METHODS SUPPLEMENT

Intervention Model

The intervention comprised the two sets of strategies summarized below. The first included those offered to *community-based opioid analgesic misuse and abuse prevention coalitions,* and the second comprised those primarily offered to *health care providers*. The intervention was implemented starting in March 2013. Data collection for this evaluation included pre-intervention years for baseline starting in January 2007 and covered available data through December 2014. Dichotomous intervention variables were constructed for each strategy for each county-month, with '0' indicating no activity and '1' indicating implementation activity.

Continuous measures of implementation were explored, but were untenable because of data quality concerns. Additionally, the utilization of differing data sources for each strategy, and the specificity of activities captured by strategy, necessitated a simplified model of implementation in order to enable comparable definitions of implementation. An alternate three-level exposure model, with an intermediate planning-only indicator, was also explored. Because it yielded similar results while decreasing precision, it was not considered further.

Further details about the statewide implementation of the Project Lazarus model can be found in:
Brason FW II, Castillo T, Dasgupta N, Ferrell N, Irwin J, Mack K, McEwan S, Patkar A, Smart A, Thomas A, Varnell D. Sanford C, Ringwalt C, McCort A, eds. Lessons learned from Implementing Project Lazarus in North Carolina (2016). Injury Prevention Research Center, University of North Carolina. Available at: https://iprc.unc.edu/files/2016/08/Lessons-Learned-White-Paper-FINAL-8-15-16.pdf ; accessed May 25, 2017).

Table 1. Intervention strategies, data sources, and implementation criteria.

Strategies offered to community coalitions		Data Sources	Implementation criteria
1.Community education	Implement community- and school-based prevention education; Red Ribbon and billboard campaigns that include warnings not to share medications; radio and newspaper spots; and presentations at community-based and stakeholder forums to raise awareness concerning the problem of prescription drug overdose	Surveys of coalition leaders	Coordinators reported awareness meetings and community trainings
2. Diversion control	Collect unused medications during pill "take-back days"; fixed disposal sites in public locations; training of specialized law enforcement officials in the prevention of drug diversion	Data from unused medication take-back events; trainings of law enforcement on diversion control practices, based on process logs	Coordinators reported takeback events, new permanent drop box installation, or take-back events that were recorded by *Operation Medicine Drop*
3. Support programs for	Develop support groups and other extra-clinical services for patients with pain and supervision of local pain clinics; vet	Surveys of coalition leaders	Coordinators reported any support groups active in the area

patients with pain	local pain clinics for referrals; education for patients with pain on reducing risks of overdose		
Strategies offered to health care providers		Data Sources	Implementation criteria
4. Provider education	Provide large-group training sessions on pain management with continuing education credits for prescribers; face-to-face meetings and follow-up medical-peer education on the management of chronic pain and appropriate opioid prescribing; and dissemination of physician and case manager tool kits that contain information on: (a) screening and assessment for chronic pain and substance abuse; use of SBIRT (screening, brief intervention and referral to treatment) for patients with problematic alcohol or drug use; and referral of patients with pain and opioid use profiles to care management specialists, including active follow-up for all referrals to specialists; and (b) management of patients with chronic pain, including clinical pain management algorithms, patient-prescriber pain management agreements, education of patients and their families, clinician education about prescribing naloxone to patients at risk of opioid-induced respiratory depression; monitoring and referral to specialized treatment, including enhanced use of the PDMP; referral to the Medicaid “Lock-In” program for Medicaid patients with high numbers of opioid prescribers and prescriptions	Records from prescriber training and surveys of coalition leaders	Coordinators reported any meetings with hospitals and provider trainings, educational visits to Medicaid clinics; the Governor’s Institute reported training on Substance Abuse
5. Hospital ED policy change	Promote opioid prescription policies in hospital EDs that include limits on the amounts of controlled substance dispensed and require the provider to check their patient’s prescription history on the PDMP	Surveys of coalition leaders	Coalitions reported adoption or implementation of any new hospital ED policy

6. Expanded access to drug treatment	Increase the availability of and access medication assisted treatment (clinic- and office-based), and trainings to increase the number of providers authorized to prescribe buprenorphine for office-based addiction treatment.	Outpatient pharmacy-dispensed prescriptions for oral buprenorphine and data from admissions to drug treatment facilities	County was in the highest tertile of rates of patients receiving oral buprenorphine or methadone maintenance
7. Naloxone policies	Develop local policies facilitating naloxone distribution for patients at high risk for overdose and nonmedical opioid users, provide naloxone kits and education as to their appropriate use with their families and peers, and develop overdose plans that include the recognition of signs and symptoms of an opioid overdose and techniques to reverse it while awaiting emergency assistance.	Surveys of coalition leaders (Naloxone reversals were *not* quantified to assess the direct impact of take-home naloxone programs.)	Coalitions reported a change in community naloxone policy, Coordinators reported a local government agency passing a new naloxone policy, or Coordinators reported new community-based naloxone programs

Data Sources and Definitions

Surveys

Community-based coalitions were identified at the time they were funded by Community Care of North Carolina (CCNC). Contact information was used to email each coalition leader a periodic web-based survey that included questions concerning what activities they had planned and implemented, for each month included in the reporting period, related to each of the seven strategies constituting the Project Lazarus model. Survey completion was a condition of funding.

