Study Protocol with Statistical Analysis Plan

# Developing and Testing the Opioid Rapid Response System

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## Background and Objectives

Opioid-involved overdose remains a major public health challenge in the United States. In 2022, 81,806 opioid-involved overdose deaths were recorded, an increase from 49,860 deaths in 2019 (National Institute on Drug Abuse [NIDA], 2024). Naloxone can reverse an opioid overdose, but its public health benefit depends on rapid recognition, activation of emergency services, and timely administration (Substance Abuse and Mental Health Services Administration [SAMHSA], 2018).

Rapid response can be difficult in both rural and urban communities because distance, geographic dispersion, or congestion may delay emergency assistance. Additional barriers include inconsistent naloxone access, limited training opportunities, and delayed emergency response (Carr et al., 2025; Saunders & Rudowitz, 2023). These challenges support a coordinated model that prepares nearby laypersons to identify suspected overdose events and provide immediate assistance while emergency services are activated or en route.

The Opioid Rapid Response System (ORRS) is a technology-supported intervention designed to recruit and train lay community members to respond to suspected opioid overdose events. ORRS builds on the PulsePoint platform by pairing app-based emergency notification capacity with online overdose-response training (Carr et al., 2025; PulsePoint Foundation, n.d.).

The study objectives are:

Refine and complete the ORRS intervention.

Evaluate the effectiveness of ORRS in a randomized controlled trial.

## Study Design

This study includes formative focus groups followed by a two-arm, parallel, individually randomized controlled trial. The formative focus groups are used to inform training content and usability. The randomized trial evaluates ORRS by comparing participants assigned to ORRS training with participants assigned to an informational control condition.

Potential participants complete eligibility screening and online consent before study participation. After consent, eligible participants are randomized within their community using a computer-generated sequence administered by Ewald and Wasserman. Randomized participants complete a baseline/pretest survey, the assigned online intervention or control condition, an immediate posttest survey, and follow-up surveys approximately 1, 3, and 6 months after completing the assigned training or control condition.

## Study Population and Setting

The randomized trial enrolls lay adult volunteers from communities with active PulsePoint licenses. The study communities are located in Arizona, Pennsylvania, and Washington, including Casa Grande, Cochise County, Copper Canyon/Verde Valley, and Tucson in Arizona; Elk County, McKees Rocks/Stowe Township, and South Oakland/The Hill District in Pennsylvania; and Clark County and Spokane County in Washington.

**Inclusion criteria**:

Age 18 years or older.

Residence in a community with an active PulsePoint license.

English-speaking.

**Exclusion criteria**:

Certified first responder status, such as police officer or firefighter.

Failure to meet the inclusion criteria.

Individuals who are found ineligible during screening receive an automated message indicating that they do not meet study criteria.

**Recruitment and Enrollment Methods**

Recruitment is conducted through community-facing channels administered by Ewald and Wasserman in collaboration with the study team. Recruitment channels include social media, U.S. postal mailings to commercially available household records, flyers, organizational emails, community referrals, and snowball sampling. Recruitment materials use personal, communal, or combined identity appeals. Each recruitment route uses a unique URL or QR code so that the study team can track the recruitment source and compare recruitment approaches. Additional community outreach may be used if needed to support enrollment.

**Study Arms and Procedures**

**ORRS Intervention**

ORRS is an interactive web-based training platform that can be accessed through desktop or mobile browsers. The training is organized into sequential multimedia modules. Training content covers recognition of suspected overdose, scene safety, intranasal naloxone administration, basic supportive response, and PulsePoint navigation. Supplementary content addresses stigma reduction and how intranasal naloxone works.

Participants access ORRS through a unique link provided after the pretest survey. The link connects training-use data with the participant record. The training platform records dosage and usability information, such as training completion time, and includes knowledge checks. After the immediate posttest, participants receive an emailed resource document with naloxone access information, CPR resources, and instructional resources.

**Control Condition**

The control condition is an online educational program about opioids and opioid overdoses. It provides general information but does not provide the ORRS behavioral training in overdose management or naloxone administration. Control participants are offered access to ORRS after completing the final follow-up assessment.

