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*Center for Health Law,
Policy and Practice*

**CLOSING DEATH'S DOOR:
ACTION STEPS TO FACILITATE EMERGENCY OPIOID
DRUG OVERDOSE REVERSAL IN THE UNITED STATES**

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Disclaimer

The views expressed in this White Paper are those of the authors and do not necessarily reflect the views of the Temple University Beasley School of Law or the Drug Policy Alliance.

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My daughter died of a heroin overdose on November 5, 2005. It is just possible that if she had access to Naloxone in her home and her fiancé was able to give it to her, she might be alive today. . . I testified in Sacramento to get a pilot program started in California. Administering Naloxone may save a life and give someone a second chance at life and rehabilitation.

- Mother of Jennifer Carol Lee¹

Through a support group, I got to know people who have used naloxone to save their children during an opioid overdose, so when I had a chance to obtain some at the meeting, I did. Our son overdosed on heroin in April, 2009. We discovered him in his room, turning gray with a respiration rate of barely 3 breaths per minute. After trying in vain to wake him up, we administered naloxone. He started breathing very slow, ragged breaths. The ambulance took 12 minutes to arrive and if my husband and I had not administered the drug, our son would have probably been dead or severely brain damaged from the lack of oxygen. The police and the hospital were really, really (and not in a good way) interested in where we got the drug and how we knew how to use it.

- Mother of Michael

Executive Summary

Opioid Overdose is a Major Public Health Crisis

Having overtaken such high-profile causes of death as AIDS and homicide, drug overdose is quietly competing with vehicular accidents as a leading cause of accidental injury death in this country. Opioid drugs are driving this surge, contributing to the loss of well over 16,000 Americans every year. Beyond the dedicated work of a small group of public health officials, researchers and practitioners, the government and the broader public health community have been slow in taking stewardship of this crisis.

The rising death toll has several causes. Heroin users are at risk of opioid overdose because of the fluctuating potency and adulteration of street drugs, as well as changes in tolerance after a period of abstinence, such as time spent in jail or drug treatment. With better availability of opioid pharmaceuticals to treat serious pain, prescription drugs have become a substantially bigger source of overdose risk, though research on the key risk factors for pharmaceutical opioid overdose, its circumstances, and successful intervention strategies remains too sparse. Although more research is needed, it is abundantly clear that timely, coordinated, and well-balanced action is necessary to assure that society can get the benefits of adequate pain care while minimizing overdose risk.

Closing the Death's Door: Timely Intervention Saves Lives

Addiction treatment, smart regulation, medical and public education, and robust research are all important long-term answers to curbing the drug overdose epidemic. However, after all other prevention and law enforcement efforts have failed and a dangerous dose of opioids is consumed, *death* can still be prevented. Timely administration of naloxone, an effective antagonist, supported by simple first-aid measures, fully revives the victim in the vast majority of cases. This cheap, generic prescription drug is widely and safely used by emergency rooms and first responders for precisely this purpose. Opioid overdoses typically take substantial time to turn deadly and are often witnessed by others, leaving ample scope for life-saving intervention.

Too often, emergency medical help is not sought or comes too late. Research in the domain of heroin use suggests that witnesses to overdose involving illegal drugs are reluctant to call 911 out of fear of police involvement and mistrust of health care providers. Sometimes, witnesses do not recognize overdose symptoms as life-threatening. Rural overdoses can happen far from first responders.

In communities across the country, concerned citizens, non-profit public health organizations and governments are taking action to save the lives of people who have overdosed on opioids. They have initiated naloxone prescription programs (NPPs). These initiatives train drug users and others to identify the symptoms of overdose, call 911, provide rescue breathing, and administer emergency doses of naloxone.

Preliminary results show that NPPs can save thousands of lives without harmful side effects. Emergency naloxone administration by trained lay people appears to be safe and effective. It does not substantially reduce 911 calls or promote more aggressive drug use. Indeed, preliminary data suggest that NPP training may actually reduce risky behavior and increase the likelihood that

individuals will seek substance abuse treatment. Importantly, these interventions empower parents, partners, and others to effectively respond to a critical situation involving a loved-one, friend, or community member battling addiction.

In several states, legislatures have acted to encourage physicians to participate in NPPs and to remove legal barriers to possession and administration of naloxone by lay people. Some states have also addressed the fear of calling 911 with “Good Samaritan” legislation that provides limited legal immunity for bystanders who summon emergency medical services. Based on this positive evidence and its potential benefit in the sphere of prescription drug use, medical licensing boards and other professional bodies are beginning to recommend overdose education and distribution of naloxone to patients receiving prescriptions for opioid medications as well as those involved in non-medical use of opioids, including heroin users.

Barriers to Action

Despite the promise of NPPs and the urgent need for effective response to the overdose crisis, the spread of NPPs has been slow. Legal concerns arising from naloxone’s classification as a prescription drug have slowed the implementation of NPPs programs. The need to involve licensed prescribers in training and distribution of naloxone has added expense and the challenge of recruiting willing providers. Recent spikes in the price of naloxone have raised fears that what had once been a cheap drug might become too costly for under-funded programs to buy. Fundamentally, the stigma of illegal drug use makes it harder to attract attention, participation and funding.

The 2008 Summit on Opioid Overdose: Findings

An interdisciplinary group of substance abuse experts, public health researchers, advocates, and practitioners assembled at Temple University Beasley School of Law in December 2008 to address the challenges facing opioid overdose reversal programs. Participants reviewed the available epidemiological evidence on opioid overdose and analyzed the barriers to timely response. There was general consensus on the following statements:

- ◆ Pharmacological and epidemiological data on naloxone indicate that it has no abuse potential, a low risk of serious side effects and no physiological function other than to reverse and temporarily block the effect of opioid drugs. Though further research is badly needed, experience with NPPs consistently suggests that the drug can be safely administered by lay responders;
- ◆ Healthcare professionals can play a unique role in promoting overdose reversal using naloxone by screening and educating at-risk patients and their caregivers, as well as by prescribing take-home doses of the drug. However, they often lack the knowledge, attitudes, and incentives, to conduct such key prevention interventions;
- ◆ Evaluations of naloxone interventions have been hampered by insufficient funding and ideologically-motivated interference with public health intervention and research;
- ◆ Scale-up of naloxone access interventions has been slowed by concerns about legal and logistical difficulties caused by naloxone’s status as a prescription drug;
- ◆ Intranasal delivery of naloxone can help prevent needle stick injuries and facilitate its administration by lay responders, but regulatory barriers and high costs limit its availability;

- ◆ Recent sharp price increases demonstrate that naloxone availability is dependent on the decisions of a small number of companies and suggests a designation of naloxone as an orphan drug;
- ◆ Improved access to naloxone represents a promising avenue for intervention and research to address the growing opioid overdose epidemic within a comprehensive strategy that integrates education, access to treatment and addiction treatment services;

Summit Recommendations

Based on two days of discussions, the Summit generated the following recommendations:

1. Federal, state, local and private funders should boost funding of research and intervention efforts aimed at curbing opioid overdose;
2. Public health, law enforcement, and academic experts should collaborate on identifying and educating at-risk groups, as well as the public at large, about effective prevention and reversal of opioid overdose, including the administration of naloxone;
3. Academic and government actors should engage professional groups and organizations, including healthcare, emergency response, and drug control practitioners, to raise awareness about opioid overdose and facilitate the translation of promising intervention strategies, including increased access to naloxone;
4. Civil society organizations and funders should lend support to coalitions of people affected by overdose, including parents' groups in order to help them effectively communicate their experiences and needs, help raise public awareness, and facilitate future policy reform;
5. Academic and civil society organizations should advocate for state-level policy reform aimed at eliminating legal barriers to overdose reversal interventions, including authorization for lay naloxone administration and "Good Samaritan" immunity for overdose witnesses who call 911;
6. Federal agencies should address regulatory barriers to wider naloxone access, and should specifically take an active role in advancing re-labeling and re-formulation of naloxone for over-the-counter sale and/or intranasal delivery; and
7. Academic, government, and civil society actors should work with the pharmaceutical industry to improve access, reduce cost, and facilitate regulatory changes designed to improve overdose reversal using naloxone.