Also surveyed were regional coordinators supported by CCNC, the State's administrative Medicaid agency. Each of these periodically specified, by means of a web-based survey, activities related to these seven strategies that they had implemented in each of the months covered by the reporting period.

Overdose Mortality

Mortality records are made available via the Howard W. Odum Institute for Research in Social Science at UNC by the NC State Center for Health Statistics (NCCHS). Vital records in NC have used ICD-10 since 1999. Based on the method used at NCDPH, a definition of opioid overdose deaths was used that included a broad combination of mental health (F) and external cause of mortality (X, Y) codes, and poisoning codes (T) to identify specific substances. The included cause-of-death codes were: F11.0, F12.0, F13.0, F14.0, F15.0, F16.0, F19.0, X40-X44, Y10-Y14. Because more detailed toxicology data is not available in the publicly available dataset, drug overdose deaths are limited to the specificity available in ICD-10: opium, heroin, "other opioids," methadone, other synthetic narcotics, and other and unspecified narcotics (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6, respectively).

Table 2. Definitions for overdose mortality, North Carolina, 2009-2014

Unintentional and undetermined opioid overdose mortality definitions

1.	Any diagnosis of:	F11.0
2	Any diagnosis of:	F12.0, F13.0, F14.0, F15.0, F16.0, F19.0X40, X41, X42, X43, X44 Y10, Y11, Y12, Y13, Y14
	AND one of:	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6

Overdose-related ED Visits

NC DETECT was created by the NC Division of Public Health to address the need for early event detection and surveillance, utilizing timely electronic data from a variety of sources. It includes electronic data from the state's non-federal hospital-affiliated acute care emergency departments. Data elements included: date/time of visits, patients' county of residence, final diagnostic codes, and discharge disposition.

The North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) is an advanced, statewide public health surveillance system. NC DETECT is funded with federal funds by North Carolina Division of Public Health (NC DPH), Public Health Emergency Preparedness Grant (PHEP), and managed through a collaboration between NC DPH and the University of North Carolina at Chapel Hill Department of Emergency Medicine's Carolina Center for Health Informatics (UNC CCHI). The NC DETECT Data Oversight Committee does not take responsibility for the scientific validity or accuracy of methodology, results, statistical analyses, or conclusions presented.

Data from NC DETECT comprised of records of ED visits using a broadly defined definition of overdose based on International Classification of Disease 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes and external cause of injury codes (E-codes) that include any of [965.0 (965.00-.09); E850.0-E850.2] This case definition was developed by the Injury and Violence Prevention Branch (IVPB) of the NC Division of Public Health (DPH), in conjunction with CCHI, to yield "Acute overdoses involving any illicit or prescription opioids, taken for any intent."

For morbidity models, ED visits were scaled using a county-month inverse "probability of transmission" weight, with corresponding rescaling by the mean inverse weight to adjust the standard errors. The "probability of transmission" weights reflect the occasional lapses in transmission in ED data to NC DETECT, due to upgrades and other changes in hospital information technology systems, etc.

Prescription Data

Data from the Controlled Substances Reporting System (CSRS, the state's Prescription Drug Monitoring Program or PDMP) were used to construct county-month counts of patients and prescriptions for opioid analgesics. These state government-run programs are electronic databases that can be queried at the point of care by clinicians to review a patient's history of receiving controlled substances. Selected law enforcement officers and medical examiners are allowed access to the database when they are investigating specific cases. PDMPs are funded largely by federal grants through the Department of Justice, supplemented by funding from state governments. Data on all outpatient controlled substance prescriptions dispensed in North Carolina were captured by the CSRS starting January 2009, and provided by the NC Division of Mental Health, Developmental Disabilities, and Substance Abuse Services (DMHDDSAS). Data are generated when a prescription for a controlled substance is dispensed at regulated pharmacies in North Carolina. The data captured comprised each field of information legally required to be included in a North Carolina prescription for a controlled substance. The data are stored locally at the pharmacy and transmitted periodically to a central

database. These data included unique identifiers for prescribers, dispensers, and patients; location (county level); quantity, dose, days supply, and National Drug Code of the prescription; and age and sex of the patient.

