PROTOCOL TITLE:

Naloxone Auto-injector as a Universal Precaution for Patients with Opioid Substance Use Disorder (DSM-V)

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REGULATORY FRAMEWORK:

Please indicate all that apply:

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1. Objectives

To conduct a pilot study of a naloxone auto-injector in a "Universal Precaution" manner for patients with opioid substance use disorder. Our three objectives are:

1) To decrease the number of fatal and nonfatal overdose deaths by use of the naloxone auto-injector by co-prescribing in the University of New Mexico Addiction and Substance Abuse Program (UNM ASAP).
2) To study the characteristics of the study subjects who performed the overdose reversals (vs. the study subjects who did not) using a biostatistical logistic regression analysis
3) To qualitatively study the in-depth characteristics of study subjects who a) documented many overdosed reversals/"saved" many community members, b) documented one overdose reversal/"saved" one community member, and c) did not document any overdose reversals.
4) Study the 2 mg Evzio autoinjector product to prospectively analyze the difference in doses (2 mg vs. 0.4 mg) needed to reverse an overdose. The goal will be to recruit 100 patients in one year and document between 20-30 overdose reversals in the community.

Note: Between April 4th 2016 and April 4th 2017, 383 study subjects were enrolled and there were 93 reported overdose reversals. We are currently enrolling new patients at the rate of 6-10 new patients per month.

2. Background

a. The use of naloxone auto-injectors to block the pharmacological effects of opioid medications may have a positive impact on the overdose deaths from prescription opiates if utilized in a manner similar to other emergency devices. Several formulations are available including intravenous, intramuscular, and subcutaneous injections, all of which are commonly used administration routes. Adverse events due to opioid overdose can occur in many situations, and risk of death increases if treatment is not administered immediately. Because of respiratory depression, there is not enough time for patient transport to the emergency room before treatment is initiated. The risk of death, and/or cerebral hypoxia/anoxia increases substantially. A formulation of naloxone that is easy to administer under any condition could be utilized as a "rescue kit" in the same conceptual manner of "Universal Precautions" as a glucagon injection is used for a person that uses insulin to control blood sugar in an emergency.

According to the National Survey on Drug Use and Health, between 55% of patients dying of an unintentional opioid overdose obtain their medication from a friend or relative.[1] 17.3% of patients dying of an unintentional opioid overdose obtain their medication directly from one doctor. Additionally, unintentional opioid overdoses remain the third leading cause of childhood poisonings at 7.9% of all childhood poisonings (after cosmetics and cleaning products).[2]

b. Drug Prescription Overdose Death in the United States and New Mexico

Death due to opioid overdose is a serious issue in the Unites States. The Center for Disease Control reports that 14,800 people in the United States died of prescription opioid overdose in 2008, more than triple the figure from 1999.[5] Additionally, 475,000

emergency room visits due to misuse and abuse of prescription opioid were reported in 2009.[5]

Opioid use and related deaths are critical issues in New Mexico. In 2008, New Mexico had the highest opioid overdose death rate in the Unites States --27.0 deaths per 100,000 population, 2.3 times higher than the U.S. average of 11.9 in 2008.[5,6] Although the death rate was reduced to 21.6 deaths per 100,000 population in 2009, it rose to 23.3 deaths in 2010 and 25.9 deaths in 2011. Both figures still exceed the U.S. average.[7] Moreover, not only is the opioid death rate high in New Mexico, the overdose death rate for the illicit drug heroin is also high. Although the rate per 100,000 population of opioid overdose deaths was the worst in 2010 in New Mexico, the rate of prescription painkillers sold was 6.7 per 100,000 population, which was not the highest opioid sales rate in the United States (highest: Florida, 12.6 per 100,000 population; the US average: 7.3 per 100,000 population).[5] A confounder to this issue is that at this time the national mortality data provided by the Centers for Disease Control and the mortality data for New Mexico provided by the Office of the Medical Investigator are not able to define if deaths are due to illicit opiate use such as heroin, prescribed opiate use or both. This indicates that drug overdose deaths may be due to greater misuse of pain medications in New Mexico.

Furthermore according to the Office of Adolescent Health, 8% of adolescents (ages 12-17) in New Mexico used pain relievers, including opioids, for nonmedical purposes whereas the U.S. average was 6% in 2011.[8] The rate of exposures to tobacco, alcohol, and other illicit drugs was also higher in New Mexico than the U.S. average.[8] The availability and use of drugs at an early age may contribute to the reasons why New Mexico has one of the highest rates of drug over dose death in the nation.

