STATISTICAL ANALYSIS PLAN

HEALing Communities Study Main Trial Results

NCT04111939

Proposal Number: MP0048

SAP VERSION: 5.0

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PI/SPONSOR: Sharon Walsh, PhD (University of Kentucky)
Jeffrey Samet, MD (Boston University)
Nabila El-Bassel, PhD (Columbia University)
Bridget Freisthler (Ohio State University)
Emmanuel Oga, MD (RTI International)
Gary Zarkin, PhD (RTI International)
LaShawn Glasgow, PhD (RTI International)
Redonna Chandler, PhD (NIDA)
Jennifer Villani, PhD (NIDA)

PREPARED BY: RTI International and the HCS Statistics and Data Analysis Work Group (StaDA-WG).

AUTHORS: Nathan Vandergrift and Barry Eggleston for the HEALing Communities Study Data Coordinating Center Statistical Operations (DCC StatOps) group.

SAP REVIWERS: Philip Westgate (University of Kentucky), Debbie Cheng (Boston University), Daniel Feaster (University of Miami), Soledad Fernandez (Ohio State University) for the HCS Statistics and Data Analysis Work Group (StaDA-WG).

Contents

1 ADMINISTRATIVE INFORMATION

1.1 Trial Name

HEALing Communities Study: Developing and Testing an Integrated Approach to Address the Opioid Crisis

1.1.1 Trial Registration

ClinicalTrials.gov - NCT04111939

1.2 Protocol Version

HCS Study Protocol version 1.20

1.3 SAP Revision History

Ver.	Justification for change	Date	Approved
1.0	SAP approved by the HCS StaDA-WG on May 5, 2021 and by the HCS Steering Committee on May 21, 2021.	2021-05-21	NAV*
1.1	At the behest of the Steering Committee reducing the scope of MP0048 to opioid overdose deaths.	2022-09-08	NAV*
1.2	Modified Section 6.2.4 to clarify when a Poisson or Negative Binomial model would be used. Modified the section 6.2.6 to include investigations into interactions between intervention and Age, Race/Ethnicity, and Sex. Modified Section 6.7 to define additional tables to cover additional subgroup analyses.	2022-10-19	NAV*
1.3	Modified Sections 6.2.6 and 6.7 to reflect decisions made by DCC StatOps and StaDA-WG regarding FDR and potential displays.	2023-05-12	NAV*
2.0	Finalized language in section 6.5 on the reporting of AE/SAE. Created pdf of SAP.	2023-06-05	NAV*
3.0	Added language to section 6.2.6 to indicate that individual point estimates will be provided for all subgroups for descriptive purposes at the urging of the HCS SC who made this request at their meeting 2023-06-30.	2023-07-06	NAV*
4.0	Added language to section 6.2.5 to indicate post-hoc sensitivity analyses that were conducted.	2023-08-11	DCB*

	Revised language in section 6.2.6 to describe reporting of individual point estimates and confidence intervals for all subgroups. Added language to section 6.4 to indicate post-hoc analyses that were conducted.		
5.0	Added NCT number to first page. Added language to section 6.4 to indicate post-hoc estimation methods for "deaths averted" calculation.	2023-11-16	NAV*

*Note: NAV = Nathan Vandergrift, Director of DCC StatOps; DCB = Denise C Babineau, Senior Research Statistician, DCC StatOps

1.4 SAP Roles and Responsibilities

Nathan Vandergrift, Barry Eggleston, and Denise Babineau (RTI International) for the HEALing Communities Study Data Coordinating Center Statistical Operations (DCC StatOps) group. These members will provide the written explanations for the Statistical Analysis Plan (SAP) as well as any displays used.

Philip Westgate (University of Kentucky), Debbie Cheng (Boston University), Daniel Feaster (University of Miami), Soledad Fernandez (Ohio State University) for the HCS Statistics and Data Analysis Work Group (StaDA-WG). The StaDA-WG will review, edit, and approve the SAP.

1.5 List of Abbreviations

Abbreviation:	Definition:
$	Dollar
%	Percent
±	Plus or Minus
≤	Less than or equal to
<	Less than
=	Equals
≥	Greater than or equal to
>	Greater than
AE	Adverse event
CI	Confidence interval
CTH	Communities That HEAL
DCC	Data Coordinating Center
DCC StatOps	Data Coordinating Center Statistical Operations
DSMC	Data and Safety Monitoring Committee
EBP	Evidence-based practice
EMS	Emergency medical service
FDR	False discovery rate
GEE	Generalized estimating equation
HCS	HEALing Communities Study
ITT	Intention-to-treat
KY	Kentucky

MA	Massachusetts
N/A	Not Applicable
NIDA	National Institute on Drug Abuse
NY	New York
OD	Overdose
OH	Ohio
ORCCA	Opioid-overdose Reduction Continuum of Care Approach
OUD	Opioid use disorder
PP	Per protocol
RS	Research site
SAE	Severe adverse event
SAP	Statistical analysis plan

2 INTRODUCTION

The goal of the HCS is to reduce opioid overdose (OD) deaths.

2.1 Background and Rationale

The U.S. opioid OD epidemic has been declared a national emergency.[2,3] Currently, a menu of EBPs for OUD prevention and treatment spanning the OUD continuum of care exists. Unfortunately, uptake and implementation of these EBPs remains low in numerous community settings including addiction treatment, harm reduction general medical care, social support services, schools, and the justice system. This failure is in part due to a lack of evidence-based approaches for assisting communities in the development and deployment of a data-driven, custom-designed response strategy to deliver comprehensive integrated EBPs. Many of the study counties/communities lack integrated service systems for OUD.

Using a data-driven, multi-pronged, community-based approach is necessary to change the course of the epidemic. The HEALing Communities Study (HCS) is a 5-year, multi-site, parallel arm, cluster randomized wait-list controlled trial to test the immediate impact of implementing an integrated set of EBPs from the CTH framework delivered across healthcare, behavioral health, justice, and other community-based settings in highly affected communities. The HCS is designed to detect a 40% reduction in the rate of opioid OD deaths between randomized arms after two years of intervention, with the primary comparison planned for the evaluation period, defined as the 12-month period from July 1, 2021 to June 30, 2022.