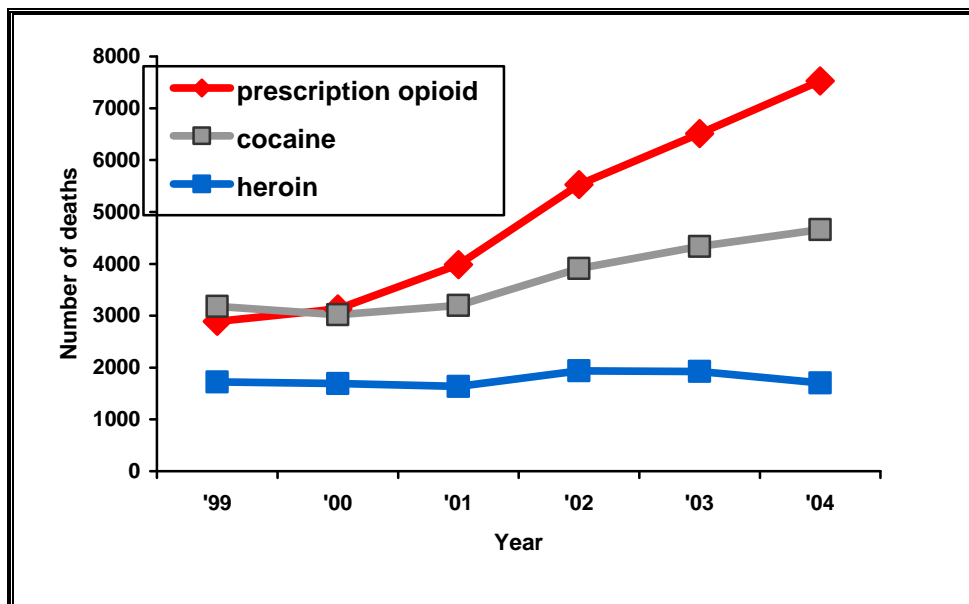
I. INTRODUCTION

A. Fatal Opioid Overdose

The United States is experiencing a drug overdose epidemic fuelled by opioids.²⁻⁵ In 1999, opioid overdose was found to be the cause of death of 3,543 Americans; by 2004, that number had climbed to 9,091.⁶ Today, victims of fatal overdose from this family of drugs could number well above 16,000 per annum⁷—passing such high-profile killers as AIDS, homicide, and accidental firearm deaths. Although piecemeal injury surveillance makes it impossible to precisely estimate national incidence, opioid overdose today is probably the second leading cause of unintentional injury death in this country, rivaled only by automobile accidents. The human toll of this epidemic is devastating families, communities, and businesses; financial costs to taxpayers are substantial.⁸

For decades, opioid overdose was associated with the use of street drugs, especially heroin. The sustained incidence of overdose death among heroin injectors led to research describing the phenomenon, identifying risk factors and systemic failures. Occasionally, an unfortunate celebrity struggling with heroin addiction would be found dead in a hotel room, and overdose would get a superficial work-up in the headlines. However, aside from several spikes in fatalities among injection drug users (IDUs) related to fluctuations in heroin purity, population-wide rates of heroin overdose deaths remained relatively constant (See Figure 1), and so did the general apathy towards this issue. The stigma attached to illicit drug use, and the view that drug abuse was a crime, contributed to the lack of resources that were dedicated to an effective public health response.

Figure 1. Estimated Number of Overdose Fatalities by Primary Agent, 1999-2004⁹



(Source: Leonard J. Paulozzi. The Epidemiology of Prescription Drug Overdoses in the United States, Congressional Testimony to United States Senate Subcommittee on Crime & Drugs, Committee on the Judiciary, and the Caucus on International Narcotics Control (March 12, 2008))

Over the last decade, opioid overdose has grown and evolved into a very different kind of public health problem. Today, the epidemic affects all sectors of society regardless of class, ethnicity or geography, and is being driven mainly by prescription opioid analgesics.^{5, 10}

The growth in prescription of therapeutic opioids had several causes. The most important were incontrovertible empirical evidence of high levels of untreated pain among patients in the US and elsewhere, and a general consensus within the medical community that chronic pain needed to be more aggressively treated.¹¹ The availability of new drug formulations and vigorous pharmaceutical marketing efforts also contributed to wider use of effective pain medicine¹²

As the number of opioid drug users rose, so did population rates of opioid overdose deaths. Given limited information, it is not yet possible to define the causes of this correlation. Wider use probably led to rising overdose incidence among legitimate users and those around them with access to diverted medications, including family members, and friends. Greater production and distribution volume probably also increased the opportunity for and extent of diversion from various links of the pharmaceutical supply chain. Popularization of prescription drug use and increased law enforcement efforts directed at suppressing supply of illicit drugs like heroin also may have contributed to the expansion of black market demand for prescription opioids, especially among people lacking access to legitimate pain care. As legal and illicit supply of opioids increased, the public remained ill-informed—and sometimes misinformed—about the addiction and overdose risks accompanying the use of many of these drugs. Consumption of pills acquired outside of the normal prescription channels placed users at especially high risk for overdose, since they were not subject to standardized dosage controls and did not get professional advice on how to reduce risks attendant to their drug use.

B. The Mandate for the Philadelphia Overdose Summit

Developing effective strategies to address the overdose crisis requires a comprehensive understanding of its various and diverse components (see box). These include self-treatment for real pain among people without access to adequate medical care, lack of effective monitoring and treatment for addiction, and the financial incentives driving the legal prescription drug industry and illicit markets. At this stage, our knowledge on many of the key issues is deficient. Surveillance is far from systematic or complete; research has been poorly funded; health agencies have limited resources; communication between the different sectors that can help stem the epidemic—including healthcare, public health, and law enforcement—has been poor.

Yet for all the gaps in a complete picture of the problem, there is sufficient evidence for action. Much remains to be done to deal with the root causes of overdose, but one promising avenue for immediate action has been the development of public health interventions aimed at promoting effective life-saving

responses once an overdose has occurred. Today, public health interventionists, health care providers and policy-makers are working to help people witnessing overdoses to respond more effectively: by providing education on overdose recognition; by training and equipping lay people to provide first aid and administer naloxone; and by emphasizing the importance of and eliminating

In formulating a response to overdose, it is important to emphasize that therapeutic use of opioids in legitimate medical practice – for cough suppression, pain relief, palliative care and treatment of drug dependency – had long been unjustifiably limited by a combination of drug control policies that skewed medical practice and negative social attitudes towards opioid drugs. Over the course of the last two decades, the American healthcare and drug control systems have made great strides in improving patient access to these essential and socially beneficial medicines. It would be tragic if action on overdose interfered with adequate access for those with legitimate need for opioid medicines.

legal barriers to calling 911 as soon as possible. The imperative to pursue the promise of these strategies motivated the convening of the Philadelphia Overdose Summit.

Overdose reversal interventions are necessary only when preventative measures (such as user and physician education, prescription monitoring systems, buy-back programs, supply-chain management) have failed. These up-stream strategies are absolutely critical to opioid overdose control; they urgently warrant research, development, funding and expeditious roll-out. However, as thousands of Americans are losing their lives, preventing these deaths becomes an immediate priority on the public health agenda. The Summit brought together an interdisciplinary group of substance abuse experts, public health researchers, advocates, and practitioners to review the epidemiological evidence on opioid overdose, identify barriers to timely reversal, and formulate an action agenda to curb the rising death toll.

II. OVERDOSE FATALITY AND INNOVATIVE ACTION TO FACILITATE REVERSAL

A. Factors associated with opioid overdose

Epidemiological research on circumstances of opioid overdose fatality, its attendant risk factors, and successful intervention strategies is generally sparse. The bulk of the literature focuses on overdose incidents and interventions among heroin users because overdose in that group has been an endemic problem for many decades, with periodic acute episodes caused by sudden fluctuations in the purity of street drugs. Only recently have studies emerged documenting the problem among prescription drug users. Below, we describe the existing data and document the lack of research support that is crucial to expanding the knowledge base on this key domain of opioid overdose prevention. (Proposed study questions and designs are provided in Appendix 1.)

Among injection drug users, studies have identified several factors associated with heroin overdose death (HOD), including being under 40,¹³⁻¹⁵ more frequent use,¹⁶ length of injection history (with more experienced users more likely to overdose),^{17, 18} poor health,^{15, 19} depression,^{15, 20} administration by injection (rather than snorting or smoking),^{16, 18} recent and prolonged homelessness,¹⁸ presence of chronic disease,²¹ using heroin in an unaccustomed place or circumstances,²² injecting drugs in public,²³ and being white or Latino as compared with African American.^{18, 24, 25} Although females are at a higher risk of overdose, males are vastly over-represented among the victims, comprising up to 80 percent in some studies.²⁶ Polydrug use, especially involving central nervous system depressants, such as alcohol, benzodiazepines, or additional opioids is strongly associated with heroin overdose.^{15-17, 21, 23, 27-35} Use of cocaine or amphetamine in conjunction with heroin is also significantly associated with overdose in some studies.^{16, 28, 36, 37} Structural environment and neighborhood characteristics were associated with the likelihood of fatal overdose, including the quality of the built environment, poverty, and social under-investment.³⁸

Opioid overdose death typically occurs over the course of several hours and is preceded by an increasingly coma-like somnolent state.^{29, 33, 39} The onset of heroin overdose symptoms from the use of heroin adulterated with highly-potent synthetic substitutes is much more rapid. A vast majority of episodes occur in the presence of others.^{18, 19, 22, 29, 40-42} The percentage of IDUs who report having ever witnessed an overdose typically exceeds 70 percent.^{14, 32} Similarly, 80 percent of IDUs who reported an overdose that did not turn fatal said someone else was present at the time.⁴³

Precipitous increases in HODs at the community level are usually associated with fluctuations in heroin purity, which make it difficult for regular users to calibrate their intake.^{27, 44 45} Voluntary or involuntary lapses in heroin use can also precipitate dramatic risk of HOD once drug

use is reinitiated.³⁰ This is seen in the heightened risk following prison release⁴⁶ and completion of drug treatment.^{18, 47, 33}

Research on prescription drug overdose is much less developed. Although it only begins to define the nature of the problem, a comprehensive study of West Virginia overdose deaths in 2006 provides a detailed picture of the problem and its victims in one place and time. The study found that opioid analgesics contributed to the vast majority of unintentional drug poisoning deaths (93%) in that state. Victims tended to be male (67%), with 39 years both the mean and median age.⁴⁸ They were much more likely to be single or divorced than married. Less education and greater poverty were associated with greater risk of overdose fatality. Twenty-nine percent of the victims with evidence of opioid analgesic use had valid prescriptions for these drugs. (In other states this number has varied from about 40% to 80%.^{49, 50}) Some appeared to be legitimate patients whose deaths were attributable to improper dosage, accidental misuse or polydrug interactions. “Doctor shopping” (the practice of obtaining duplicate prescriptions from 5 or more providers) was associated with 23 % of the deaths.⁴⁸ Doctor shoppers tended to be much more evenly distributed between the sexes and tended to come from the wealthier communities. Methadone—solid oral tablets prescribed only for pain and not addiction—was associated with a high percentage of the deaths (40%); it was also among the least likely drugs to be legitimately obtained (only 32 % of the victims with evidence of methadone use had prescriptions for it), although in nearby North Carolina nearly 80% of methadone decedents had prescriptions.