Although drug overdose death rates varied by county in New Mexico, figures from the New Mexico Department of Health (NMDOH) show that the age-adjusted drug overdose death rate in New Mexico was 24.1 per 100,000, and illicit drug use and prescription drug use were equally contributed to the deaths.[7,9] Bernalillo County, where the University of New Mexico Hospital study site is located, has the highest population in New Mexico (estimated 662,564 in April 2010), and approximately 30% of New Mexico's residents live in Bernalillo County.[10] Bernalillo County experienced the 10th highest drug overdose death rate (25.4 per 100,000) in New Mexico between 2008 and 2012.[7] This is greater than the U.S. average and the rate of New Mexico. Therefore, prevention of drug overdose deaths is a socially and epidemiologically critical issue in Bernalillo County, and any interventions for the prevention of drug overdose deaths must be established immediately.

c. Use of naloxone in the field to treat opioid overdose

- Treatment of Drug Overdose

The increase in deaths due to opioid overdose has contributed to the development of community-based overdose prevention programs, such as Project Lazarus, overdose education and naloxone distribution (OEND), and Project DAWN.[11-13] Naloxone is considered the primary antidote for opioid overdose and is vital in preventing fatal events. It is a competitive *mu* opioid-receptor antagonist that reverses opioid intoxication and is given via a parenteral, intranasal, or pulmonary route.[14] Naloxone's onset of action is seen in less than two minutes and lasts 20 to 90 minutes.[14] Dosing of naloxone is empirical, depending on many factors, including the quantity of opioid ingested, relative

affinity for the *mu* opioid-receptor, patient weight, and degree of penetration of the opioid into the central nervous system.[14] Initially, a 0.04 mg dose of naloxone should be given intravenously for respiratory depression and other symptoms associated with opioid overdose.[14] If the patient does not respond, the dose should be increased every two minutes to a maximum of 15 mg.[14] For intramuscular or subcutaneous administration, a single dose of 0.4 mg is given, and it may repeat every 2 to 3 minutes until emergency medical assistance becomes available.[14]

- ***Project Lazarus*[11]**

Wilkes County, which is in western North Carolina, had a population of approximately 66,500 in 2010. Their population was primarily composed of workers who historically suffered from chronic pain due to work-related injury. In 2009, the unintentional drug overdose death rate in Wilkes County was 46.6 per 100,000 population, or four times greater than the U.S. average. Thus, reducing unintentional drug overdose deaths was critical for Wilkes County.

The Wilkes County Health Department and the University of North Carolina took the initiative to launch a drug overdose prevention study. Its objectives:

- Establish a community-activated drug overdose prevention study and build a partnership among healthcare providers.
- Monitor data regarding unintentional drug overdose deaths before, during, and after the study.
- Prevent unintentional drug overdose deaths in the county.
- Use a naloxone rescue kit for people at risk of drug overdose deaths.
- Evaluate the project.

To accomplish these objectives, the research team educated primary-care physicians and people who were at risk of drug overdose death. The physicians received training to manage patients with chronic pain and to prescribe opioid safely with the naloxone rescue kits. The patients received education on pain management and opioids at a prescriber's office and received the naloxone rescue kit for free.

In 2010, the research team significantly reduced the number of unintentional drug overdose deaths to 29.0 per 100,000 population. Additionally, the number of drug overdose deaths due to prescription opioid was reduced to 10% (2010) from 82% (2008) of all drug overdose deaths in Wilkes County.

In only one year, the program was able to successfully reduce the number of unintentional drug overdose deaths in Wilkes County. The education for primary-care physicians and for high-risk patients of drug overdose deaths, along with the naloxone rescue kit, contributed to the dramatic changes.

- ***Overdose education and nasal naloxone distribution (OEND) program in Massachusetts*[12]**

The OEND program is also well-known clinical study that successfully decreased drug overdose deaths in Massachusetts. The Massachusetts Department of Public Health took the initiative for the study, the objective of which was to investigate the education of drug overdoses for people at high risk of drug overdose death and for bystanders (defined as "social service agency stuff, family and friends of opioid users"). The investigators

monitored the rate of drug overdose deaths and acute care utilization (e.g., emergency room visit) in Massachusetts.