2.2 Study Objectives

The HEALing Communities Study (HCS) will test the impact of the CTH intervention on the rate of opioid OD deaths and associated outcomes in 67 highly affected communities in Kentucky (KY), Massachusetts (MA), New York (NY), and Ohio (OH). The HCS is designed as a multi-site, parallel arm, cluster randomized, wait-list controlled trial evaluating the impact of the CTH intervention compared with usual care in wait-list control communities. HCS communities were randomly assigned to either the CTH intervention or wait-list control using covariate-constrained randomization (Moulton, 2004; see Section 3.2[13]). Henceforth, we will refer to the communities randomized to the CTH intervention arm first as Wave 1 communities and those assigned to the wait-list control arm as Wave 2 communities. The evaluation period will be from July 1, 2021 until

June 30, 2022. After the end of the evaluation period, Wave 2 communities will receive the CTH intervention.

2.2.1 Primary Objective

To compare the rate of opioid OD deaths per 100,000 adults during the evaluation period between Wave 1 and 2 communities.

2.3 Study Hypotheses

2.3.1 Primary Hypothesis

We expect that there will be a difference in the rate of opioid OD deaths per 100,000 adults during the evaluation period between Wave 1 and Wave 2. In particular, we expect that the rate of opioid OD deaths per 100,000 adults during the evaluation period in Wave 1 is lower than Wave 2.

The null (H_0) and alternative (H_A) statistical hypotheses are:

H_0: The rate of opioid OD deaths per 100,000 adults during the evaluation period in Wave 1 is equal to Wave 2.

H_A: The rate of opioid OD deaths per 100,000 adults during the evaluation period in Wave 1 is not equal to Wave 2.

3 STUDY METHODS

This section of the SAP contains information about the study design and statistical analysis to be performed to assess the study objectives and hypotheses outlined in Section 2.

3.1 Trial Design

The HCS is a multi-site, parallel arm, cluster randomized wait-list controlled trial composed of 67 communities from four research sites (RSs): KY, MA, NY, and OH. Communities were randomly assigned to the CTH intervention arm (Wave 1, N = 34 communities) or the wait-list control arm (Wave 2, N = 33 communities).

3.2 Randomization

The 67 HCS communities were randomly assigned to the CTH intervention arm (Wave 1) or the wait-list control arm (Wave 2) communities. Randomization was stratified by RS (i.e., KY, MA, NY, OH). For each RS, we used covariate-constrained randomization (Moulton, 2004[13]) to ensure balance between Wave 1 and Wave 2 communities on three key community characteristics at baseline:

1. Rate of opioid OD deaths averaged over 2016 and 2017;
2. population size average of 2016-17 (except MA which was the ACS to 2017); and
3. rural/urban status from 2017.

Covariate-constrained randomization sets limits the differences in select variables between arms in a trial. For the HCS, we cluster-randomized communities within each RS and constrained randomization to balance three community-level factors:

1. less than 0.2 standard deviation difference of the overall mean between Wave 1 and Wave 2 in the rate of opioid OD deaths,
2. less than 0.2 standard deviation difference of the overall mean between Wave 1 and Wave 2 community population, and
3. an equal number of communities with rural/urban status where possible and for those RSs with an odd number of communities, no more than a difference of 1 rural/urban community between intervention arms.

Results of the covariate-constrained randomization can be found in Appendix 1.

The HCS communities' assignment will not be blinded. The communities will be informed of the assignment to the CTH intervention. In addition, the research teams at each RS will know the assignments of communities to Waves 1 and 2 as they work to implement the CTH within communities. Although the HCS communities and RS research teams will not be blinded, the statisticians performing the analysis will do so with the communities de-identified. Once the analyses are completed, the assignments to intervention arm will be associated with the analytic results.

3.3 Sample Size

A total of 67 communities were randomized and will be analyzed in an intention-to-treat (ITT) framework using a negative binomial regression model, as described in Section 6.2.1.1. As designed, this study has >99% power to detect a 40% (i.e., relative rate 0.60) reduction in the rate of opioid OD deaths during the evaluation period in Wave 1 compared to Wave 2 communities. Power was calculated by empirical simulation using pilot data from all 67 communities. This included actual community rural/urban status, community population sizes and corresponding numbers of opioid OD deaths from 2016 and 2017.

The simulation study had 20,000 replications to ensure very small error in estimated power (i.e., 95% confidence intervals (CIs) corresponding of calculated power is no wider than 0.011 for power ≥0.80). This simulation study is advantageous relative to a basic (closed form) power calculation approach due to the ability to account for the high variation in community sizes, as well as its ability to adapt to the analytical approach (negative binomial regression model) that will be used. To conduct the simulation study, data from the 67 HCS communities were used to empirically drive population assumptions.

For each community, we used the average reported community population and the average number of opioid OD deaths from 2016 and 2017. We fit a negative binomial regression model to these data to extract estimates for the marginal parameters in the regression model, as well as the dispersion parameter, k, corresponding to between-community variation as expected in cluster trials. We note that this model did not include an intervention effect, because the pilot data are reflective of control conditions, and the desired intervention effect is dictated by the assumed rate reduction for which we calculate power. Furthermore, due to the unknown influence the baseline rate of opioid OD deaths will have on future rates, and more importantly, in order to provide conservative power calculations (greater power will potentially be achieved in our actual analysis via a reduction in unexplained variability due to the use of the baseline rate of opioid OD deaths as a covariate in the regression model), this variable was not included as a covariate in the regression model for the simulation study. In short, we obtained a value of 0.0431 for k and, with the resulting regression parameter estimates, marginal probabilities ranged from 0.000255 to 0.000436.

In our simulation study, we assumed that the population parameters just described were reflective of the true parameters for the Wave 2 communities during the evaluation period. The analyses were conducted as described in Section 6.2.1.1, with the exception that the baseline rate of opioid OD deaths was not incorporated into the model as a covariate, thus providing conservative power estimates.

Table 1 provides power estimates for a variety of differences in the rate of opioid OD deaths during the evaluation period between the Wave 1 and Wave 2 communities. As can be seen, we have greater than 99% power to detect a 40% (i.e., relative rate 0.60) reduction and at least 83% power for any reduction of 20% or more.