A sizable proportion of fatalities occurred among people who were not prescribed the drugs at all. Importantly,

[t]hose in the group using diverted drugs resemble those traditionally associated with the abuse of street drugs in that more than two thirds were men, half were younger than 35 years, and most were unmarried or divorced. Consistent with this profile, individuals who had used diverted drugs were more likely to have used a nonmedical route of exposure (e.g. sniffing) and to have combined prescription with illicit drugs in their fatal overdose and were more likely to have a recognized history of substance abuse.⁴⁸

Prescription opioids appear to be readily available to non-medical users. Nationally, almost 5 percent of the US population 12 or older had used a prescription pain killer for non-medical needs in the last 12 months.⁵¹ Most of the respondents of the national household survey were intermittent nonmedical users. However, while the use of opioids is necessary in causing a fatal poisoning, it is almost never sufficient in and of itself; the vast majority of individuals exposed to opioids do not overdose or experience respiratory depression. It is the broad societal context of opioid exposure (medical, nonmedical) *combined* with a lack of knowledge about the dangers and tools for the prevention of fatalities which drives the epidemic.

Although research suggests that diversion of opioid medicines is an important contributor to overdose deaths, data on the pathways and circumstances of diversion remain extremely sparse and fragmented. It is clear that theft from different points in the supply chain, such as pharmacies, hospitals, or clinics, is substantial.^{52, 53} Prescription opioids are sometimes stolen by friends, family, or neighbors directly from their intended users.⁵⁴ In a national survey, only 3.9 percent of prescription opioid abusers reported obtaining their most recently abused analgesics from a dealer.⁵⁵ The largest proportion (56%) reported procuring their supplies free from people they knew; with less than 20 percent reporting a doctor’s prescription as the source.⁵⁵

None of the available data offer a comprehensive, generalizable picture that would enable the distillation of a robust set of risk factors to serve as a foundation for tailored interventions in this realm. For example, it is unclear what role the Internet or mail-order distribution plays at present in the overall supply of opioid analgesics that eventually lead to overdose deaths, nor what proportion of drugs that disappear from home medicine cabinets are sold or simply given to others. What is clear is that the prescription opioid overdose epidemic cannot be attributed simply to lax prescribing, nor effectively addressed by law enforcement pressure on doctors or the wholesale reduction of drug supplies. A comprehensive and informed response is needed to ensure that the benefits of good care for pain and drug dependence can be delivered with a minimum amount of collateral damage.

B. Intervening to Reverse Opioid Overdose

While serious efforts to reduce overdose risk are badly needed, the nature of opioid overdose leaves ample scope for life-saving interventions even after all forms of prevention have failed. Opioids kill by depressing respiration, a process that can be effectively reversed outside of a medical setting by rescue breathing and the administration of naloxone—a safe and inexpensive antagonist.⁵⁶ Also known by its brand name Narcan®, this drug has no psychoactive properties or abuse potential; serious side-effects from acute administration are extremely rare and are primarily related to opioid withdrawal rather than inherent qualities of the medicine. Depending on the pharmacodynamic response of the victim and blood levels of the opioid responsible for the overdose, re-administration could be needed to avoid a return of respiratory depression, especially when involving longer-acting or extended-release opioid formulations, but in practice it appears rarely to be warranted.⁵⁷ When summoned to the scene of possible drug overdose, first responders routinely administer naloxone through injection without first making a diagnosis of opioid poisoning. This speaks to the safety of the drug in medical use, and its excellent safety profile in a wide portion of the population.

In too many cases, emergency medical assistance is not summoned when an overdose occurs. Sometimes the victim is alone, so that it is too late to intervene by the time they are discovered; this may be the case with users in rural areas, or those without families, including older adults. Some emergency response may be delayed because witnesses do not recognize overdose symptoms as a life-threatening, or think they can be dealt with by “folk remedies” like splashing cold water on the face.^{20, 25} For example, when asked to describe an opioid overdose, lay participants in trainings routinely note the movie *Pulp Fiction* where an individual thrashes around and flails her arms during a heroin overdose, as opposed to the slow descent into respiratory depression which would have been the biologically correct portrayal. Anecdotally, this is one of the most indelible impressions of heroin and opioid overdose in the national psyche.

The main impetus for innovation in overdose reversal has been the fact that emergency medical assistance is too often not summoned when an overdose occurs, even when there are bystanders who could call for help. Among heroin users, the fear of calling for medical assistance is a primary contributor to death after overdose.^{21, 26, 41, 58, 59} Studies have found that emergency personnel are only called in half or fewer of overdose events.^{29, 43} Companions of overdose victims delay or resist contacting 911 because police tend to accompany medical emergency personnel to drug overdose calls.^{2, 60, 61} Though evidence is still lacking, a similar mistrust among prescription drug users may deter emergency help-seeking during opioid emergencies.

There also appear to be circumstances under which even a prompt 911 call will not bring help in time. Drugs obtained from illegal sources vary in purity, composition, and are more likely

to be administered improperly, vastly accelerating the onset of overdose symptoms. In 2006, for example, several US cities experienced an epidemic of overdose tied to the adulteration of the heroin supply with a synthetic opioid, fentanyl. The fentanyl was so powerful that it vastly accelerated the onset of overdose symptoms, as evidenced by the fact that many of the more than one thousand victims were discovered with needles still in their arm.⁶² New Mexico, which pioneered the NPP approach to preventing overdose deaths, was reacting in part to the challenge of getting help to rural drug users who were located long distances from emergency response teams.

Concerted action to improve survival after an overdose has occurred has taken two forms: programs that provide access to overdose response training and emergency naloxone directly to those at risk or in a position to help, and interventions aimed at reducing the fear of bystanders to call for emergency help.

C. Interventions to Reduce Barriers to Seeking Emergency Medical Help

The optimal response to an overdose is timely medical intervention. Although the fear of police involvement and legal consequences may be exaggerated, a national study showed that overdose bystanders are sometimes charged with and convicted of serious crimes after calling for help.⁶³ Part of the response is public education and social marketing to encourage people to call 911. In Australia, police have publicized a policy of not arresting people at overdose scenes as part of a multi-sector anti-overdose intervention. To encourage more witnesses to call 911, two U.S. states have passed laws that eliminate or reduce the legal consequences of seeking help. As part of a comprehensive overdose package, New Mexico enacted a law providing limited immunity to both the caller and the victim from drug possession charges. In 2008, Alaska enacted a sentence-mitigation provision for a person convicted of a drug offense who “sought medical assistance for another person who was experiencing a drug overdose contemporaneously with the commission of the offense.”⁶⁴

Emergency call immunity laws can be a political challenge. Immunizing the possession of drugs, even small quantities in a Good Samaritan situation, derogates from a “zero-tolerance” approach to drug control generally. Direct tension with laws in a number of states that specifically create a crime of “drug-induced homicide,” which can be applied in the case of fatal overdose to individuals who supplied the fatal drug or assisted in its administration, is also evident. From the public health point of view, the question is whether these laws promote or hinder 911 calls. The benefit of saving the life of an overdose victim, however, certainly outweighs any retributive rationale for prosecuting bystanders for their role in an unintentional overdose.

D. Overdose Prevention Programs including Diagnosis, First Aid and Naloxone

Limited programs to encourage emergency lay naloxone administration started in Europe in 1995.^{58, 65, 66} In the U.S., naloxone was first distributed to IDUs in 1999 through underground programs in Chicago and San Francisco. As of May, 2009, 57 NPPs were operating in 17 U.S. states.⁶⁷ Traditionally, these efforts have been based in harm reduction agencies, such as syringe exchange initiatives, but they are currently expanding to include other settings, serving at-risk populations, including methadone management therapy clinics, detox centers, homeless shelters, and correctional settings.

The basic intervention model is to bundle a brief training for drug users and their partners or peers with other education or prevention services. Standard curriculum includes content on the signs and symptoms of overdose, distinguishing between different types of overdose, rescue

breathing and the rescue position, the importance of calling 911, and how to administer naloxone. Training on the appropriate use and dispensing of naloxone is provided by or under the supervision of a licensed prescriber, usually a physician. Participants are usually given naloxone at the training to carry with them; programs have provided both injectable and intranasal formulations. These initiatives have been well-received by drug users and other participants, including family members, partners, and friends of both medical and non-medical opioid users.⁶⁸ Trainees report being able to recognize opioid overdoses and administer first aid and naloxone; they have been observed to do so with ability comparable to trained emergency medical health care providers.⁶⁹⁻⁷¹ Participants are eager to provide the life-saving interventions as well as to disseminate information about overdose through their networks.⁷¹ Reported serious side-effects of lay naloxone administration are extremely rare, and are usually associated with the onset of withdrawal symptoms or health problems unrelated to naloxone.⁷² Importantly, participant users have also been reported to reduce drug use and be more receptive to initiating drug treatment than non-participants.⁷³⁻⁷⁵ This pattern counters fears that naloxone users will engage in riskier drug use,¹ suggesting instead that the information and sense of empowerment acquired by NPP trainees actually helps them attain the kind of self-efficacy that can help individuals dealing with substance abuse problems.⁷⁶

There is also an important and innovative effort in North Carolina to develop a model aimed at involving health care providers in overdose prevention and reversal. Project Lazarus is a response to the high proportion of prescription drug fatalities in the state's overdose toll.⁷⁷ With support from the state medical board, the project aims to make it standard practice for physicians to prescribe an emergency dose of intranasal naloxone with prescription opioid analgesics.⁷⁷ Availability of naloxone plays a key part in a larger intervention, which uses physicians, and an educational DVD, to teach prescription drug users to diagnose and respond to overdose, as well as instructions for securely storing and disposing of unused medication to prevent diversion.