**Measures and Assessment Schedule**

Self-report surveys are used to evaluate program effects. The baseline/pretest and immediate posttest surveys assess cognitive and psychological outcomes related to overdose management, recognition of overdose signs, efficacy, intent to intervene, and response-related concerns. The surveys also collect participant demographics, overdose-event experience, naloxone-related experience, and PulsePoint app use.

Follow-up surveys at approximately 1, 3, and 6 months assess behavioral outcomes related to responses to overdose-related events, naloxone administration, and naloxone carrying. The naloxone-carrying outcome is assessed among ORRS participants.

### Sample Size

The planned randomized trial sample size was 1,600 participants, with approximately 800 participants per condition across approximately nine communities. The sample-size rationale was based on detecting small-to-medium effects, with Cohen's d expected to be approximately 0.2 to 0.6, while allowing for an estimated 50% attrition rate in an individually randomized parallel design. Due to budget and timeline constraints, final recruitment totaled 773 participants.

## Statistical Analysis Plan

### General Data Review and Descriptive Analyses

Before modeling, the study team will review the randomized trial dataset for completeness, duplicate records, invalid values, and out-of-range responses. Confirmed data errors will be corrected before analysis. Descriptive statistics will be used to summarize participant flow, baseline characteristics, intervention/control completion, assessment completion, and study variables. Frequencies and percentages will be used for categorical variables, and means and standard deviations will be used for continuous variables when appropriate.

### Intervention Effect Analyses

The main randomized comparisons will estimate the effect of ORRS assignment compared with control assignment. Randomized condition will be coded as an indicator variable, with control as the reference group and ORRS as the intervention group. Regression models will be used to examine posttest cognitive and psychological outcomes, including overdose management, recognition of overdose signs, efficacy, stigma, intention to intervene, and response-related concerns. When available and appropriate, the corresponding baseline/pretest value will be included as a covariate.

### Follow-up Behavioral Outcomes

Behavioral outcomes assessed during follow-up will be analyzed using regression models appropriate to the scale of each outcome. These outcomes include PulsePoint notification use, response to overdose-related events, and naloxone administration. Because overdose-response events and naloxone administration may be uncommon, behavioral outcomes may be summarized across the 1-, 3-, and 6-month follow-up assessments or analyzed using combined follow-up indicators. Corresponding baseline measures will be included as covariates when available and appropriate.

### Naloxone-Carrying Outcome

Because the naloxone-carrying outcome is assessed among ORRS participants, this outcome will be analyzed among participants assigned to ORRS. Analyses may include descriptive summaries and regression models using available ORRS-participant data.

### Missing Data

Missing data are expected because the study includes repeated assessments over time. Missing outcome or covariate data will be handled using full information maximum likelihood and/or multiple imputation, as appropriate for the analysis model and available data. These approaches will use

available observed information, including randomized condition, outcomes, baseline/pretest values, demographic covariates, and other relevant study variables when available.

**Multiplicity and Model Assumptions**

No formal multiplicity adjustment is specified. Regression model type will be selected based on the scale and distribution of each outcome. Basic model diagnostics and convergence will be reviewed as applicable.

## References

Carr, D. L., Hecht, M. L., Shiota, M. N., Zalake, M., Krieger, J., & Choi, H. J. (2025). Protocol for a national randomized controlled trial evaluating the Opioid Rapid Response System for overdose death prevention. Contemporary Clinical Trials, 150, 107835. https://doi.org/10.1016/j.cct.2025.107835

National Institute on Drug Abuse. (2024, August 21). Drug overdose deaths: Facts and figures. National Institutes of Health. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

PulsePoint Foundation. (n.d.). PulsePoint Respond. Retrieved June 27, 2026, from https://www.pulsepoint.org/download

Saunders, H., & Rudowitz, R. (2023, September 19). Will availability of over-the-counter Narcan increase access? KFF. https://www.kff.org/policy-watch/will-availability-of-over-the-counter-narcan-increase-access/

Substance Abuse and Mental Health Services Administration. (2018). Opioid overdose prevention toolkit: Five essential steps for first responders. U.S. Department of Health and Human Services. https://library.samhsa.gov/sites/default/files/five-essential-steps-for-first-responders.pdf