Table 1. Power calculation for underlying reduction in the rate of opioid OD deaths during the evaluation period between intervention and wait-list control arms. Empirical SE estimates were utilized. Treatment allocation was not included in the initial model to extract parameter estimates, only covariates (RS and rural/urban status). A new treatment allocation was determined within each replication, balanced within RS (KY, MA, NY, OH; except for OH which has 19 communities).

Intervention Effect	Relative Rate of Opioid OD Deaths	Power
40%	0.60	0.999
25%	0.75	0.961
24%	0.76	0.943
23%	0.77	0.925
22%	0.78	0.899
21%	0.79	0.866
20%	0.80	0.832
19%	0.81	0.792

3.4 Framework

The primary objective is to evaluate the impact of the CTH intervention versus wait-list control on the rate of opioid OD deaths during the evaluation period.

3.5 Statistical Interim Analysis and Stopping Guidance

There are no planned interim efficacy analyses, safety analyses, or interim stopping rules.

3.6 Timing of Final Analysis

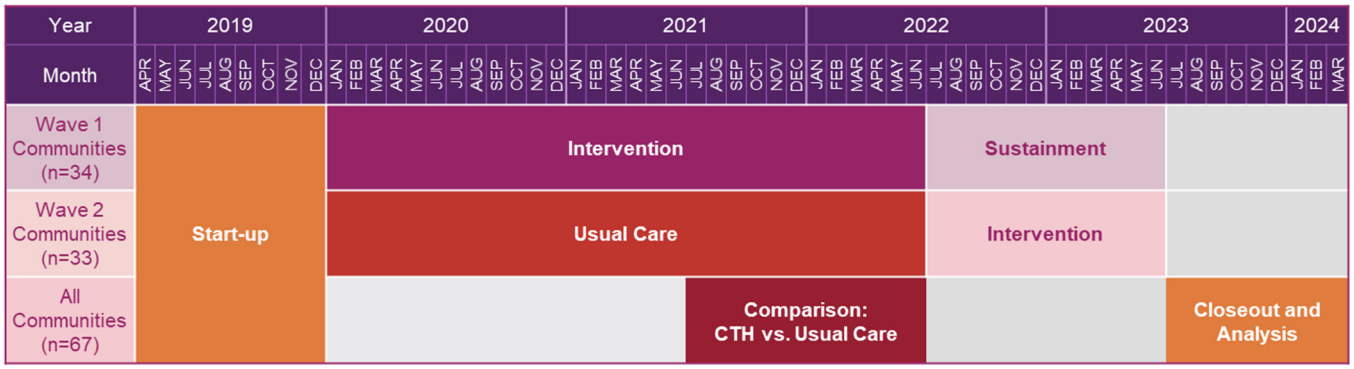
Data collection for the evaluation period is expected to be complete within 9-12 months from the end of the evaluation period. Subsequent data cleaning and analysis will be completed within 3-6 months and dissemination of results will take place immediately after. If the data are ready prior to this time, final analyses will commence early.

3.7 Timing of Outcome Assessments

The duration of the HCS is April 2019 through March 2024 (Figure 1). During this 5-year period, the CTH intervention will be carried out in two waves. Startup activities for the four academic RSs and the Data Coordinating Center (DCC) began in April 2019 and continued through December 2019. Wave 1 communities began implementing the CTH intervention for 30 months (January 2020 through June 2022), during which time Wave 2 communities provided usual care. The primary outcome measurements were assessed for Waves 1 and 2 during the evaluation period. In July

2022, Wave 2 communities began to implement the CTH intervention for 12 months (July 2022 through June 2023). After the evaluation period, Wave 1 communities will be observed for sustainment of the CTH intervention for a 12-month period (July 2022 through June 2023).

Figure 1: HEALing Communities Study timeline



4 STATISTICAL PRINCIPLES

4.1 Confidence Intervals and P-values

All statistical computations will be performed by HCS biostatisticians from the DCC StatOps. For descriptive summaries of study data, the following will be presented:

- Nominal/categorical measures will be summarized in tables listing frequency and percentage;
- Continuous measures will be summarized by presenting means, standard deviations, and medians;
- Ordinal measures will be summarized depending on the number of levels. An ordinal measure with five levels or less will be summarized as a nominal measure. An ordinal measure with more than five levels will be summarized as a continuous measure.

The balance or imbalance of these characteristics will be studied and reported, particularly for analyses comparing the two intervention arms. Graphical displays may be used to show distributions (box plots, density curves). The reported p-values will be based on two-sided tests at an α=0.05 unless otherwise specified. When p-value correction is appropriate, Benjamini-Hochberg (1995)[14] False Discovery Rate (FDR) adjustments will be used to address multiplicity and preserve Type I error rate.

Unless required otherwise by a journal, the following rules are standard:

- Moment statistics, including mean and standard deviation, will be reported at 1 more significant digit than the precision of the data.
- Order statistics, including median, minimum and maximum values, will be reported to the same level of precision as the original observations. If any values are calculated to have more significant digits, then the value should be rounded so that it is the same level of precision as the original data.
- Following SAS rules, the median will be reported as the average of the two middle numbers (by order) if the dataset contains an even number of observations.

- Test statistics including t and z test statistics will be reported to two decimal places.
- P-values will be reported to 3 decimal places if > 0.001. If less than 0.001, p-values will be reported as '<0.001'. P-values will be reported as 0.05 rather than .05.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5 round down, if ≥5 round up.

4.2 Adherence and Protocol Deviations

A listing of protocol deviations for each site including the date and narrative will be supplied.

4.3 Analysis Populations

The analyses will be done using an ITT framework defined as the inclusion of all communities randomized into the HCS and analyzed according to the intervention arm to which the community was randomized.

If specified, sensitivity analyses of each outcome will also be performed using a Per Protocol (PP) framework, defined as the inclusion of all randomized communities who complete the HCS protocol with no major deviations and analyzed according to the intervention arm to which the community was randomized. As of 5/12/2023, the ITT population includes 67 communities and the PP population includes 66 communities.

5 TRIAL POPULATION

5.1 Screening data

Communities were recruited prior to the implementation of the HCS so that no consideration of community representativeness may be given.