The raw data were tabulated by active pharmaceutical ingredient (API) and dosage form (e.g., solid oral, patch) for opioid analgesics. Opioid analgesics were defined as solid oral, transbuccal, or transdermal formulations containing codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone and oxymorphone. Prescriptions with APIs comprising the top 99.9% of all prescription records were retained; data cleaning removed non-controlled substances and appended metadata on drug class. Patients were assigned a unique identification number provided by the database vendor (Health Information Designs, Auburn, Alabama, USA), which takes name, date of birth, and residential ZIP code into account, and was provided as a one-way hash algorithm and was continuous over data-years.

Addiction treatment data

Data on drug treatment admissions was available from the NC Treatment Outcomes and Program Performance System (NC-TOPPS), the statewide system for quality and outcomes monitoring. Data on past and recent drug use history and counts of patients entering methadone treatment were collected for all residents entering participating treatment programs. De-identified patient-level data were obtained for NC residents, aged 18 years or older, receiving services for substance-related disorders from January 1, 2009 through December 31, 2014. Variables collected in the Adult Initial Interview form version 7/01/2012 included date of the initial interview (month and year), consumer's county of residence, and methadone treatment information. In models, this data source was used to quantify methadone maintenance admissions. To create the addiction treatment strategy variable, NC-TOPPS-derived counts of the number of methadone patient admissions (mostly urban areas) were added to PDMP-derived counts of the number of patients receiving outpatient pharmacy prescriptions for oral buprenorphine (common in non-urban areas), to calculate population-based rates of treatment utilization for opioid substitution therapies. Caveats include that some patients may receive Subutex and Suboxone for pain management, and in-clinic dispensing of buprenorphine, in addiction treatment programs, which we could not capture, also occurred. The extent of misclassification from these caveats is unknown.

County Health Status

In order to control for fundamental differences in health status between counties (e.g., "healthy county effect") and over time, a construct from the Robert Wood Johnson Foundation (RWJF) County Health Rankings was used. This "county health factors" variable is a composite Z-score which comprises health behaviors, including tobacco use, diet and exercise, alcohol and drug use, and sexual activity; clinical care, including access to and quality of care; social and economic factors, including education, employment, income, family and social support, and community safety; and physical environment, including air and water quality, housing and transit. This was available for 2010 onwards; for 2009 the data from 2010-2016 were used to linearly extrapolate county months. Annual data were linearly interpolated to generate county-month scores.

Law enforcement trainings and drug disposal sites

Counts of training and disposal events and the number of active permanent drop-boxes were abstracted by county-month from multiple sources. Trainings were intended to inform local law enforcement on drug diversion control measures. Locations and dates of NC State Bureau of Investigations (SBI) trainings for law enforcement officers were abstracted from training records provided by SBI. Data were available starting in 2011. Disposal events and disposal boxes were intended to reduce the community-level supply of unused medications.

Statistical Models

Model Form

The general form of the Poisson regression model is given below. For mortality and morbidity outcomes separately, immediate impact models were defined as:

$$\text{Rate} = \ln(a/n) = \ln(a) - \ln(n)$$

$$\Rightarrow \ln(a) = \beta_0 + [\beta_1 X_1 + \ldots + \beta_7 X_7] + [\beta_8 X_8] + [\beta_9 X_9] + [\beta_{10} X_{10}] + [\beta_{11} X_{11} \ldots \beta_{13} X_{13}] + \ln(n)$$

Where a is a mortality or morbidity count, and β_0 is the intercept.

$[\beta_1 X_1 + \ldots + \beta_7 X_7]$ are the dependent (exposure) variables that designate the presence or absence of the seven intervention strategies for any given month and county. Each strategy is represented as dichotomous variable with no implementation as the referent (coded 0), and implementation (coded 1).

$[\beta_8 X_8]$ is the county-month rate of outpatient prescriptions dispensed for opioid analgesics in units of 1,000, with total resident population as the denominator.

$[\beta_9 X_9]$ is the county health status variable of linearly interpolated annual z-scores of Health Factors from RWJF County Health Rankings. This variable is a marker for general community health status and was included to control for potential confounding by changes to general community health status over time and between counties.

$[\beta_{10} X_{10}]$ is a variable for calendar year included to remove linear trends over time, “secular” effects.

$[\beta_{11} X_{11} \ldots \beta_{13} X_{13}]$ is an indicator variable for seasonality, implemented with indicator coding for spring, summer and fall, with winter as the referent. These variables are included to de-trend for seasonal effects on overdose incidence, which was observed in preliminary data analysis. For opioid overdoses in 2010, a Walter and Elwood analysis of seasonality using the exact method test suggested the presence of seasonality (chi-square 5.8, p=0.05, 2 df) with a peak in March (82.9 degrees) and good model fit (chi-square 17.1, p=0.10, 2 df). Seasonality persisted after taking background deaths into account (chi-square 8.8, p=0.032, 2 df), with good model fit (chi-square 13.3, p=0.272, 2 df), but reaffirmed that the peak was in late May (147.4 degrees) for opioid deaths relative to all other deaths.