Data on the effects of Project Lazarus are not yet available, but the focus on medical professionals has to be a crucial component of overdose prevention efforts. Healthcare providers are in the unique position to screen for overdose risk factors and facilitate overdose reversals through education and prescription of naloxone.^{48, 78} Most people with serious addiction will see a medical professional every six months,⁷⁹ and in many states, prescription overdose poisoning victims had seen a doctor in the months prior to their death. A licensed provider (including physicians as well as allied healthcare professionals, depending on state law) can screen and identify at risk patients — those receiving prescriptions for opioid agents or those with a history of opioid abuse.⁶⁴ Based on this information, providers can inform patients and their caretakers about risks of overdose and educate them about the indications for and mode of naloxone administration. Patients or their authorized representatives can fill the naloxone prescriptions at participating pharmacies and keep the drug on-hand in case of an emergency.

NPP participants have reported saving 298 lives in San Francisco since November 2003. In Chicago, NPP participants have reported saving almost 1,000 lives since 1999, with a concurrent 30 percent decrease in reports of fatal overdose in Cook County.^{75, 76, 80} In New Mexico, it is reported that 451 lives were saved by NPP trainees since 2001,⁸¹ though continued high HOD mortality rates suggest that NPPs are functioning at scale. Other reports of number of “saves” include 280 lives in Oakland, California, since 2001,⁸² 104 in New York City,⁸³ and 143 lives in Baltimore since July, 2006.⁸⁴ Without increased funding, robust evaluation of these programs is not possible. Nonetheless, the data indicate that NPPs are a promising and, potentially, extremely cost-effective public health tool worthy of further development.

A number of legislatures have agreed. Five states have implemented policy reforms to authorize or facilitate NPPs.⁶⁴ There are no legal barriers to prescribing naloxone to individuals at

risk of overdose, but legislation is necessary to legalize such prescribing to lay savers. The first state to act was New Mexico. In 2001, the legislature authorized naloxone distribution programs using lay savers and provided immunity to doctors and laypersons who administer naloxone to others. New York followed in 2005 with legislation authorizing opioid antagonist administration programs. Under a California statute, local governments in seven counties may operate programs directly or “register” programs operated by non-governmental agencies. The law permits prescriptions to trained third-party savers within an authorized program. As this report was being written, House Bill 0497 passed both houses of the Illinois General Assembly and is awaiting the Governor’s signature. It authorizes a comprehensive overdose prevention program that includes training and equipping of lay savers with naloxone and legal protection for participating health care providers and lay savers.

Connecticut took a more limited step in 2006. Its law seeks to allay healthcare practitioner concerns about participating in an overdose prevention program by providing immunity from civil or professional liability to a provider who prescribes, dispenses, or administers naloxone “to a drug user in need of such intervention.” Unfortunately, it does not extend the protection to a doctor who provides naloxone to a friend or family member of an opioid drug user being trained in an NPP. Perhaps for that reason, its impact in encouraging healthcare providers to prescribe naloxone to facilitate overdose reversal has been negligible—by some reports, only one practitioner in the state currently issues such prescriptions.⁸⁵

Other locales have launched programs that utilize legal mechanisms on a more local level. The Boston Public Health Commission promulgated a regulation authorizing an Opioid Overdose Prevention and Reversal Program.⁸⁶ Project Lazarus did not seek authorization through a statute or regulation, but rather obtained the support of the State medical board via a policy statement encouraging the prescribing of naloxone to patients receiving certain powerful opioid medications. Finally, programs in a number of places have gone into operation without specific authorization or government sanction, relying on the unquestioned authority of physicians and other licensed professionals to prescribe necessary non-scheduled medicines to the people who need them.⁶⁴

III. FACTORS LIMITING OVERDOSE REVERSAL INITIATIVES

Drug overdose has not gotten the attention – or the action -- that a killer of this magnitude should receive. Though its death toll exceeds that of AIDS, homicides, and automobile crashes in some places, organized work to promote overdose reversal has tended to be a labor of love, underfunded or not funded at all, carried on by persistent champions in the face of indifference or outright hostility. The problem has become not “what should we do?” but “how can we get it done?” The reversal initiatives we described above are in place in some crisis hot spots and ready to be implemented in others; all that is required is funding, support for rigorous evaluation and better research – and the will to act. The participants at the Summit discussed the factors limiting wider action on overdose, with a particular focus on the barriers affecting reversal programs. Like the causes of overdose itself, the causes of inaction are many and complex.

A. Ideological Climate and Stigma Limit Emergency Response and Political Will to Address Overdose

For too long, the “war on drugs” has been fought as a war on drug users. Stigmatized as degenerates and threats to social orders, users of illegal drugs have too often been deemed to deserve whatever harms befall them. In spite of extensive contrary evidence, harm reduction

interventions have been opposed because they were believed to “encourage” drug abuse or simply protect people from its most serious consequences. This stigma has attached to overdose reversal, and has manifested itself in a number of ways.

Given the magnitude of the problem, it has been far harder than it should be to get action from legislators and public health agencies. People in government, including police and public health agencies, have had limited incentive or resources to support overdose reversal programs. Stigma suppresses “demand” for action. Overdose deaths are often hidden as shameful. Even when the victim is a celebrity and coverage is widespread, public interest does not grow into a demand for action, partially because of the lack of knowledge that viable prevention options exist. Though many famous people have died of overdose, there is no high profile celebrity foundation or spokesperson dedicated to ending this scourge. Public officials who contemplate action are deterred by the risk of being seen as enabling risky drug using behavior and creating new black markets by introducing naloxone to the streets.⁸⁷

Stigma is rooted in secrecy and silence, which makes the lack of research funding to date all the more painful. Both the size of the problem and the number of important unanswered questions would, absent the stigma and fear of political controversy, make overdose prevention and reversal prime topics for funding. So far, however, there have been only four US research projects on overdose reversal interventions supported by various sources, all of which carried very little funding and resulted in studies that were of pilot or qualitative nature. All other applications to NIH (at least 5 over the last four years) and CDC to evaluate overdose prevention strategies have been rejected.

This may be changing. The best champions against stigma are those who suffer it most – drug users and their loved ones. In the past, overdose victims—both users who survived an overdose incident and survivors of victims who did not—remained largely silent. There is now a number of emerging victims’ and parents’ groups who are beginning to speak out on the issue. At last count, about 20 such groups existed in United States. These range from abstinence-oriented parent organizations to user groups providing overdose reversal training and distributing naloxone.⁸⁸ There is currently no funding or coordination for these victims-focused advocacy activities, with the rare exception of a few faith-based initiatives.

In government, the 2008 national elections have brought some new attitudes on drugs. Notably, the new national “drug czar,” Gil Kerlikowske, has publicly stated his intention to move away from a “war on drugs” and towards a public health approach. During a recent hearing on Capitol Hill, he specifically noted the relative neglect of drug overdose: “In the past few weeks, we've had three deaths from swine flu or the H1N1 virus, and, in the same period, we've had thousands of people overdose and die. This a public health issue.”

There have been promising signs on the research funding front. In 2008 the CDC announced a request for proposals to fund two 2-year projects on prescription drug overdose, but this announcement was extremely limited in scope and available funds. Vast scale-up in such funding can help identify effective programmatic, policy, and other efforts to promote overdose reversal, as well as other overdose fatality prevention initiatives. However, research focusing on NPPs was not funded through this mechanism, despite a specific provision in the request for proposals which included evaluation of naloxone-based initiatives.

The increasing role of prescription drugs in the overdose problem has also had its effects. Overdose has always been an equal opportunity killer, and newspapers would periodically profile the deaths of heroin-using stock brokers and lawyers. Still, the stigma of illegal drug use persisted. Prescription drug users don’t necessarily trigger the same stereotypes as heroin users. A substantial proportion of overdose deaths are now observed among users of drugs that were properly prescribed

and procured at a pharmacy, possibly without adequate safety warnings. An increasing proportion of these victims are main-stream American women, with common medical problems and legitimate pain management needs.⁸⁹ In addition, physician errors with new opioid dosage forms have also led to overdose deaths.⁹⁰ The mainstreaming of the overdose problem may nudge the public's perception of this public health crisis as a fringe issue affecting only people engaged in criminal behavior.

The numbers themselves are changing the picture. Sky-rocketing incidence of overdose has provided much-overdue exposure to this issue, including both high-profile scientific⁴⁸ and lay press accounts.⁹¹ As more and more families and communities wake up to the human toll of this silent epidemic, the political urgency to address the issue with effective solutions will grow both on the state and federal level.