5.2 Eligibility

The National Institute on Drug Abuse (NIDA) selected four RSs in KY, MA, NY, and OH for the HCS. Across these four RSs, 67 communities were selected and agreed to participate in the HCS. To be selected for this study, a community must meet all of the following criteria established by NIDA:

- The community must be located in one of the four participating RSs: KY, MA, HY, or OH.
- Of the communities selected in each RS, 30% or more must be rural.
- Across all of the HCS communities in each RS, there must be a minimum of 150 opioid-related OD deaths (at least 15% of which come from rural communities) and a rate of at least 25 opioid-related OD deaths per 100,000 adults, based on 2016 data.
- In its response strategy, the community must express willingness to address the implementation of medication for OUD, OD prevention training, and naloxone distribution across the community.
- The community must express willingness to develop partnerships across health care, behavioral health, and justice settings for EBPs to address opioid misuse, OUD, and ODs.

In addition to the NIDA-defined eligibility criteria listed earlier, the RSs used additional eligibility criteria to further refine their community selection (see Appendix 2).

5.3 Recruitment

Communities were recruited prior to the implementation of the HCS. A description of the criteria utilized to select the final set of 67 communities will be included in the CONSORT diagram and associated text in the final analysis report and manuscript.

5.4 Withdrawal / Follow-up

We expect very few communities to withdraw from the trial. For those communities that withdraw, we will summarize their characteristics at baseline (population size, rate of opioid OD deaths, rural/urban status) compared to communities that remain in the trial. We will also summarize, if appropriate, the timing and reasons for withdrawal.

5.5 Baseline Community Characteristics

Baseline counts and rates of opioid OD deaths in HCS communities, and other outcome measures needed for the statistical analysis, will be collected based on the 12 months from January 2019 to December 2019 immediately preceding the study initiation and implementation of CTH intervention in Wave 1 communities. Additionally, baseline counts and rates will be used for dashboard visualization measures, where available. Baseline data may be used in additional RS-specific analyses, including geospatial analyses using address information (e.g., from death certificate data, including address of death and address of residence) where permitted by RS's state-specific data use agreements.

6 STATISTICAL ANALYSIS

6.1 Outcome Definitions

The definition of the trial outcome for the primary objective is number of opioid OD deaths during the evaluation period. This outcome has reference number 1 in Version 2.0 of the HCS Outcome Measure Technical Specifications document. The source of data is death certificates, supplemented (if needed) with medical examiner, coroner, and toxicology data. Detailed technical specifications for this outcome are available in Version 2.0 of the HCS Outcome Measure Technical Specifications document.

6.2 Analysis Methods

The HCS is a multi-site, parallel arm, cluster randomized, wait-list controlled trial of the CTH intervention. All statistical computations will be performed by HCS biostatisticians from DCC StatOps. For the analysis and modeling of the data, general methodological standards will be followed throughout including assessing model assumptions, incorporating appropriate covariates, and, where appropriate, conducting sensitivity analysis to assess robustness of findings. Statistical models will generally be adjusted for the covariates in the randomization.

6.2.1 Statistical Methods

The primary analysis will be conducted under an ITT framework. Descriptive statistics will be produced as outlined in Section 4.1.

The purpose of the primary objective is to assess the impact of the CTH intervention on the rate of opioid OD deaths during the evaluation period in the HCS communities (i.e., deaths with an underlying cause of drug poisoning) where opioids were determined to be contributing (alone or in combination with other drugs) to the drug poisoning. To address this objective, the statistical model outlined below will evaluate the primary hypothesis (see Section 2.3.1) by testing the difference in the rate of opioid OD deaths during the evaluation period between Wave 1 and Wave 2 communities.

1. **Outcome Variable**: Number of opioid OD deaths during the evaluation period as defined in Section 6.1.
2. **Statistical Model**: Negative binomial.
3. **Offset**: The natural log of the community population size during the most recent year from available data.
4. **Covariates**: The natural log of the baseline rate of opioid OD deaths, rural/urban status, and RS (KY, MA, NY, OH). If there are any communities where the baseline rate of opioid OD deaths is 0, the log transformation cannot be applied and so the baseline rate of opioid OD deaths will be used across all models of this outcome.

The negative binomial regression model described in Westgate et al. (2022)[15] will be utilized to analyze the count outcomes, providing the scientific rigor that is required for the analysis of data arising from a cluster/community randomized trial. The model will include intervention arm (Wave 1 versus Wave 2) as the main independent variable. In addition, the model will control for the following covariates: the RS (KY, MA, NY or OH) in which the community belongs, the rural/urban status of the community, and the natural log of the baseline rate of opioid OD deaths for the community. The reported natural log of the population size for each community during the evaluation period will be utilized as an offset in the model, so that the primary analysis will model the marginal probability of an opioid OD death during the evaluation period in the population as a function of covariates described above. The interpretation of the intervention arm coefficient from the proposed model will therefore be the natural logarithm of the ratio of population probabilities of opioid OD deaths during the evaluation period (i.e., the natural logarithm of the relative rate for opioid OD deaths during the evaluation period for Wave 1 vs Wave 2 communities). Thus, the model will estimate the relative rate of opioid OD deaths during the evaluation period between the two intervention arms. We note that alternatively, the analysis can also be interpreted as a model for the rate of opioid OD deaths during the evaluation period per individual, evaluating changes in rates between intervention arms (i.e., rate ratios). RS, rural/urban status, natural log of the baseline rate of opioid OD deaths (or untransformed version for the baseline rate of opioid OD deaths), and population size during the evaluation period are accounted for in the model to increase statistical power as each of these factors and were included in the constrained randomization scheme.

We consider the model below for the analysis of the primary hypothesis.

$$\boldsymbol{\mu_i} = \boldsymbol{e^{ln(n_i)+x_i^T\beta}} = \boldsymbol{n_i e^{x_i^T\beta}}$$

where:

$\boldsymbol{\mu_i}$ = expected number of opioid OD deaths during the evaluation period in community i

$\boldsymbol{n_i}$ = population size during the evaluation period in community i. The natural log of population size in community i will enter the negative binomial model as an offset.