The study recruitment was held in 351 communities in Massachusetts between 2006 and 2009. Nineteen communities, which reported five or more drug overdose deaths annually between 2004 and 2006, were targeted to initiate interventions for drug overdose. Study participants were opioid users (defined as current use or at recovery stage) who were at risk for drug overdose and their bystanders. The investigators provided education on drug overdose and on management of drug overdoses to patients who were opioid users and their bystanders. The education was a modified version of the Harm Reduction Coalition and the Chicago Recovery Alliance, and participants learned current circumstances of drug abuse, risk reduction of drug overdose deaths, emergency rescue breathing, and administration of intranasal naloxone. The rescue kits were distributed to all study participants. The naloxone rescue kits were dispensed to 2,912 people. The kits were used in 327 times, and opioid users used 286 unique individuals (87.5%).

Overall, naloxone was effective in improving unresponsiveness and respiratory depression. The success rate was 98% (opioid users: 98%; bystanders: 100%), and one or two doses of naloxone did rescue patients with unresponsiveness and respiratory depression. Among all study participants who used the naloxone rescue kit, 95% used it for someone other than themselves, such as friends, partner or family, or strangers. Among opioid users, only 6% used the rescue kit for themselves. Among bystanders, 43% used the rescue kit for friends, 41% for partners or family, and 16% for strangers.

The results of this study illustrate that availability of the naloxone rescue kits saved not only people at risk of opioid overdose death but also their friends, family members, or strangers whose risk of opioid overdose death was unidentified. Additionally, the higher the study enrollment rate, the more effective the rescue kit was in preventing drug overdose deaths.

- ***Similar studies with naloxone in New Mexico (studies in Taos, Roswell, and Santa Fe)[15]***

In New Mexico, the NMDOH conducted a similar pilot study with naloxone for the prevention of drug overdose deaths in the Taos, Roswell, and Santa Fe areas. The pilot study started in January 2013, and the investigators monitored the following items at enrollment to determine which risk factors a study candidate had for drug overdose deaths among opioids and other illicit drug users, such as history of substance abuse, diagnosis of psychiatric diseases, concurrent liver, kidney, and/or respiratory disease(s), high daily dose of opioids.

The investigators also assessed reasons for the use of a naloxone rescue kit (overdose, outdated, lost, stolen, or destroyed); who the kit was used for (person who is prescribed opioid or not); other medications (heroin, cocaine, benzodiazepine, alcohol, “meth”); utilization of healthcare providers/institutions; and utilization of emergency call.

The NMDOH reported that the investigators in three areas have continued recruitment of study candidates.

Innovation of Proposed Study

Currently, a significant amount of attention is being directed to the use of COT. Given

that New Mexico ranks third in the United States for the rate of accidental overdose deaths associated with prescribed opioid use, this attention is warranted. Prescribing intramuscular and intranasal naloxone rescue kits to high risk patients receiving chronic opioids to treat chronic pain has been employed recently as one effort that might decrease the accidental overdose rate associated with these medications. In past studies, risk stratification criteria have been employed to select patients on chronic opioid therapy who may benefit most from the use of an intramuscular or intranasal naloxone rescue kit. This method could inadvertently exclude patients who also may benefit from this therapy. Patients who do not fit the current definition of high risk criteria, such as anyone on chronic opioid therapy with comorbid dementia who forgets they already have taken their opioid mediation and the takes a second dose, or a patient whose metabolism of an opioid is changing, still may be at risk for adverse events associated with chronic opioid therapy. Rather than using inclusion criteria to select patients who receive naloxone auto-injector, a model that does not define "high risk" patients a priori, may offer improved benefits from the use of naloxone auto-injector. If a "universal precautions" method is employed, much in the same manner as epinephrine injection dispensed to patients with a history of anaphylaxis, or a glucagon pen and/or glucose tablets being dispensed to patients who use insulin to treat diabetes, the prescribing of naloxone auto-injector to all patients on chronic opioid therapy for chronic pain may have a greater impact on the accidental overdose morbidity/mortality rate associated with the use of chronic opioid therapy. Additionally, it may be beneficial to make naloxone available as a universal precaution for people who were not prescribed opioid to decrease mortality due to drug overdose. According to previous naloxone studies, a significant amount of opioid mortality occurs among those for who the opioid wasn't prescribed.[11,12]

Year 1- ASAP Study

Since April 2016, we have enrolled 358 patients at ASAP in our prospective nonrandomized clinical trial using the Evzio autoinjector. We have documented 82 overdose reversals thus far. Only one of the reported overdose reversals was from the study patients at ASAP, while the other 81 overdose reversals were from community members received naloxone from the study patients. For every 100 patients enrolled in the study, approximately 23 overdose reversals have been reported. We have submitted a peer-reviewed article about this data, and are now waiting to hear back regarding acceptance of the submission.