B. Lack of Training and Stigma Limits Role of Healthcare Practitioners

Limited physician understanding of substance abuse problems and addiction is well-documented.^{92,93} Relatively few primary care physicians receive training in this realm.⁹⁴ Screening for substance abuse is not systematic and may be discouraged by financial pressures.⁷⁸ More generally, physicians share general societal attitudes towards substance abusers as a difficult population not amenable to intervention.⁹⁵ In addition, geographical barriers, poverty, and uneven distribution of medical resources may influence access to substance abuse treatment, pain management services, or emergency services and their quality,^{48,96,97} inducing self-medication (for pain and drug withdrawal) and contributing to overdose risk.

Provider-side interventions to reduce drug-associated harms are both feasible and practical. Programs encouraging physicians to screen for problematic drug use and prescribe syringes to at-risk injection drug users have shown promise.⁹⁸ However, physicians remain largely under-informed about opioid overdose risk, so engaging them in screening for, educating about, and prescribing naloxone to address this problem is a challenge.⁹⁹ Although nursing and other allied clinical health professionals can issue prescriptions for naloxone in most states and frequently provide other care to at-risk patients, their knowledge and attitudes on interventions to facilitate opioid overdose reversal have not been systematically evaluated. Overall, healthcare visits provide an opportunity to speak to patients about their addiction issues, including risks of overdose; as a rule, this opportunity is wasted.^{79,100}

In the US, naloxone is typically included among the standard EMS supplies and is routinely used when paramedics encounter an unresponsive or unconscious victim, even in the absence of suspected drug use. Some fire and police departments also stock naloxone among their first aid supplies. It is not clear how many overdose fatalities result from the failure of first responders to properly diagnose and promptly administer naloxone when responding to a call. Data does show that, despite strong evidence to the contrary, paramedics oppose lay users' ability to administer naloxone correctly.^{69,101}

C. Limited Access to Naloxone

One of the key reasons that innovative, but underfunded public health programs have been able to provide naloxone prescription services without substantial public investment was that the drug was inexpensive. This is changing, however, because of the way naloxone is regulated, marketed and priced in the U.S.

i. Cost

Naloxone is a post-patent generic drug, used for multiple purposes. These include treating opioid overdose; reversing the effects of anesthesia in surgical settings; and, in combined formulations with buprenorphine (Suboxone[®]) or pentazocine (Talwin NX[®]), reducing the potential for injection. The annual demand for naloxone has been stable over the last decade. The low profit margin has led many makers of the drug, such as Wyeth, Baxter, and Endo Pharmaceuticals, to exit the market. In a world of multi-billion dollar block-busters, naloxone is virtually an orphan drug.

By 2007, only three companies – Hospira, International Medications, and Endo Pharmaceuticals – were marketing naloxone. (One company, Mallinckrodt Chemical, is the sole maker of the active agent, which the other companies process into various FDA-approved formulations.) Endo recently closed its manufacturing facility and exited the market. Hospira, subsequently increased prices in a move apparently unrelated to any real increase in production, distribution, or marketing costs. For its part, International Medications phased out the production of the single-dose 1 mL of a 0.4 mg/mL solution in favor of the larger 10 mL bottle already produced by Hospira and pre-filled syringes containing 2 mLs of a 1 mg/mL solution. The larger size containers are favored by institutional customers like hospitals and paramedics because they are more cost-effective and convenient. However, the decision to discontinue the production of the smaller bottle significantly raises supply costs of programs designed to equip lay responders with emergency doses of the drug.

The price increase is substantial. The Harm Reduction Coalition surveyed naloxone programs in Fall, 2008. Programs reported increases in the price of naloxone ranging from 30% to as high as 400%. On average, programs reported that the price for their naloxone supply had tripled in recent years. Because hospitals and large health agencies make up the bulk of the market, and the unit price of naloxone is still tiny compared to patented drugs and other medical supplies routinely ordered concurrently while replenishing naloxone stocks, the makers seem to have considerable room for price increases. Pricing is also obscured to some extent by the practice of selling naloxone as part of a package of common drugs, and by price confidentiality agreements included in sales contracts. Thus the actual causes and full extent of the price rises are not known. While most participants in the Summit were inclined to point to the market factors just described, one expert raised the possibility of a shortage of the imported active ingredient.

Programs have so far managed to find ways to cope with higher prices. In some instances, they have been able to negotiate humanitarian price concessions from the makers. In the long run, however, the price of naloxone will have a decisive impact on the viability of reversal programs relying on wide access to the drug.

ii. Prescription status

Although it is an opioid, naloxone is not classified as a controlled substance. This reduces the level of regulatory control over its possession and use, but the drug is still classified by the FDA as requiring a prescription. Drugs are limited to prescription distribution if they are habit-forming, toxic, have serious side-effects, or cannot be used by laypeople without a doctor's supervision. Evidence and experience support the prima facie case for naloxone reclassification for a non-prescription take-home indication because it carries no psychoactive properties and thus has no significant abuse potential. Moreover, lay responders have been shown to be able to use it properly

without immediate medical supervision. Its side effects are limited to transient withdrawal symptoms and relatively few serious complications.

The prescription requirement creates several hurdles for programs. First, it means that underfunded programs must find a way to recruit medical personnel authorized to issue prescriptions, which can raise costs and add logistical complexity. Because health professionals have to be involved, these programs must deal with practitioner concerns about malpractice liability, which can be powerful even when not well-founded in fact.⁹³

Second, the prescription requirement imposes a health care model on NPPs. Before the drug can properly be provided to a participant, a licensed healthcare professional authorized to issue prescriptions must complete an exam or another interaction with a patient (as required by state law) and give the patient information about the indications for the drug, its proper use, and its risks and benefits. While some of these functions can be delegated to allied health providers working under standing orders or other appropriate practice guidelines, the medical model is cumbersome and limits the discretion of programs to follow other procedures that may be appropriate and supported by evidence. The North Carolina Medical Board has agreed to an abbreviated medical encounter for naloxone prescribing, similar to the reduced requirements underlying community-based seasonal influenza vaccination. Many states make it a crime to possess a prescription drug without a prescription, so participants in training programs are potentially in jeopardy if they do not have, or fail to carry, a prescription.

Finally, the prescription requirement limits who takes part in reversal programs. In strict legal terms, a prescription is only appropriate if it is issued to a patient for the patient's own medical need. A lay saver who is not a drug user but is trained to help others at risk of overdose, strictly speaking, has no personal medical need for the drug. Moreover, providing naloxone under those terms would amount to deputizing the lay person as a medical practitioner, which contravenes the basic idea of licensure and criminal laws that prohibit the unlicensed practice of medicine.⁶⁴

Though unlikely to give rise to real legal problems in fact, concerns about issues related to naloxone's prescription status present obstacles for the planning and implementation of overdose education and prevention initiatives. The limitation on prescribing to lay savers has been a particular problem, holding up the start of programs for months or years in some places.

D. Intranasal Delivery of Naloxone is Un-approved, Expensive

Currently, naloxone is licensed only for parenteral—meaning, infusion or injection—administration.⁵⁶ Especially in the context of prescription opioid abuse, prospective lay savers may not know how to use syringes, may be concerned with potential liability, or may be deterred by the real and perceived risk of needle-stick injuries. Such injury is also an important occupational risk among first responders and others who are called upon to administer the drug in an emergency.¹⁰² Intranasal delivery mechanisms, preliminarily shown to be a promising alternative,^{23, 103-106} address these risks, and have been adopted by some NPPs. They can be used now because reasonable and informed off-license use of drugs falls within the scope of healthcare providers' professional discretion; but the lack of FDA approval precludes mass production of nasally delivered dosage units and insurance reimbursement. Instead, nasal delivery kits must be assembled by program staff or compounding pharmacies using “after market” kits, and are not available routinely in pharmacies.

An intranasal delivery system would be considered by the FDA to be a “new drug” requiring separate approval.¹⁰⁷ A change in mode of administration would normally require a “new drug application” (NDA) and re-formulation of the drug to optimize it for a new delivery modality.

By law, this necessitates "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."¹⁰⁸ The agency will provide guidance as to the exact nature of the studies required to demonstrate that the new modality and formulation are "safe and effective."¹⁰⁷ This research is normally conducted by and paid for by the applicant (pharmaceutical companies), as are the considerable fees to the Agency. Overall, this process requires robust new clinical data, extensive paperwork, and considerable financial backing. In the absence of specific regulatory approval, intranasal (off-label) use of naloxone will remain substantially limited in scope. Programs that want to use this mode must purchase generally expensive after-market kits and assemble them themselves or through a compounding pharmacy. As compared with injectable naloxone, the cost of intranasal kits is currently about 14 times higher per dose.

Considerable new pharmacokinetic and clinical trial research is needed to assess what formulation and delivery mechanisms can be deemed safe, and effective, for the wider and more cost-effective utilization of IN naloxone to prevent opioid overdose fatalities, to optimize the dose, and to determine the stability of new formulations over time, and environmental conditions. With adequate support from funders like NIDA, such research can also generate critical additional information on the most promising ways to educate users about naloxone administration and programmatic schemes to distribute the drug in a way that maximizes its lifesaving value. (As this White Paper went to press, advocates for wider naloxone availability were in discussions with manufacturers about another new delivery option, an auto-injector similar to the epi-pen used in bee-sting kits. Development of this delivery mechanism would generally require the same regulatory process as an IN version.)