$\boldsymbol{x_i^T\beta}$ = linear predictor of covariates, parameters

The linear predictor contains the coefficients estimated from the negative binomial regression model. The primary analysis model will consist of the following linear predictor:

$$x_i^T\boldsymbol{\beta} = \boldsymbol{\beta_0} + \boldsymbol{\beta_1} * \ln(\boldsymbol{OPDEATH_{BL}}) + \boldsymbol{\beta_2} * \boldsymbol{RURAL} + \boldsymbol{\beta_3} * \boldsymbol{SITE2} + \boldsymbol{\beta_4} * \boldsymbol{SITE3} + \boldsymbol{\beta_5} * \boldsymbol{SITE4} + \boldsymbol{\beta_6} * \boldsymbol{TX}$$

Where:

$\boldsymbol{\beta_0}$ = intercept, the rate of opioid OD deaths during the evaluation period when all covariates = 0

$\boldsymbol{\beta_1}$ = effect of the natural log of the baseline rate of opioid OD deaths on the rate of opioid OD deaths during the evaluation period in Wave 2 communities

$\boldsymbol{\beta_2}$ = effect of rural community status on the rate of opioid OD deaths during the evaluation period, compared to urban community status

$\boldsymbol{\beta_3}, \boldsymbol{\beta_4}, \boldsymbol{\beta_5}$ = effects of individual RSs on the rate of opioid OD deaths during the evaluation period, compared to RS = 1

$\boldsymbol{\beta_6}$ = effect of the CTH intervention on the rate of opioid OD deaths during the evaluation period, compared to wait-list control; exponentiating this value yields the relative rate of opioid OD deaths during the evaluation period comparing Wave 1 to Wave 2 communities

In model specification above, the coefficient and associated estimates for the intervention effect (β_6) are of primary interest. This coefficient represents the adjusted ln(relative rate) of opioid OD deaths during the evaluation period comparing Wave 1 to Wave 2 communities (e.g., if relative rate = 0.60, ln(relative rate) = -0.51).

The negative binomial regression model described above will be fit utilizing PROC GLIMMIX in SAS 9.4 or higher (see Appendix 3 for example SAS code). Of note, GLIMMIX will utilize maximum likelihood to estimate parameters. However, we will utilize small sample adjusted empirical standard error estimates following Ford and Westgate (2017)[16], with code given by "empirical=FIRORES" and "empirical=root" respectively, and degrees of freedom equal to the number of communities minus the number of regression parameters. As of 5/12/2023, the ITT analysis of data from 67 communities and using the above negative binomial model, the degrees of freedom will be 60. The process for calculating the p-value for the hypothesis test for the treatment effect will be:

a) Fit the model in GLIMMIX using the "empirical=FIRORES" option, and extracting the estimated treatment effect and the estimated standard error,
b) Fit the model in GLIMMIX using the "empirical=root" option, and extracting estimated standard error,
c) Calculate the average of the standard errors from steps a) and b),
d) Calculate the t-statistic from the treatment effect value from step a) and divide it by the average standard error from step c),
e) Assume the degrees of freedom for the t-statistic calculated in step d) is equal to number of communities (67 or 66) minus number of regression parameters (7), and calculate the p-value for the t-statistic from step d).

In the unlikely event this estimator is computationally infeasible, we will use one of the following SAS options: "empirical=FIRORES", "empirical= FIROEEQ", or "empirical =DF".

The results of the model will be used to estimate and report:

- The adjusted relative rate (and 95% CI and p-value) of the rate of opioid OD deaths during the evaluation period between Wave 1 and Wave 2.
- The adjusted rate (and 95% CI) in the rate of opioid OD deaths during the evaluation period within Wave 1.
- The adjusted rate (and 95% CI) in the rate of opioid OD deaths during the evaluation period within Wave 2.

Note that adjusted rates and 95% CIs will be calculated using least squares means.

6.2.2 Covariates

Covariates that will be included in the models for the primary hypothesis will be the RS (KY, MA, NY, OH), the natural log of the baseline rate of opioid OD deaths, and rural/urban status.

6.2.3 Assumption Checks

It is possible that a Poisson model could be used in lieu of a negative binomial model. To evaluation this, the overdispersion parameter, k, of the negative binomial model will first be estimated using PROC GLIMMIX and its 95% CI will be estimated by refitting the model using PROC GENMOD as PROC GLIMMIX does not generate a CI for k. If the negative binomial is appropriate for the data collected, the value of k should reflect overdispersion and be a positive value, but if k is close to zero then GLIMMIX may fail to converge. If PROC GLIMMIX fails to converge, then k will be set to 0 and a working Poisson model will be fit to the data in PROC GLMMIX.

Other model assumptions such as linearity will be assessed by plotting residuals from the models against the value of the linear predictor (predicted outcome values), and residuals versus values of covariates employed in the models (e.g., baseline rate of opioid OD deaths). No obvious trends should be evident (i.e., uniform horizontal band present) and scatter of residuals should not depend on the linear predictor.

6.2.4 Alternate Analysis Methods

A negative binomial response is assumed (the overdispersion parameter $k > 0$). If this assumption does not hold, then a Poisson response may be adequate. If the negative binomial model does not fit adequately, as mentioned in Section 6.2.3, then k will be set to 0 and a Poisson model will be fit to the data.

6.2.5 Sensitivity Analysis

Morrow County, OH withdrew from the study post randomization but prior to the study initiation in January 2020. In response to this one and possibly more communities withdrawing from the HCS study and thereby yielding lower power for the subsequent PP analysis, additional power simulations were conducted to account for withdrawal scenarios. This section reports the findings from the additional simulations.

Table 3 below shows power estimates that were generated by considering the following:

- Morrow County, OH only withdraws from the HCS;

- Morrow County and one to four additional communities per RS per intervention arm combination withdraws from the HCS (from 8 to 32 additional communities).

These power calculations were conducted as described in Section 3.3 for the primary analysis power estimation. Based on these simulations, the withdrawal of Morrow County, OH does not affect the power of the study in a substantial manner, nor does the withdrawal of one or two additional communities.

Table 3. Power calculations for underlying reduction in the rate of opioid OD deaths during the evaluation period between Wave 1 and 2 communities, assuming numerous community drop-out scenarios. Empirical standard error estimates were utilized. Treatment allocation was not included in the initial model to extract parameter estimates, only covariates (RS and rural/urban status). A new treatment allocation was determined within each replication, balanced within RS (KY, MA, NY, OH; except for OH which has 19 communities).

