional drug-related overdose fatalities if: (i) the death was pronounced in Rhode Island; (ii) the final manner of death was deemed an accident by the medical

[4] https://doi.org/10.1016/j.drugpo.2017.05.029

examiner, and (iii) a drug is listed on the death certificate as the primary cause of death or a significant contributing factor. This analysis will be conducted using the same methodology as described above.

In two per-protocol sub-analyses, we will determine the effect of the intervention on the primary study endpoint among those who: (1) reported using fentanyl test strips during at least one intervention visit (months one, two, and three) compared to all participants assigned to the control arm; and (2) participants who completed one, two, and all three intervention visits using an ordinal variable, compared to all participants assigned to the control arm.

Finally, to account for potential treatment contamination (e.g., use of fentanyl test strips in the control arm, lack of use in the treatment arm), we will employ an instrumental variable approach to estimate the contamination-adjusted intention to treat (CA ITT) effect.[5] We will consider 'receipt of treatment' to be self-reported use of fentanyl test strips at months one, two, or three follow-up visits.

Examine whether the treatment effect is mediated by differential uptake of risk reduction behaviors in the intervention arm (Aim 2). If the RAPIDS intervention shows efficacy in reducing overdose rates among the sample (Aim 1), we will explore the extent to which this relationship works through several possible mediators. For mediation analyses, first, we will examine, in multivariable regression models, which mediators, if any, are significantly changed by the intervention (i.e., the rate of change differed by treatment assignment). For those that are significantly impacted by the intervention, we will conduct path analysis using structural equation modeling to determine whether the effect of the intervention on overdose was through the hypothesized mediator(s). Structural equation modeling (SEM) allows for the simultaneous estimation of total, direct, mediated and indirect effects of a causal variable (i.e., the intervention) on the outcome (i.e., overdose) through a set of mediator variables. SEM can handle outcomes and mediators with a variety of distributions (including, Gaussian, Poisson and Binomial). Inferences for indirect effects can be estimated using bootstrapped confidence intervals.

Determine whether intervention efficacy varies across participant subgroups (Aim 3). This is an exploratory aim. We will examine if heterogeneity of intervention effect is modified by key baseline characteristics of interest, including: age; sex; type, frequency, and route of drug use; baseline level of overdose risk (e.g., lifetime history of overdose); and pre-intervention motivations for fentanyl test strip utilization. We will perform stratified subgroup analyses to determine if treatment effects vary between groups of individuals.

[5] 10.1136/bmj.c2073

4. Interim Analyses

Interim analyses of study data are planned according to the alpha spending rule [Lan and DeMets, 1994]. The proportion of expected events (i.e., self-reported non-fatal overdose) is considered as the information statistic. The *p*-values will be constructed to maintain the overall study power of 0.05, two-sided. If the test statistic exceeds the boundary, then the study could be considered for early termination due to emerging differences between the two arms. The PI shall recommend to the Data and Safety Monitoring Board (DSMB) that two interim analyses be conducted over the course of the study. One would be conducted early on during the trial (e.g., once approximately one-third of the target sample size has been recruited and followed out to 12 months) to assess potential harms, and a second interim analysis would be conducted later on (after approximately two-thirds of the target sample size has been enrolled and followed to 12 months) to assess for benefit/efficacy.

5. Study Stopping Rules

The study investigators will report all adverse events and significant adverse events to the DSMB. Moreover, all adverse and significant adverse events will be summarized by the study biostatistician monthly for the first six months and then each quarter. These reports will be reviewed and commented on by the DSMB, which may recommend early termination of the trial given evidence of harm based on these and other safety data. Note that, since the study outcome (e.g., self-reported overdose) is defined as an SAE, these events are unblinded to the study biostatistician, principal investigator, and DSMB as they are reported.

We do not propose that the trial be stopped for futility, as additional information collected at the 12-month follow-up may be useful for public health program planning & practice. However, early evidence of efficacy from the second planned interim analysis may provide justification for the DSMB to recommend stopping the trial early. Analysis of efficacy in the second interim analysis will be undertaken as described above.

Finally, the entire trial will stop if any investigator 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.

Additionally, should research come out during the RAPIDS trial that demonstrates increased risk of using fentanyl test strips, the RAPIDS trial may be changed or stopped.

6. Sample Size Calculations

We provide power calculations for key outcomes below, based on an enrollment of 500 participants (n=250 per arm). To ensure we have a sufficient number of participants and to account for attrition,

we have received IRB approval to enroll up to 550 if necessary. The following assumptions are based on findings from our pilot intervention study. First, at baseline, 37% of participants reported a lifetime history of overdose, and 11% reported an overdose in the past six months. As such, for the primary analyses, we assumed that 20% of participants in the control arm will experience an overdose during the 12-month follow-up period. Second, we conservatively assumed an 80% retention rate in the trial, although we were able to retain 90% of pilot participants.

Given these assumptions, we have >80% power to detect a 50% reduction in overdoses. Similar effect sizes were assumed for an ED-based overdose prevention intervention, and have been deemed as a benchmark for success by key stakeholders. For the exploratory endpoint in Aim 1 (time to first fatal overdose or suspected overdose resulting in an EMS record), we conservatively assumed that only 38% of self-reported overdoses would result in death or attendance by EMS, based on previously published data, for a rate of 8 per 100 person-years in the control arm. We have ≥80% power to detect a 50% reduction in the hazard of fatal overdose or ED visit for an overdose.

Finally, we used a method to estimate sample size for evaluating mediation by joint testing of both links in an indirect pathway from exposure to mediator to outcome (Aim 2). Given the assumptions described above, we have >80% power to detect a statistically significant mediated effect for a coefficient for exposure on mediator and mediator on outcome of at least 0.8 (i.e., a relative risk of $\exp[0.8] \cong 2.3$), respectively.