3. Study Design

3.1. The previous study at ASAP is a prospective observational study using the naloxone 0.4 mg auto-injector which took place April 4th, 2016 through April 30th, 2017.

3.2. Evaluation of patients enrolled include: # overdoses reversed, # naloxone doses needed, urine toxicology, history of overdoses witnessed, history of being reversed by naloxone, demographic information, medical history, etc.

3.3. For this current study, we propose the following new additional studies:

- A biostatistical logistic regression analysis to study the characteristics of the study subjects who performed the overdose reversals (vs. the study subjects who did not).

- A qualitative study to examine in-depth the characteristics of study subjects who a) documented many overdosed reversals/"saved" many community members, b) documented one overdose reversal/"saved" one community member, and c) did not document any overdose reversals
- Study the 2 mg Evzio autoinjector product to prospectively analyze the difference in doses (2 mg vs. 0.4 mg) needed to reverse an overdose. The goal will be to recruit 100 patients in one year and document between 20-30 overdose reversals in the community.

4. Inclusion and Exclusion Criteria

Inclusion Criteria

A. All patients treated with naltrexone, methadone or buprenorphine as medication assisted treatment at the UNM Addiction and Substance Abuse Program (UNM ASAP) aged 18 or older.
   - Over 70% of patients at UNM ASAP on medication assisted treatment use methadone
B. Subjects who sign a consent form.

Exclusion Criteria

A. Subjects who are allergic to naloxone and its inactive ingredients.
   - Inactive ingredients: buffering agents
B. Subject younger than 18.

5. Number of Subjects

The University of New Mexico Addiction and Substance Abuse Program (UNM ASAP) will be the research site, to include all subjects with a DSM-V diagnosis of substance use disorder. The UNM ASAP treats approximately 600 patients for substance use disorders with diagnosis of opioid dependence disorder annually. Ninety percent of these patients are treated daily as a part of their federally funded methadone maintenance treatment program. The remainder are treated with buprenorphine or naltrexone as opioid replacement therapy. Naltrexone has an FDA indication to treat opioid dependence.

We will explain the study to all potential candidates; however, 20-30% of the patients may decline to participate in the study.
We are enrolling study subjects at a current rate of approximately 6-10 subjects per month and anticipate this continuing throughout the year. Additionally, we can anticipate that our current study population is reporting a steady overdose reversal rate of 23% for every 100 patients enrolled. This number has not changed since July 2016.

Power analysis: the occurrence of opioid overdose death at the UNM ASAP is approximately 10% annually. With a sample size of 500 people we will have 80% power to detect a 20% difference in mortality at alpha level of 0.05.

6. Study Timelines

The research team submitted the initial IRB application at the beginning of October 2015. Recruitment at UNM ASAP will start in January 2016, after receiving IRB approval. The research team will follow the study subjects for one year and will close the study when qualitative interviews have been completed.

If the IIS is approved, the research team will begin the logistic regression analysis as soon as possible. Once the IRB approves the qualitative modifications, the face-to-face 1:1 interviews will begin with the study subjects.
The recruitment for the Second Year Study will begin June 1, 2017 at UNM ASAP, after receiving IRB approval for protocol amendment. The research team will follow a study subject for one year and will close the study when qualitative interviews have been completed.

7. Study Endpoints

There are four endpoints in this study:

1. Number of fatal over dose deaths and near fatal overdoses averted by use of naloxone auto-injector co-prescribing from the University of New Mexico Addiction and Substance Abuse Program (UNM ASAP)
2. To study the characteristics of the study subjects who performed the overdose reversals (vs. the study subjects who did not) using a logistic regression analysis
3. To qualitatively study the in-depth characteristics of study subjects who a) documented many overdosed reversals/"saved" many community members, b) documented one overdose reversal/"saved" one community member, and c) did not document any overdose reversals
4. Study the 2 mg Evzio autoinjector product to prospectively analyze the difference in doses (2 mg vs. 0.4 mg) needed to reverse an overdose. The goal will be to recruit 100 patients in one year and document between 20-30 overdose reversals in the community. (Between April 4th 2016 and April 4th 2017, 383 study subjects were enrolled and there were 93 reported overdose reversals)We are currently enrolling new patients at the rate of 6-10 new patients per month.