Intervention Effect[1]	Relative Rate Of Opioid OD Deaths	Morrow ONLY[2]	1	2	3	4
40%	0.60	>0.999	>0.999	0.999	0.999	0.997
30%	0.70	0.995	0.993	0.992	0.982	0.968
25%	0.75	0.957	0.956	0.950	0.916	0.891
23%	0.77	0.927	0.916	0.907	0.869	0.835
22%	0.78	0.898	0.888	0.877	0.833	0.802
21%	0.79	0.869	0.863	0.846	0.801	0.770
20%	0.80	0.835	0.818	0.812	0.759	0.736

[1] Percent reduction in rate for Wave 1 versus Wave 2 communities.
[2] Scenarios in which only Morrow County, OH withdrew, with the addition of the potential withdrawal of 1, 2, 3 or 4 additional communities.

With this in mind, the primary analysis described in Section 6.2.1.1 will be replicated using a PP framework. In this case, the degrees of freedom that will be used for all hypothesis tests will be changed from 60 to 59 to account for Morrow County's withdrawal.

The following sensitivity analyses were also conducted after Version 3.0 of the SAP was implemented and results disseminated.

1. To assess the impact of using negative binomial or Poisson regression to model the rate of opioid overdose deaths during the evaluation period, we will compare the following:
    a. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a GEE-type negative binomial regression model.
    b. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a GEE-type Poisson regression model.
2. To assess the impact of using various functional forms of the baseline rate of opioid overdose deaths as a covariate, we will compare the following:
    a. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a model that uses the baseline rate of opioid overdose deaths as a covariate.

   b. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a model that uses the log of the baseline rate of opioid overdose deaths as a covariate.
3. To assess the impact of assuming that the effect of urban/rural status on the rate of opioid overdose deaths during the evaluation period is the same across research sites, we will compare the following:
   a. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a model that does not include an interaction between urban/rural status and research site.
   b. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a model that includes an interaction between urban/rural status and research site.
4. To assess the impact of assuming that the effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period is the same across research sites, we will compare the following:
   a. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a model that does not include an interaction between wave and research site.
   b. The effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period under a model that includes an interaction between wave and research site. In this case, the effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period is an average of the site-specific estimates of the CTH intervention on the rate of opioid overdose deaths.

To assess the impact of 2 or more of these assumptions on the effect of the CTH intervention on the rate of opioid overdose deaths during the evaluation period, we will also combine sensitivity analyses across these 4 types, resulting in a total of 16 sensitivity analyses.

6.2.6 Subgroup Analysis

There are 5 planned subgroup analyses using the following stratification variables:

- RS (KY, MA, NY, OH)
- Rural/urban status
- Sex (female, male, missing)
- Race/ethnicity (Black, Hispanic, White, Other)
- Age (18-34 years, 35-54 years, 55+ years)

For each subgroup, a separate model will be fit using the ITT framework. Each model will be similar to the model used for the primary analysis described in Section 6.2.1.1 but will also include fixed effects for the stratification variable as well as an interaction between wave and the stratification variable. When the stratification variable is sex, race/ethnicity, or age, RS and rural/urban status will also be included in the model as fixed effects. The subgroup analysis using sex, race/ethnicity, and age will need to account for repeated measures across the levels of the stratification variable within a community and so a Generalized Estimating Equation (GEE)-type negative binomial (or Poisson) regression model will be used.

Note that subgroup analyses for the community level variables, RS and rural/urban status, will use the same data structure as that used for the primary analysis. The subgroup analysis using sex, race/ethnicity, and age requires the data structure to be modified such that there is a separate record for each stratification variable level within a community. While design variables such as RS, rural/urban status, and baseline rate of opioid OD deaths will not change for each of these records, the dependent variable, offset, and baseline rate of the outcome of interest will need to be modified so that they are specific to each stratification variable level.

To account for multiple comparisons arising from subgroup analyses performed within this analysis, the FDR will be controlled for all effect modification interaction tests between wave and the stratification variable as well as pairwise tests between levels of a stratification variables using Benjamini-Hochberg (1995)[14] FDR-adjusted p-values using the following process:

- Step 1: All p-values from all interaction tests will be gathered together and the Benjamini-Hochberg (1995)[14] procedure will be applied to obtain FDR-adjusted p-values.
- Step 2: Amongst all interaction tests where the FDR-adjusted p-value is statistically significant at a 0.05 level, all p-values from all corresponding pairwise tests will be gathered together and the Benjamini-Hochberg (1995)[14] procedure will be applied to obtain FDR-adjusted p-values.

For each test of effect modification, adjusted rates within Wave 1 and 2 and the adjusted relative rate between Wave 1 and 2 within each level of a stratification variable (as well as 95% simultaneous CI using a Bonferroni correction that were added after Version 3.0 of the SAP was implemented and results disseminated) will be reported, in addition to the FDR-adjusted p-value associated with the interaction test.

- If the test for effect modification is not statistically significant at the 0.05 level, no further reporting will be performed.
- If the test for effect modification is statistically significant at the 0.05 level, the following will be reported:
    - estimate of the ratio of the relative rate between Wave 1 and 2 (as well as 95% simultaneous CI using a Bonferroni correction) between any 2 subgroups; and
    - pairwise FDR-adjusted p-value between any 2 subgroups.

6.3 Missing Data

The analyses for the primary hypothesis will be done using an ITT framework defined as the inclusion of all communities randomized into the HCS, analyzed according to intervention arm. There will be no missing data for the primary outcome of HCS main trial as all data will be obtained from administrative data sources. Multiple imputation or other missing data methods will not be performed to account for suppressed data at the subgroup level within a community (e.g., sex, race/ethnicity, age). In this case, subgroups with suppressed data will be excluded from the analysis and the amount of suppressed data will be summarized.

6.4 Additional Analyses

Additional analyses include those pertaining to the Opioid-overdose Reduction Continuum of Care Approach (ORCCA). The ORCCA consists of three menus of EBPs that were implemented in Wave 1 communities. Within each menu, EBPs were implemented in different combinations of strategies

(e.g., active opioid overdose education and naloxone distribution at high-risk venues), sectors (e.g., healthcare), and venues (e.g., healthcare-emergency department). Each strategy-sector-venue combination is referred to as a triad. A triad is the primary identifier for a strategy that is planned and then implemented within a community. For each triad that is selected by a community, respondents were asked specific questions relating to:

- intent to reach special populations;
- development of an implementation plan for the strategy;
- initiation of the implementation plan;
- the number of partner organizations/practices that are implementing the strategy; and
- a brief description of the strategy.