IV. KEY AREAS OF ACTION TO ADVANCE OPIOID OVERDOSE REVERSAL

The Summit convened an interdisciplinary group of substance abuse experts, public health researchers, advocates, and practitioners to address the challenges to effective, large scale opioid overdose reversal interventions. The participants reviewed the epidemiological evidence on opioid overdose and analyzed the barriers to timely overdose reversal. There was a high degree of agreement on the situation today and the actions that are needed.

A. More information on the epidemiology of opioid overdose to improve intervention design and tailoring

Overall, surveillance of drug overdose has been hampered by lack of uniformity in post-mortem practices at the local level, and gaps in national data collection and analysis, including multi-year time delays in releasing data. Existing surveillance networks are incomplete, poorly-coordinated, and severely limited by the divergent definitional and classification nomenclature. Until very recently, research describing the basic demographic characteristics, risk factors, and circumstances of opioid overdose was almost exclusively limited to heroin users; information from previous prescription opioid overdose epidemics is decades old and was conducted before the new formulations intended for widespread outpatient management of non-malignant pain. Although demographic and risk factor data on prescription drug-related fatalities has begun to emerge, it remains extremely limited in scope and generalizability, which severely impedes public health response to this issue.⁴⁸ Interventions to curb prescription overdose deaths cannot be properly designed and implemented without understanding what individual, social, and structural factors best

predict it. Data on the demographic and other characteristics of the different types of overdose victims are urgently needed. Understanding the mechanisms and distribution pathways of prescription opioid diversion will help identify at-risk populations, as well as to implement up-stream interventions. Research comparing those who experience fatal overdose with those who survive these episodes would help shed light onto the barriers shaping medical response and risk factors for overdose mortality. Studies of survivors can also help build a more complete, in-depth understanding of overdose risk factors than any data based solely on post-mortem analysis. This research should include both quantitative and qualitative work

B. Outreach, Education for the General Public, Patients and Healthcare Providers

By educating the public about the risks and the signs of opioid overdose, public health professionals can improve the chances that appropriate and timely action will be taken to reduce overdose risk. Such interventions can take a variety of forms and flow through a number of channels, including general social marketing campaigns, as well as targeted interventions targeting groups with specific risk factors; the more reliable the data about these risk factors, the more likely the success of designing appropriate efforts.

Overall, greater awareness among physicians and allied health professionals about opioid overdose is needed. This is critical because providers have a unique opportunity to identify and address problematic opioid use at the point of service, because they may be able to facilitate overdose reversal, and because they can screen for drug abuse and dependence and refer patients to appropriate treatment. By providing short educational interventions and prescribing companion doses of naloxone, healthcare practitioners may be able to reduce the incidence of fatalities among patients with underlying biological co-morbidities, as well as their friends and family who divert prescription drugs.

C. Rigorous and systematic evaluation of field interventions to facilitate overdose reversal and facilitate scale-up

Research is also needed to evaluate NPPs. While there is enough evidence to scale up these interventions based on the precautionary principle, we still need to do rigorous research to document how and how well they work, and to deal with concerns about unintended consequences. The NPP model is still relatively novel, and we need evaluation data to improve it over time.

Despite positive preliminary data, several challenges have been identified. Some studies have found that IDUs remain hesitant to call 911.^{58, 109} According to the piecemeal evaluation data, emergency medical personnel are called in only a minority of cases.¹¹⁰ Many of these initiatives have struggled to implement robust formal evaluations.^{68, 83, 110?, 111} Overall, these and other piecemeal reports from NPPs are promising, but they do not represent rigorous evaluations of program effectiveness. Appendix 1 includes a number of research questions that have yet to be answered by these researchers.

D. Evaluation of and wider enactment of legal reforms or other policy interventions that can promote overdose reversal

A number of states have implemented policy reforms to address the current crisis. State legal reform is necessary to legalize the prescription of naloxone directly to lay savers. Other locales have launched programs that utilize legal mechanisms on a more local level, related to

program participation, naloxone prescription, and other activities.⁶⁴ Legislative authorization may facilitate program proliferation, increase the chances of government funding, reinforce the urgency of the opioid overdose problem, promote reimbursement by third party insurance and drug benefit providers, and eliminate real and perceived legal barriers to enlisting lay savers. Laws or regulations authorizing naloxone distribution that endorse particular organizational designs, training requirements or approaches to service delivery may become outdated and will need to evolve as the epidemic progresses. Others laws may create a misperception that programs that do not conform to the prescribed design are illegal. The impact of these laws on public health responses, as well as perceptions and behaviors of target groups, has not yet been studied. Another important category of legislation to be evaluated is state laws that protect 911 callers from prosecution, where the knowledge, attitudes, and practices of bystanders and law enforcement actors may or may not respond to the legal reforms. Laws allowing pharmacists to prescribe naloxone should also be considered and evaluated, although no such law currently exists in the US.

States – and researchers – need to review and evaluate the consequences of “drug-induced homicide laws,” meant to punish those who supply drugs to overdose victims. These have been applied on many occasions in cases where one user brought drugs to share with another or helped the victim ingest the drug. It would be tragic if such laws, meant to deter conduct leading to overdose deaths, actually increased the risk by deterring people from seeking help. Legal reforms to grant bystander immunity are an important component of a comprehensive policy response to this epidemic; their impact (both direct as well as in terms of changing public perceptions) has yet to be rigorously evaluated.

E. More research on efficacy of intranasal as compared to intramuscular naloxone

Intranasal (IN) naloxone can reduce the perceived barriers to its administration and may lower the risk of injury to the victim and the administrator of the drug. Among IDUs, IN administration may be preferred to other methods. This suggests that witnesses of an overdose in the prescription drug context, where they are less likely to be familiar and comfortable with injection equipment, would be equally, if not more favorable to this mode of naloxone administration. Beyond the one prospective randomized study, there is a dearth of epidemiological studies about the efficacy of intranasal *versus* intramuscular naloxone among lay administrators.²³ Small-scale studies comparing IN with injectable naloxone have generally found IN to be effective, but a follow-up injection was needed to supplement IN administration in a small proportion of the cases. Paramedics in the San Francisco Department of Public Health and lay overdose responders in Boston have been using IN administration of naloxone for the past two years.¹¹¹ There are little data or resources available to properly evaluate these natural experiments beyond observational studies.¹¹¹

F. Generating Market Incentives to Wider Availability of Naloxone and other Activities to Facilitate Overdose Reversal

As a generic prescription drug, naloxone does not have promise as a substantial income-generating line for its manufacturers. In fact, interest in producing this agent has dwindled in recent years, with implications for access and costs described above. This perceived lack of financial incentive also has important implications for research, as the pharmacokinetic, usability, and other studies required for the re-formulation of the drug or its re-classification for over-the-counter (OTC) sales requires substantial investment from industry actors.

Educational outreach to patients and providers about naloxone has the potential to substantially boost demand for the drug. The rise in numbers of pharmacies carrying this drug will also lead to renewed purchase to replace expired preparations. Policy and clinical practice guideline reforms that promote prescription and utilization of naloxone would similarly generate substantial new revenue streams for its manufacturers and distributors. However a labeled indication will need to be approved in order for insurers and pharmacy benefit payers to reimburse for pharmacy sales of naloxone, reinforcing the need for immediate research funding.

Finally, companies profiting from the production and distribution of opioid analgesics also have a responsibility to address overdose. Risk Evaluation and Mitigation Strategies (REMS) and other initiatives undertaken by these entities should include overdose prevention, including better labeling, patient and provider education, and facilitation of research and programmatic efforts that include naloxone distribution. Aside from a business ethics rationale for such activity, there are regulatory and product liability considerations that should drive such action on the part of the pharmaceutical firms. To date, only one pharmaceutical company has reached a tentative agreement with one program to fund naloxone distribution and evaluation of its effectiveness. REMS mechanisms need to focus more on better surveillance and response to overdose, acknowledging the responsibility of companies in ensuring the safe use of their product.

V. SUMMIT RECOMMENDATIONS

After reviewing the work of reversal initiatives, and discussing the barriers and areas of need, Summit participants agreed upon the following recommendations:

- 1. Federal, state, local and private funders should boost funding of research and intervention efforts aimed at curbing opioid overdose.**
 - a. NIDA should fund substantial new research on the individual and structural factors associated with opioid overdose deaths, both quantitative and qualitative. CDC and state health agencies should work to improve surveillance, including standardized definitions for identifying overdoses, and should make surveillance data quickly available to the public. NIH, SAMHSA, CDC, and DEA should partner to better track and describe prescription drug diversion pathways, and specifically how they are related to overdose. The CDC and FDA should collaborate on evaluating intervention programs, including those targeting patients, provider-side outreach and education, as well as data tracking and monitoring systems that can provide timely, meaningful warnings about likely overdose risks;
 - b. The FDA should cooperate with NIDA in the identification and funding of basic science needed to assess new formulations and modes of delivery of naloxone;
 - c. Researchers and local health agencies should form interdisciplinary research teams to study overdose and evaluate interventions.
- 2. Public health, law enforcement, and academic experts should collaborate on identifying and educating at-risk groups, as well as the public at large, about effective prevention and reversal of opioid overdose, including the administration of naloxone.**
 - a. Cross-sectoral and public-private partnerships are essential to conducting these education and social marketing efforts. Experience in other countries suggests that law enforcement agencies are key partners.
 - b. These partnerships should pursue the expansion of a naloxone distribution network to accompany social marketing efforts.

