ATTACHMENT C1

Summary of Previous Epi-Aid DORIs

West Virginia – Response to increase in overdoses with unknown risk factors: In 2006 the West Virginia Department of Health and Human Resources (WVDHHR) contacted CDC for assistance with an investigation of a continued and steady rise in unintentional poisoning deaths from the use of prescribed, controlled medications, specifically prescription narcotics (painkillers), in residents. Prescription painkillers are typically prescribed by primary care and internal medicine physicians, dentists, and sometimes specialists. Once they are prescribed and dispensed, prescription painkillers are frequently diverted to people using them without prescriptions. Prescription painkillers work by binding to receptors in the brain to decrease the perception of pain. These powerful drugs can create a feeling of euphoria, cause physical dependence, and, in some people, lead to addiction. Prescription painkillers also cause sedation and slow down a person's breathing. A person who is abusing prescription painkillers might take larger doses to achieve a euphoric effect and reduce withdrawal symptoms. These larger doses can cause breathing to slow down so much that breathing stops, resulting in a fatal overdose. The CDC team traveled to West Virginia to support the WVDHHR with their epidemiologic investigation of drug poisoning fatalities to identify the drugs involved, the health of the decedents, and the decedents' prescription drug utilization practices (e.g., possible indications for use, frequency of use, route of administration, and nonmedical use) to implement appropriate measures to prevent further overdoses.

The team collected or reviewed data at several different steps as the investigation progressed. The data needs at each step were dependent on and dictated by the results of the previous steps. The investigative steps included:

- Develop a Case Definition: A case was identified as a death of a WV resident occurring in WV in 2006 whose underlying cause was an unintentional drug poisoning (International Classification of Diseases, 10th Revision [ICD-10] codes X40-X44) as listed on a death certificate.
- Abstraction Form and Database Creation: An abstraction form was prepared and adapted into a relational database, comprised of two linked datasets; one for decedent information and the other for drug specific information for those drugs listed as contributory to death in the autopsy report.
- Identification of Drug Poisoning Cases and Ascertainment of Case Records: Cases were identified by searching an electronic database of vital records at WVDHHR for all deaths with an underlying cause of death ICD-10 code of X40-X44. A list of cases was created and compared to cases seen at the Office of the Chief Medical Examiner (OCME). Decedent records were obtained from the OCME files and abstracted on site. The Board of Pharmacy (BOP) was also queried for reports for each decedent meeting case definition criteria to obtain information about controlled substance dispensation.
- Abstraction of Data Elements: Abstractors worked in the field during a 10-day period to obtain information from autopsy reports, toxicology reports, death scene investigation reports, death certificate supplements, medical records, and BOP reports.
- Analysis: Analyses were conducted to assess (a) drug misuse and abuse in overdose deaths using associated risk factors (e.g., presence of street drug on toxicology, use of injection, lack of prescription, history of substance abuse, inappropriate number of prescribers); (b) pain and its treatment, (c) mental illness and its treatment, and (d) methadone treatment. Analyses also made use of postmortem findings including blood

concentrations of drugs, contributory autopsy findings, list of problems, routes of administration, history of cardiovascular or pulmonary disease, metabolites, and height and weight.

In this investigation, the team was faced with prescription drug overdose events with unknown risk factors. To understand the epidemiology of the events, the team needed to gather data to confirm the existence of such events, find case-patients, obtain confirmatory autopsy, toxicology, and medical records, and conduct analyses. Based on the results of these steps, the team recommended distribution of basic descriptive epidemiologic information about the drug poisoning epidemic to health professionals and law enforcement officials; development of a statewide task force to address the problem of unintentional drug poisonings; and support of the state Board of Pharmacy with the resources and guidance necessary to use information on the prescribing of controlled substances to track the problem, proactively identify exceptional prescribing practitioners, dispensing pharmacists, and users of controlled prescription drugs, and monitor future control efforts.

Rhode Island – Response to increase in overdoses with rare/unknown cause: In 2014 the Rhode Island Department of Health (RIDoH) contacted CDC for assistance in investigating an increasing number of deaths due to drug overdose. From 2009 to 2012 the total number of unintentional overdose deaths rose steadily from 137 to 182. This was mostly associated to an increase in deaths due to non-prescription, illicit drugs. Deaths due to these substances rose from 53 to 97 throughout this 4-year period. Since January 1, 2014, Rhode Island experienced twice as many overdose deaths as in equivalent time periods during previous years. From January through March 2014, approximately 50 overdose deaths occurred with 44 having toxicology reports completed. Findings from the toxicology reports for the majority (n=31) of these deaths revealed the presence of fentanyl, a synthetic opioid that is 50 to 100 times more potent than morphine and 30 to 50 times more potent than heroin.