To summarize this information across Wave 1 communities, Table 6 (see Section 6.7) may provide frequencies and percentages of strategy and sector for each of Menu 1: Overdose Education and Naloxone Distribution (OEND), Menu 2: Medication for Opioid Use Disorder (MOUD), and Menu 3: Safer Prescribing. Summaries will be presented by RS (KY, MA, NY, OH), by geographic location (urban, rural), and overall. The table will only include summary statistics on menus that are relevant to the manuscript. For this manuscript, all menus will be summarized.

Depending on the scope of the manuscript, frequencies and percentages for specific strategy-sector-venue strategies may also be included. Inclusion will be informed by: 1) the ORCCA Overview, which maps outcome measures to ORCCA menus and strategies; and 2) the sector and venue definitions provided in Appendix D of the ORCCAT SOP, which were vetted by the Common Implementation Metrics workgroup.

After Version 3.0 of the SAP was implemented and results were disseminated, one additional analysis was conducted to estimate the effect of the CTH intervention of the relative rate of opioid overdose deaths between the evaluation and baseline periods. In this case, a repeated measures marginal model (similar to those described in Section 6.2.6 for age, sex, and race/ethnicity subgroup analyses) was fit to the number of opioid overdose deaths during the baseline and evaluation periods. Fixed effects included wave, research site, urban/rural status, time period (baseline or evaluation period), and a two-way interaction between wave and time period as well as an offset term given by the natural log of the community population size during the most recent year from available data. A residual covariance structure was specified to account for correlation among outcomes measured at baseline and evaluation periods within the same community. In this case, the effect of the CTH intervention was estimated using the ratio (and 95% CI and p-value) between the following two estimates:

- The adjusted relative rate (and 95% CI) of opioid overdose deaths between the evaluation and baseline periods in Wave 1 communities.
- The adjusted relative rate (and 95% CI) of opioid overdose deaths between the evaluation and baseline periods in Wave 2 communities.

After Version 3.0 of the SAP was implemented and results were disseminated, the study team requested an estimate of the number of “deaths averted” from implementing the CTH intervention in Wave 1. Two methods were used to estimate the number of deaths averted: (1) a crude method that does not account for overdispersion or covariates, and (2) a model-based average marginal effects method (Greene, 2000) using the estimated parameters from the negative binomial used for the primary analysis.

1. Crude method: apply the observed rate in Wave 2 communities (number of OOD deaths/population, the Wave 1 counterfactual) to the Wave 1 population. We then subtract the actual observed deaths from the Wave 1 counterfactual to get the estimated deaths averted.
2. Negative binomial based method: use the parameter estimates from the negative binomial model used for the primary analysis to estimate Wave 1 predicted deaths using Wave 2 parameters (Wave 1 counterfactual). We then used the Wave 1 parameters to estimate Wave 1 predicted deaths (Wave 1 as Wave 1). We subtracted the Wave 1 as Wave 1 from the Wave 1 counterfactual to get the estimated deaths averted.

6.5 Harms

In the HCS main trial, emergency medical service (EMS) runs for suspected opioid-related OD, as defined by each research site, were monitored as a safety measure. The four HCS RSs already had access to EMS runs that could be requested at monthly frequency, with a 15-day lag after the end of each month. The HCS estimated the rate of suspected opioid-related OD deaths by month in a community as number of events per 1,000community residents. In this manner, EMS runs provided the HCS main trial DSMB team with an early warning sign of an increase in the rate of opioid overdose deaths in HCS communities. A three-month moving average of the rate of opioid OD deaths was calculated using the EMS data. If a single month had an estimated rate that was more than three standard deviations above this moving average, then an adverse event (AE) was considered to have occurred. If a single month had an estimated rate that was more than four standard deviations above this moving average, then a serious adverse event (SAE) was considered to have occurred. The HCS also follows a metric-based approach to identify safety signals. If any of the following metrics are observed, a detailed review of the events will be conducted to evaluate their relatedness to the HCS. Monthly metrics are triggers observed in a single month across all communities: a) five AEs, b) two SAEs, or c) one SAE + three AEs. Cross-month metrics are triggers observed across all months in a single community: a) three consecutive AEs, b) consecutive AE and SAE. For final analysis, AE and SAE events and rates per 1,000 will be summarized by wave, RS, and wave by RS. Also, the actual number of opioid-related EMS OD runs and rates per 1,000 will be summarized by wave, RS, and wave by RS.

6.6 Statistical Software

The SAS statistical package (version 9.4 or higher) will be utilized for all analyses. The R software package may be used to create figures and other graphical displays.

6.7 List of Potential Displays

Listing of proposed table shells and figures for specified analysis.

- Figure 1: CONSORT Diagram
- Table 1. Baseline Demographic Characteristics of N=67 Communities Participating in the HEALing Communities Study by Wave (January 2019 – December 2019)
- Table 2a. Descriptive Means of the Rate of Opioid Overdose Deaths During the Evaluation Period in the Intention-to-Treat Population
- Table 2b. Descriptive Means of the Rate of Opioid Overdose Deaths During the Evaluation Period in the Per Protocol Population

- Table 3a. Descriptive Sums of the Rate of Opioid Overdose Deaths During the Evaluation Period in the Intention-to-Treat Population
- Table 3b. Descriptive Sums of the Rate of Opioid Overdose Deaths During the Evaluation Period in the Per Protocol Population
- Table 4. Effect of the CTH Intervention on the Rate of Opioid Overdose Deaths During the Evaluation Period
- Table 5. Modification of the Effect of the CTH Intervention on the Rate of Opioid Overdose Deaths During the Evaluation Period by Strata (RS, Rural/Urban Status, Sex, Race/Ethnicity, Age) in the Intention-to-Treat Population
- Table 6a. Actively Implemented Strategies from ORCCAT Menu 1: Overdose Education and Naloxone Distribution by Study Site for N=33 Wave 1 Communities Participating in the HEALing Communities Study
- Table 6b. Actively Implemented Strategies from ORCCAT Menu 2: Medication for Opioid Use Disorder by Study Site for N=33 Wave 1 Communities Participating in the HEALing Communities Study
- Table 6c. Implemented Strategies from ORCCAT Menu 3: Safer Prescribing by Study Site for N=33 Wave 1 Communities Participating in the HEALing Communities Study
- Table 7. Safety Outcomes by Wave and Research Site in the Intention-to-Treat Population
- Table 8. Protocol Deviations by Research Site in the Intention-to-Treat Population by Wave
- Other figures and tables that may be needed for didactic purposes.