- 3. Academic, community and government actors should engage professional groups and organizations, including healthcare, emergency response, and drug control practitioners, to raise awareness about opioid overdose and facilitate the translation into practice of promising intervention strategies, including increased access to naloxone.**
 - a. Education about overdose may occur through publications in professional literature, presentations at conferences, and other channels.
 - b. It is important that healthcare and law enforcement professional bodies are actively involved in efforts to build support of future policy reform.
 - c. These efforts should be organized to support, evaluate, and rapidly replicate successful provider-focused outreach.
 - d. The creation, dissemination, and implementation of clinical practice guidelines by and for opioid prescribing professionals is a critical component to preventing overdose and facilitating overdose reversal. Improved information and compliance with methadone prescription recommendations among general practitioners and pain specialists is a key priority in this area.
 - e. Policy reform efforts and translation of intervention strategies must address overdose prevention at the point of care, where issues like non-reimbursement for naloxone prescription can impede access.
- 4. Civil society organizations and funders should support advocacy by people affected by overdose, including parents' groups in order to help them effectively communicate their experiences and needs, help raise public awareness, and facilitate future policy reform.**
 - a. An umbrella group is needed to help survivors' groups speak with a unified voice and to provide technical support for "champions" of victims' interests
 - b. This umbrella group is also needed to sustain outreach to providers, policy and industry decision-makers, and people at risk of opioid overdose.
 - c. Researchers, policymakers, and funders must strive to understand and incorporate victims' perspectives and input into research and policy efforts.
- 5. Academic and civil society organizations should advocate for state-level policy reform aimed at eliminating legal barriers to overdose reversal interventions, including authorization for lay naloxone administration and "Good Samaritan" immunity for overdose witnesses who call 911.**
 - a. Model legislation is needed that addresses legal barriers to overdose reversal programs, including: restrictions on who can prescribe, possess, and dispense naloxone; malpractice and other liability protection for naloxone prescription and administration; lay saver certification schemes; and legal immunity to witnesses and victims of overdose who summon first responders.
 - b. A network of researchers and advocates should provide technical assistance to advocates for local, state-level and inter-state overdose surveillance, and funding for overdose prevention and overdose reversal programs.
 - c. The network should disseminate best practices and facilitate their adoption by state legislatures and medical boards.
- 6. Federal agencies should address regulatory barriers to wider naloxone access, and should specifically take an active role in advancing re-labeling and re-formulation of naloxone for over-the-counter sale and/or intranasal or auto-injector delivery.**

- a. There is an unmet need for a champion with the capacity to pursue FDA-directed regulatory activities for expanded naloxone access and re-labeling for OTC sale and (with less urgency) IN or auto-injector administration.
 - b. Continued advocacy is needed to generate political will and a sense of urgency about opioid overdose at the national level.
 - c. Advocates should support Congressional legislation addressing overdose, such as HR 2855 (Appendix 2), which includes surveillance, research, and programming activities and an awareness-raising “Finding of Congress” about reducing lay saver liability.
7. **Academic, government, and civil society actors should work with the pharmaceutical industry to improve access, reduce cost, and facilitate regulatory changes designed to improve overdose reversal using naloxone.**
- a. Naloxone program managers and their allies should investigate the possibility of engaging with manufacturers on cost (e.g., bulk discounts to naloxone distribution programs).
 - b. These efforts will be strengthened by research into and development of a business case for supporting overdose reversal efforts based on models that assume wider distribution and prescription of naloxone.

VI. CONCLUSION

Despite its devastating impact and epidemic proportions, opioid overdose has gotten far too little attention from public health authorities, academics, and the media.¹¹³ The discrepancy between the resources dedicated to alleviating this problem versus some other, far less deadly public health issues, tellingly highlights the stigmatization of drug abuse.⁷⁶ This is especially true in the context of heroin use, where resource allocation disparities raise ethical questions in view of the racial and class characteristics associated with this form of addiction.^{76, 114}

Each overdose fatality is a result of a series of failures. More research on causes, vectors, and risk factors will help identify the most promising modes of intervention. However, the implementation of systems-based and supply-side mechanisms is likely to be slow and, as experience with other controlled substances suggests, may not always produce the desired results. The availability of naloxone provides a unique opportunity to stem the tide of deaths.

Efforts to facilitate opioid overdose reversal are hampered by a number of barriers. Scientific review panels at Federal agencies, including NIDA and CDC have not funded proposals for evaluating naloxone-based interventions. Stigma, professional culture, and political forces have restricted information on the issue, deterred provider involvement, and silenced victims. Many clandestine opioid users lack access to adequate healthcare services, so they also face barriers accessing emergency doses of naloxone—a prescription drug.

The reclassification of naloxone in either or both the injectable and nasal delivery modes as OTC drugs would be a major step in increasing access and decreasing opioid overdose deaths in America. This drug is neither habit-forming, nor toxic, carries no serious side-effects, nor can be used to treat a condition laypersons cannot accurately diagnose or safely address with its administration. Lastly, in formulating the response to the opioid overdose crisis, care must be taken to maintain access to safe, effective, and cost-effective analgesic agents for those with legitimate pain management needs.

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**APPENDIX 1:
RECOMMENDED RESEARCH QUESTIONS AND STUDY DESIGNS FOR FUTURE WORK TO ADVANCE
OVERDOSE REVERSAL**

1. Additional randomized trials with larger samples and follow-up to determine whether intranasal (IN) is as effective as intramuscular (IM) administration of naloxone in terms of (a) length of time until complete reversal and (b) successful reversal rate.
2. Are there any negative consequences of IN administration that do not exist for IM administration?
3. Are prescription opioid users interested in having and using naloxone? Do they prefer IM or IN mechanisms?
4. Can non-IDU witnesses to opioid overdose correctly diagnose and respond to an overdose event?
5. Can these bystanders administer naloxone effectively? Are they more likely to administer naloxone correctly through IM or IN delivery mechanism?
6. Are lay people willing to administer IN naloxone in overdose situations?
7. Are people who are prescribed opioid pills willing to disclose their opioid pill usage, educate about the signs of opioid overdose, share their emergency doses of naloxone, and train their family, friends about spotting and responding to opioid overdose, including naloxone administration?
8. What are the potential negative consequences of lay people administering IN naloxone?
9. If lay people have IN naloxone, will they take less precaution about the amount of opioids they use (parachute argument)?
10. Will lay people be less likely to call 911 in an overdose event if they reverse an opioid overdose by themselves using IN naloxone?
11. What are and how strong are the opinions of paramedics, physicians, pharmacists, policy-makers, medical insurance companies, and their various lobbying associations about providing IN naloxone to lay people?
12. Questions 3, 4, 5, 6, 7, 8, 9, and 10 should also be asked of injection heroin users.
13. Does provision of naloxone result in subsequent increased non-medical consumption of opioids?

Potential study designs to answer these epidemiological questions:

1. A randomized controlled trial of IN vs IM naloxone administration in the United States. This can be done through emergency departments (e.g. San Francisco where IN is currently used). It would need a sample size of about 200. A key feature would be to start timing reversal not from administration of the drug, but from arrival on the scene.
2. A cross-sectional survey of 400 people who are prescribed opioid pills, assessing their attitudes about IN naloxone, comprehension of labels describing naloxone administration, their ability to use a nasal spray, their ability to diagnose opioid overdose.
3. A cross-sectional survey of paramedics, physicians, pharmacists, health policy-makers, and medical insurance company representatives assessing their attitudes about providing IN naloxone to lay people.
4. A qualitative study of paramedics, physicians, pharmacists, health policy-makers, and medical insurance company representatives assessing their attitudes about providing IN naloxone to lay people.

5. A quantitative case-control or cohort study of injection drug users, comparing those who are trained and prescribed naloxone to those who are not trained and prescribed naloxone, assessing how they reacted when witnessing an overdose.
6. Secondary analysis of medical examiner data for fatal opioid overdoses in 96 largest US Metropolitan Statistical Areas (MSAs) using data from 1990 to present and comparing data during years that naloxone programs were implemented to years and MSAs where there was no naloxone programs.

APPENDIX 2:
BILL TO REDUCE OVERDOSE FATALITIES INTRODUCED IN THE HOUSE OF REPRESENTATIVES

HR 2855 IH

111th CONGRESS
1st Session
H. R. 2855

To reduce deaths occurring from drug overdoses.

IN THE HOUSE OF REPRESENTATIVES
June 12, 2009

Ms. EDWARDS of Maryland (for herself, Mr. SERRANO, Mr. HINCHEY, Mr. PIERLUISI, Mr. GRIJALVA, and Mr. LANGEVIN) introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To reduce deaths occurring from drug overdoses.

BE IT ENACTED BY THE SENATE AND HOUSE OF REPRESENTATIVES OF THE UNITED STATES OF AMERICA IN CONGRESS ASSEMBLED,

SECTION 1. SHORT TITLE.

This Act may be cited as the `Drug Overdose Reduction Act'.

SEC. 2. FINDINGS.

The Congress finds the following:

- (1) Drug overdose death is now second only to motor vehicle crashes as a leading cause of injury-related death nationally. Both fatal and nonfatal overdoses place a heavy burden on public health resources, yet no Federal agency has been tasked with stemming this crisis.
- (2) The Centers for Disease Control and Prevention reports that 33,541 deaths in the United States in 2005 were attributable to drug-induced causes. Sixty-seven percent of these deaths were due to unintentional drug poisonings and could have been prevented.
- (3) Deaths resulting from accidental drug overdoses increased more than 400 percent between 1980 and 1999, and more than doubled between 1999 and 2005.
- (4) Ninety-five percent of all unintentional and undetermined intent poisoning deaths are due to drugs, and poisoning deaths cost society more than \$2,200,000,000 in direct medical costs and \$23,000,000,000 in lost productivity costs in the year 2000 alone.
- (5) According to the Federal Drug Abuse Warning Network, most drug-related deaths involve multiple drugs including prescription opioids and alcohol. Opioid

overdose deaths are occurring among those who are taking pharmaceutical opioid drugs, like oxycodone and hydrocodone, and among heroin users.