The objective of the investigation was to define and characterize recent illicit fentanyl-related overdose decedents to allow RIDoH to target educational messages and reach out effectively to at-risk populations to prevent and control fentanyl-related overdose deaths in Rhode Island in the immediate future. The focus of the study was to characterize persons involved in the recently reported increase in fentanyl-related overdose deaths in Rhode Island, compare the extent and pattern of recent fentanyl-related overdose deaths in Rhode Island with historical data, identify risk factors associated with fentanyl-related overdose deaths in Rhode Island, and identify fentanyl-related overdoses seen in Rhode Island Emergency Departments and through Emergency Medical Services, and identify naloxone administration.

To meet these objectives, the EpiAid team collected data on fentanyl and non-fentanyl-related drug overdose deaths reported in Rhode Island during early 2014 (January – March, 2014). For comparison purposes, data were also collected from 2 years prior to the outbreak (i.e., January 1, 2012 – December 31, 2013). The investigative steps included:

- Development of a Case Definition: Fentanyl cases were defined as a death for which fentanyl was listed as an official cause of death or contributor to the cause of death; or, if the cause of death was pending or non-specific, toxicology reports should have identified fentanyl levels to be above the ELISA detection limit ($\geq$ 2 ng/ml). Non-fentanyl controls were defined as a death for which fentanyl was NOT listed as an official cause of death or contributor to the cause of death; or, if the cause of death was pending or non-specific,

fentanyl should not have been detected by ELISA. Suicides, *in absentia* medical examiner reviews, and children ages 0-15 years were excluded from this study.

- Abstraction Form and Database Creation: A data extraction form was developed and adapted into a relational. It collected information about the person (i.e., case or control), and the drug overdose incident. Specifically, variables are categorized as follows: socio-demographics, history of drug use, medical history, incident/scene factors, toxicology, and law enforcement-related data.
- Identification of Cases/Controls and Ascertainment of Records: Data were abstracted from RI's Office of the State Medical Examiners' (OSME) charts and Vital Records. Additionally, data was abstracted from RI's Prescription Drug Monitoring Program (PMP) to determine whether the decedents had been exposed to prescription fentanyl. PMP records were available for the majority (90.7%) of all decedents included in this case control study.
- Abstraction of Data Elements: Abstractors worked in the field during a 16-day period to obtain information from autopsy reports, toxicology reports, death scene investigation reports, death certificates, medical records, police reports, emergency medical services records, and PMP reports. It was supplemented by preliminary Real-time Outbreak Disease Surveillance (RODS) system data.
- Analyses: Descriptive analyses were conducted for all drug overdose deaths, fentanyl cases and non-fentanyl controls, for all time periods. Frequencies and proportions were calculated for all variables, and bivariate comparisons were made between cases and controls utilizing cross-tabulations and Chi-square analyses. Multiple logistic regression methods were utilized to assess the relationship between variables identified as risk factors for fentanyl related drug overdose deaths (binary dependent variable). Epi-curves were used to describe the trend of cases and controls across the time periods. Similar analyses were conducted to distinguish the fentanyl source (i.e., illicit source or prescription), based on PMP data. Additionally, PMP data were used to calculate the morphine milligram equivalent per day (MME/day) for each patient over a maximum of 7 years prior to their date of death. Associations between MME/day, and heroin and/or fentanyl-related deaths were explored.
- Meetings with Key Informants: In addition to intensive data extraction and analyses, the team met with representatives from local public health, healthcare, law enforcement, private and nonprofit agencies, and representatives from the U.S. Drug Enforcement Administration (DEA), to better understand RI's current drug overdose monitoring and prevention efforts.

Throughout the January 2012-March 2014 study period, an increase in Fentanyl cases – especially near the Providence high population density area – was noted. Fentanyl cases accounted for the largest proportion of all drug overdose deaths in RI during the outbreak period (Nov 2013 – Mar 2014). These findings were presented to representatives from the RIDoH, and the Office of the State Medical Examiners (OSME). In response, CDC: (a) provided technical support to RIDoH in developing an emergency regulation to mandate the reporting of all opioid overdose cases treated at Emergency Departments statewide; (b) shared a summary of this EpiAid's preliminary key findings and talking points on opioids overdose and dependence, to support RIDoH media outreach efforts; (c) emphasized the importance of administering naloxone as a first response mechanism during opioid drug overdose incidents, and recommended that RIDOH continues and expands its efforts to make it accessible for prior drug overdose patients and their families; and (d) supported RIDoH's Emergency Medical Services (EMS) team in updating their intake form to allow EMS personnel to record the dose/amount of

naloxone administered during each incident reported. Findings from this investigation will also be submitted for publication in relevant journals to inform future research in the intersection of prescription drug overdose and comorbid illness.