7 REFERENCES

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8 APPENDICES

8.1 Appendix 1: Study Randomization

Table A1.1: HCS Wave 1 Communities

Wave	RS	CID	Community Name	Rural/Urban
1	KY	02	BOYD	Urban
1	KY	03	BOYLE	Rural
1	KY	06	CLARK	Urban
1	KY	07	FAYETTE	Urban
1	KY	08	FLOYD	Rural
1	KY	09	FRANKLIN	Rural
1	KY	13	KENTON	Urban
1	KY	15	MADISON	Rural
1	MA	18	BROCKTON	Urban
1	MA	19	PLYMOUTH	Urban
1	MA	20	GLOUCESTER	Urban
1	MA	22	SALEM	Urban
1	MA	23	HOLYOKE	Urban
1	MA	25	LOWELL	Urban
1	MA	28	BARNSTABLE (BOURNE/SANDWICH)	Rural
1	MA	32	MIDDLESEX (SHIRLEY/TOWNSEND)	Rural
1	NY	34	CAYUGA	Rural
1	NY	36	COLUMBIA	Rural

Wave	RS	CID	Community Name	Rural/Urban
1	NY	38	ERIE	Urban
1	NY	40	GREENE	Rural
1	NY	41	LEWIS	Rural
1	NY	44	PUTNAM	Urban
1	NY	45	SUFFOLK	Urban
1	NY	47	ULSTER	Urban
1	OH	50	ASHTABULA	Rural
1	OH	51	ATHENS	Rural
1	OH	53	CUYAHOGA	Urban
1	OH	54	DARKE	Rural
1	OH	56	GREENE	Urban
1	OH	57	GUERNSEY	Rural
1	OH	58	HAMILTON	Urban
1	OH	61	LUCAS	Urban
1	OH	62	MORROW	Urban
1	OH	64	SCIOTO	Rural

Table A1.2: HCS Wave 2 Communities

Wave	RS	CID	Community Name	Rural/Urban
2	KY	01	BOURBON	Urban
2	KY	04	CAMPBELL	Urban
2	KY	05	CARTER	Rural
2	KY	10	GREENUP	Urban
2	KY	11	JEFFERSON	Urban
2	KY	12	JESSAMINE	Urban
2	KY	14	KNOX	Rural
2	KY	16	MASON	Rural
2	MA	17	NORTH ADAMS	Urban
2	MA	21	LAWRENCE	Urban
2	MA	24	SPRINGFIELD	Urban
2	MA	26	PITTSFIELD	Urban
2	MA	27	WEYMOUTH	Urban
2	MA	29	BRISTOL (BERKELEY/DIGHTON/FREETOWN)	Rural
2	MA	30	FRANKLIN (GREENFIELD/MONTAGUE/ATHOL/ORANGE)	Rural
2	MA	31	HAMPSHIRE (BELCHERTOWN/WARE)	Rural
2	NY	33	BROOME	Urban
2	NY	35	CHAUTAUQUA	Rural
2	NY	37	CORTLAND	Rural
2	NY	39	GENESEE	Rural
2	NY	42	MONROE	Urban
2	NY	43	ORANGE	Urban
2	NY	46	SULLIVAN	Rural
2	NY	48	YATES	Urban
2	OH	49	ALLEN	Urban
2	OH	52	BROWN	Urban
2	OH	55	FRANKLIN	Urban
2	OH	59	HURON	Rural
2	OH	60	JEFFERSON	Urban
2	OH	63	ROSS	Rural
2	OH	65	STARK	Urban
2	OH	66	WILLIAMS	Rural
2	OH	67	WYANDOT	Rural

8.2 Appendix 2: Additional RS-specific inclusion criteria for communities enrolled in the HCS

Criteria	Kentucky	Massachusetts	New York	Ohio
Number of communities	16 counties	16 cities/towns	16 counties	19 counties
Additional criteria	Selected counties that had (1) a syringe service program (marker of community readiness), (2) a jail, (3) ≥1 buprenorphine-waivered provider, and (4) ≥5 opioid overdose deaths in 2017	Selected to minimize proximity and contamination, favored communities with an anchor office-based addiction treatment program and a pre-existing substance use coalition	Selected the communities of Buffalo in Erie County, Rochester in Monroe County, and the Brookhaven township in Suffolk County to keep size comparable	Randomly selected counties stratified by urban/rural that (1) were not contiguous and (2) did not share an alcohol, drug and mental health board

8.3 Appendix 3: SAS Code Examples

Exhibit 8.3.1: An example of SAS PROC GLIMMIX code to be used for the primary analysis of the primary hypothesis.

```
PROC GLIMMIX DATA=ALLCOMM empirical = FIRORES (or ROOT) MAXLMMUPDATE=100 ;

TITLE1 "NEGATIVE BINOMIAL MODEL BASED ON GLIMMIX";

MODEL NOPDEATHS = OPDEATH_BL SITE2 SITE3 SITE4 RURAL GRP_CODE /
OFFSET=LOGCOMM_POP ddfm = none ddf = 60, 60, 60, 60, 60, 60, 60, 60 DIST=NEGBIN S;
```

where:

NOPDEATHS = primary outcome, the number of opioid OD deaths during the evaluation period for each community

OPDEATH_BL = baseline rate of opioid OD deaths for each community

SITE2, SITE3, SITE4 = indicator variables for RS, referencing comparison to SITE = 1 (insert RS that = 1)

RURAL = rural/urban status for each community (1 = rural, 0 = urban)

GRP_CODE = intervention arm (1 = CTH intervention, 0 = wait-list control)

LOGCOMM_POP = natural log of community population size during the evaluation period, which is implicitly in the equation accounting for variation in population size, and hence the variation in denominators for rates among communities

DIST = NEGBIN signifies a negative binomial error structure; essentially allowing the underlying Poisson rate of opioid OD deaths during the evaluation period to vary across communities