(6) Community-based programs working with high-risk populations have successfully prevented deaths from opioid overdoses through education and access to effective reversal agents, such as naloxone.

(7) Naloxone is a highly effective opioid antagonist that reverses overdose from both prescription opioids and heroin.

(8) Public health programs to make naloxone available to people at-risk of a drug overdose are currently operating in major cities including Baltimore, Chicago, Los Angeles, New York City, Boston, San Francisco, and Philadelphia, and statewide in 3 States including New Mexico, Massachusetts, and New York. A naloxone distribution program in Boston saved more than 170 lives in the last year alone.

(9) Between 2001 and January 2008, it is estimated that more than 2,600 overdoses have been reversed in 16 programs across the Nation.

(10) Many fatal drug overdoses occur in the presence of witnesses who can respond effectively to an overdose when properly trained and equipped.

(11) Overdose prevention programs are needed in correctional facilities, addiction treatment programs, and other places where people are at higher risk of overdosing after a period of abstinence.

SEC. 3. OVERDOSE PREVENTION GRANT PROGRAM.

(a) Program Authorized- The Director of the Centers for Disease Control and Prevention shall award grants or cooperative agreements to eligible entities to enable the eligible entities to reduce deaths occurring from overdoses of drugs.

(b) Application-

(1) IN GENERAL- An eligible entity desiring a grant or cooperative agreement under this section shall submit to the Director an application at such time, in such manner, and containing such information as the Director may require.

(2) CONTENTS- An application under paragraph (1) shall include--

(A) a description of the activities to be funded through the grant or cooperative agreement; and

(B) a demonstration that the eligible entity has the capacity to carry out such activities.

(c) Priority- In awarding grants and cooperative agreements under subsection (a), the Director shall give priority to eligible entities that--

(1) are public health agencies or community-based organizations; and

(2) have expertise in preventing deaths occurring from overdoses of drugs in populations at high risk of such deaths.

(d) Eligible Activities- As a condition on receipt of a grant or cooperative agreement under this section, an eligible entity shall agree to use the grant or cooperative agreement to carry out one or more of the following activities:

(1) Purchasing and distributing drug overdose reversal agents, such as naloxone.

(2) Training first responders, other individuals in a position to respond to an overdose, and law enforcement and corrections officials on the effective response to individuals who have overdosed on drugs.

(3) Implementing programs to provide overdose prevention, recognition, treatment, or response to individuals in need of such services.

- (4) Evaluating, expanding, or replicating a program described in paragraph (1) or (2).
- (e) Report- As a condition on receipt of a grant or cooperative agreement under this section, an eligible entity shall agree to prepare and submit, not later than 90 days after the end of the grant or cooperative agreement period, a report to the Director describing the results of the activities supported through the grant or cooperative agreement.
- (f) Authorization of Appropriations- There are authorized to be appropriated to carry out this section \$27,000,000 for each of the fiscal years 2010 and 2011, and such sums as may be necessary for each of the fiscal years 2012 through 2014.

SEC. 4. SENTINEL SURVEILLANCE SYSTEM.

- (a) Data Collection- The Director of the Centers for Disease Control and Prevention shall annually compile and publish data on both fatal and nonfatal overdoses of drugs for the preceding year. To the extent possible, the data shall be collected from all county, State, and tribal governments, the Federal Government, and private sources, shall be made available in the form of an Internet database that is accessible to the public, and shall include--
 - (1) identification of the underlying drugs that led to fatal overdose;
 - (2) identification of substance level specificity where possible;
 - (3) analysis of trends in polydrug use in overdose victims, as well as identification of emerging overdose patterns;
 - (4) results of toxicology screenings in fatal overdoses routinely conducted by State medical examiners;
 - (5) identification of--
 - (A) drugs that were involved in both fatal and nonfatal unintentional poisonings; and
 - (B) the number and percentage of such poisonings by drug; and
 - (6) identification of the type of place where unintentional drug poisonings occur, as well as the age, race, and gender of victims.
- (b) Authorization of Appropriations- There are authorized to be appropriated to carry out this section \$5,000,000 for each of the fiscal years 2010 and 2011, and such sums as may be necessary for each of the fiscal years 2012 through 2014.

SEC. 5. SURVEILLANCE CAPACITY BUILDING.

- (a) Program Authorized- The Director of the Centers for Disease Control and Prevention shall award grants or cooperative agreements to State, local, or tribal governments to improve fatal and nonfatal drug overdose surveillance capabilities, including the following:
 - (1) Implementing or enhancing the material capacity of a coroner or medical examiner's office to conduct toxicological screenings where drug overdose is the suspected cause of death.
 - (2) Training and other educational activities to improve identification of drug overdose as the cause of death by coroners and medical examiners.
 - (3) Hiring epidemiologists and toxicologists to analyze and report on fatal and nonfatal drug overdose trends.
 - (4) Purchasing resources and equipment that directly aid drug overdose surveillance and reporting.
- (b) Application-

(1) IN GENERAL- A State, local, or tribal government desiring a grant or cooperative agreement under this section shall submit to the Director an application at such time, in such manner, and containing such information as the Director may require.

(2) CONTENTS- The application described in paragraph (1) shall include--

(A) a description of the activities to be funded through the grant or cooperative agreement; and

(B) a demonstration that the State, local, or tribal government has the capacity to carry out such activities.

(c) Report- As a condition on receipt of a grant or cooperative agreement under this section, a State, local, or tribal government shall agree to prepare and submit, not later than 90 days after the end of the grant or cooperative agreement period, a report to the Director describing the results of the activities supported through the grant or cooperative agreement.

(d) Authorization of Appropriations- There are authorized to be appropriated to carry out this section \$5,000,000 for each of the fiscal years 2010 and 2011, and such sums as may be necessary for each of the fiscal years 2012 through 2014.

SEC. 6. REDUCING OVERDOSE DEATHS.

(a) In General- Not later than 180 days after the date of the enactment of this Act, the Director of the Centers for Disease Control and Prevention shall develop a plan in consultation with a task force comprised of stakeholders to reduce the number of deaths occurring from overdoses of drugs and shall submit the plan to Congress. The plan shall include--

(1) an identification of the barriers to obtaining accurate data regarding the number of deaths occurring from overdoses of drugs;

(2) an identification of the barriers to implementing more effective overdose prevention strategies and programs;

(3) an examination of overdose prevention best practices;

(4) an analysis of the supply source of drugs that caused both fatal and nonfatal unintentional poisonings;

(5) recommendations for improving and expanding overdose prevention programming; and

(6) recommendations for such legislative or administrative action as the Director considers appropriate.

(b) Definition- In this section, the term `stakeholder' means any individual directly impacted by drug overdose, any direct service provider who engages individuals at-risk of a drug overdose, any drug overdose prevention advocate, the National Institute on Drug Abuse, the Center for Substance Abuse Treatment, the Centers for Disease Control and Prevention, the Food and Drug Administration, and any other individual or entity with drug overdose expertise.

SEC. 7. OVERDOSE PREVENTION RESEARCH.

(a) Overdose Research- The Director of the National Institute on Drug Abuse shall prioritize and conduct or support research on drug overdose and overdose prevention. The primary aims of this research shall include--

(1) examinations of circumstances that contributed to drug overdose and identification of drugs associated with fatal overdose;

- (2) evaluations of existing overdose prevention program intervention methods; and
 - (3) pilot programs or research trials on new overdose prevention strategies or programs that have not been studied in the United States.
- (b) Dosage Forms of Naloxone- The Director of the National Institute on Drug Abuse shall support research on the development of dosage forms of naloxone specifically intended to be used by lay persons or first responders for the prehospital treatment of unintentional drug overdose.
- (c) Authorization of Appropriations- There are authorized to be appropriated to carry out this section \$5,000,000 for each of the fiscal years 2010 and 2011, and such sums as may be necessary for each of the fiscal years 2012 through 2014.

SEC. 8. DEFINITIONS.

In this Act:

- (1) DIRECTOR- Unless otherwise specified, the term `Director' means the Director of the Centers for Disease Control and Prevention.
- (2) DRUG- The term `drug'--
 - (A) means a drug (as that term is defined in section 201 of the Federal Food, Drug, or Cosmetic Act (21 U.S.C. 321)); and
 - (B) includes any controlled substance (as that term is defined in section 102 of the Controlled Substances Act (21 U.S.C. 802)).
- (3) ELIGIBLE ENTITY- The term `eligible entity' means an entity that is a State, local, or tribal government, a correctional institution, a law enforcement agency, a community agency, or a private nonprofit organization.
- (4) STATE- The term `State' means any of the several States, the District of Columbia, Puerto Rico, the Northern Mariana Islands, the Virgin Islands, Guam, American Samoa, and any other territory or possession of the United States.
- (5) TRAINING- The term `training' means any activity that is educational, instructional, or consultative in nature, and may include volunteer trainings, awareness building exercises, outreach to individuals who are at-risk of a drug overdose, and distribution of educational materials.