New Mexico – Response to overdoses with unknown risk factor: In 2014 the Office of the Medical Investigator (OMI) in Albuquerque, New Mexico contacted CDC for assistance in investigating a large number of reports of heavy snoring documented in the medical charts of recently deceased prescription drug overdose victims. Chronic opiate use can increase central sleep apnea events and worsen obstructive sleep apnea events; however the connection between sleep symptoms, apnea, and overdose risk is unclear. NM posed the question of whether individuals known to take opioid medications could be identified as an impending overdose by characteristic sleep pattern changes, snoring, or other sleep breathing events. The question was also raised whether patients at risk for obstructive sleep apnea or central sleep apnea who are prescribed opioid medications could be identified as particularly at risk for prescription drug overdose. If this were the case, interventions could be established targeting friends or family of these patients to look for changes in sleep patterns or changes in sleep habits and breathing behavior. Furthermore, educational opportunities could arise empowering families to identify overdoses more rapidly and calling EMS systems who could respond with ventilatory support or reversal medications such as naloxone.

The objectives of the investigation were (1) to characterize the baseline health of patients suffering PDO deaths; (2) to identify co-morbid illnesses of particular risk for contributing to prescription drug overdose; (3) to identify whether there were any reports of sleep disturbances or particularly sonorous or other abnormal respirations preceding or at the time of the fatal overdose, (4) and to identify a patient sub-group where opportunity might lie for early overdose identification and lifesaving interventions.

To meet these objectives, a retrospective descriptive analysis was conducted using OMI autopsy records. All unintentional overdose deaths within the state of New Mexico, in the year 2012, occurring among people 10 years of age or greater were considered for the study. For the purposes of this study, intentional overdoses, were excluded. The study specifically investigated the commonalities and comparisons of prescription opioid mediated deaths to those deaths mediated by heroin. The investigative steps included:

- Development of a Case Definition. A case of prescription opioid overdose death was defined as a unintentional death, determined by medical examiner to be caused by acute drug overdose, with the presence of prescribed narcotic compounds on post- mortem toxicologic screening. A heroin overdose death was an unintentional death, caused by heroin, as determined by medical examiner, with heroin or heroin metabolites in post-mortem toxicologic screening. Cases where both heroin and prescription opioids were found were excluded from this comparative study.
- Abstraction Form and Database Creation:. Epi-Info 7.1 was used to create a questionnaire for use in data abstraction. Major categories included were demographics, death scene report, circumstances of death, past medical history, chronic and acute sleep disturbances as reported by witnesses, details from the autopsy, and the major substances found on toxicology screening.
- Identification of Cases/Controls and Ascertainment of Records: The OMI identified all overdose deaths for the study period using the state mortality database. All vital records

are held at the OMI offices, and abstractors were given institutional permission to review records on-site and given all-hours access to the buildings with magnetic card access.

- Abstraction of Data Elements: Both the electronic record (autopsy report, death scene report, and toxicology) as well as the physical record (outside medical records, law enforcement reports, information later added) were reviewed. Data was inputted into the Epi-Info database. Between January 20th to Feb 2nd, 2014 CDC investigators reviewed and abstracted 489 records.
- Analyses: Preliminary analysis was conducted on site. Basic demographic and mortality descriptive epidemiology was shared with stakeholders during a debriefing session at OMI offices prior to the team's departure. Upon return to Atlanta, the data was cleaned and analyzed using SAS 9.3. Further descriptive epidemiology was performed on rates of pre-existing medical conditions, mental illness, substance abuse or dependence problems, and the presence of known sleep disorders. Odds ratios were calculated for the comparison of death by prescription opioids versus heroin by univariate analysis using exact methods.

During the study period there were 489 unintentional overdose deaths, of which 41% were caused by prescription opioids and 15% were caused by heroin. It was found that prescription opioid overdose victims were generally older, heavier, and had more pre-existing medical conditions than did the heroin overdose victims. There was a statistically significant association of snoring heard within 24 hours of death to prescription opioids, despite there being no differences in the odds of pulmonary diseases, diagnosed obstructive sleep apnea, or chronic snoring. The results of the investigation were shared with the New Mexico Office of the Medical Investigator and the New Mexico Department of Health. The state authorities plan to incorporate these findings into their efforts to increase the size of their naloxone co-prescription and community distribution programs. The findings of this study were presented to the national EIS conference, and were highlighted in the press as part of Dr. Tom Frieden's winnable battle against prescription drug overdose. Findings from this investigation will also be submitted for publication in relevant journals to inform future research in the intersection of prescription drug overdose and comorbid illness.