The offset term ln(n) is the denominator for rate calculations, and consists of the resident population of the county. Annual population was obtained from the National Center for Health Statistics and linearly interpolated by month.

To quantify the effect of each of the seven intervention strategies (coded as one dichotomized variable per strategy, i.,e., $[\beta_1 X_1 + \ldots + \beta_7 X_7]$), incidence rate ratios (IRRs) were calculated directly from the model parameters. IRRs were estimated by taking λ_1/λ_0 or λ_2/λ_0 where λ_0 represents the mean rate in counties where no implementation/planning occurred, and λ_1 is the mean rate of the dependent variable in counties where strategies has been either planned only, and λ_2 for implementation (regardless of planning). These IRRs were estimated from the model by exponentiating the relevant beta coefficient for the particular strategy of interest. The exponentiated intercept $\exp(\beta_0)$ can be interpreted as the baseline rate in the referent group, i.e., the rate of the dependent variable in the counties that have not implemented any of the components ($X_1 = X_2 = X_3 = \ldots = X_7 = 0$). If all 7 indicator variables ($X_1, X_2 \ldots, X_7$) are included in the model then one is able to estimate the effectiveness of each of the seven strategies while controlling for the presence of all the other interventions. As is standard, 95% confidence intervals for the rate ratio were computed on the $\log_e$ scale and then back-

transformed. Unadjusted models considered each intervention strategy alone (as separate models), whereas the two final adjusted models (mortality and morbidity) considered all interventions simultaneously.

Two metrics were used to select the best-fitting immediate effect models: overdispersion measures and goodness of fit. Dispersion was evaluated using the inverse degrees of freedom for deviance and Pearson chi-squared from models. Goodness-of-fit was assessed using Akaike and Bayesian information criterion (AIC and BIC), with smaller values indicating better fit relative to an intercept-only model. We assessed over-dispersion using Deviance and Pearson's chi-square divided by its degrees of freedom, and used scaled dispersion parameters to account for overdispersion. In order to implement GEE, the command XTPOISSON in Stata IC, version 13 (College Station, Texas, USA) was used, along with adjustment for OA dispensing rate, county health factors, year, and seasonality. In models with ED visit outcomes, the scaling parameters necessitated by models with overdispersion were multiplied by the mean inverse probability weight of the outcome, as described above.

Intervention Funding

Funding for intervention implementation came from eleven sources. Funding for implementation in the central and eastern parts of the state came from Kate B. Reynolds Charitable Trust (KBR), a private foundation, and the NC Office of Rural Health (ORH), a state government agency under the Department of Health and Human Services, and provided to Community Care of North Carolina (CCNC), the State's Medicaid authority, for administration and distribution through the Foundation for Health Leadership and Innovation. Funding for implementation in the western part of North Carolina came from the Center for Medicare and Medicaid Services as a Health Care Innovation Award (Grant 1C1CMS331019) administered by the Mountain Area Health Education Center (MAHEC), a regional medical services provider. Pilot implementation funding was provided by the Northwest Community Care Network (NCCN), a regional Medicaid administrator, for six western counties, 2008-14. In addition, partial funds for implementation in 11 counties were provided through the White House Drug-Free Communities Support Program. In the eastern part of the state, five additional counties received implementation funding from the Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Prevention (CSAP). The North Carolina Coalition Initiative (NCCI) provided coalition development funds for seven counties in 2013-4; funding originated from NC Department of Health and Human Services, Division of Mental Health, Developmental Disabilities and Substance Abuse Services (DMHDDSAS), and was administered through the Coordinating Center at the Wake Forest School of Medicine. The Open Society Foundations (OSF) provided funding for development of engagement materials suitable for military settings and coalition efforts in one county. Implementation funding in 2013-4 also came from CDC via CORE Violence and Injury Prevention Funding to the North Carolina Division of Public Health, Injury and Violence Prevention Branch, and distributed to local health departments for coalition development and implementation of intervention activities. Additional funding for coalition development and statewide trainings on the implementation model and the specialized program for the Eastern Band of Cherokee Nation reservation were provided as an unrestricted educational grant from Purdue Pharma (Stamford, Connecticut, USA) to the nonprofit organization Project Lazarus (Moravian Falls, North Carolina, USA). Covidien Mallinckrodt (St. Louis, Missouri, USA) provided funding for fixed disposal bins for unused medication. No pharmaceutical companies participated in the design or allocation of the intervention, evaluation, manuscript preparation, review or decision to publish.