8. Research Setting

Research facility: The study is conducted at UNM ASAP.
UNM's ASAP is a part of the behavioral health program under the UNM Psychiatric Center. ASAP specializes in providing diverse, proven substance abuse and mental health treatment, including specialized services for women. ASAP provides services to adults and adolescents with a primary substance abuse diagnosis and/or individuals who have a substance abuse disorder along with other mental health issues.
Location: 2600 Yale SE, Albuquerque, NM 87106

9. Resources Available

Study personnel
Principal investigator:
Joanna G. Katzman MD, professor, Department of Neurosurgery, School of Medicine
As medical director and founder of the UNM Pain Center and ECHO Pain clinic at the

University of New Mexico, Dr. Joanna G. Katzman has played key roles in improving access to specialty care for chronic pain patients, as well as in improving the quality of care by providing consultative, educational, and therapeutic services to patients throughout New Mexico. She has a broad background in neurology, pain and headache management, neurorehabilitation, and traumatic brain injury, and for the past three years she has effectively led the interdisciplinary team of pain specialist at Project ECHO. She will serve as an investigator on this project. This proposed project is a collaboration study with the New Mexico Department of Health and will definitely reduce drug overdose deaths, which are a serious public health issue in New Mexico.

Co-investigators (alphabetical order)

Snehal Bhatt, MD, associate professor, Addiction and Substance Abuse Program Medical Director, School of Medicine
Snehal Bhatt is a board certified physician in General Psychiatry and Addiction Psychiatry. He is on faculty at the University of Mexico, where he is the medical director for the Addictions and Substance Abuse Programs, which is a clinic serving over 800 patients with addictions, and co-occurring psychiatric illnesses. Additionally, he has been partnering with IHS Center for Telebehavioral Excellence and tribal programs to provide direct care, along with didactics and case consultations to clinicians across the nation. His current research projects include working with prisoners prior to their release in order to reduce recidivism rates, and studying the effects of psilocybin assisted psychotherapy as a treatment for alcoholism. His professional areas of interest include improving access to addictions treatment, managing co-occurring pain and addictive illnesses, teaching, and sociocultural elements of addictive illnesses and treatment.

Nina Greenberg, MS, Senior Lecturer, Department of Mathematics and Statistics, University of New Mexico
Nina Greenberg's primary responsibility is as a Senior Lecturer in Statistics at the University of New Mexico. As UNM's Department of Mathematics and Statistics Undergraduate Introductory Statistics (Stat145) course coordinator since 2009, Nina supervises about 30 sections of Introductory Statistics, with approximately 55 undergraduate students in each section, taught by a mixture of graduate teaching assistants and adjunct faculty. Nina has completed her course work towards her Master's in Public Health from UNM, she is on track to receive her degree this summer after completion of her professional paper which will analyze factors associated with years of potential life lost and malignant breast cancer. In addition to an MA in Statistics from UNM (2006), she has earned a Secondary Teacher Certificate from the University of Phoenix (2002), an MS in Marine Science from San Jose State (1992), a BA in Biology and a BS in Journalism from the University of Colorado (1985). Since August of 2016, Nina has served as a part-time Biostatistician for Project ECHO (Extension for Community Healthcare Outcomes) working to evaluate a medical provider virtual intervention for training in pain management within the U.S. Defense Health Agency. She recently conducted data analyses for a study on the co-prescribing of Naloxone to patients receiving medication assisted treatment. Nina has worked with the Indian Health

Services analyzing population demographics as well as differences in pre-and post-survey data from national virtual trainings for health care providers in pain and addiction. She has also conducted data analyses on associations between physical activity and grades in the NM-YRRS survey of adolescents in New Mexico.

Julie Griffin Salvador, PhD, Assistant Professor in the University of New Mexico, Department of Psychiatry, Division (UNM) of Community Behavioral Health (CBH).
As a trained cultural anthropologist, she focuses on use of qualitative data and ethnographic methods in her community engaged research approach, working in partnership with rural and underserved populations in New Mexico including American Indian and Hispanic communities. She has extensive experience conducting federally supported research studies, serving as lead researcher responsible for study design, proposal development, implementation, and dissemination activities. Her research projects include funding from the National Institute on Drug Abuse, the Substance Abuse and Mental Health Services Administration, and multiple research contracts with New Mexico's Behavioral Health Services Division and with the Children Youth and Families Department. Her recently completed research projects have focused on efforts to expand access to evidence-based practices for rural primary care and behavioral health care providers. She has enrolled over 300 rural providers across the state in data collection efforts to understand barriers to and solutions for improving best practice implementation. Currently, Dr. Salvador leads the SAMSHA funded Systems of Care Expansion initiative focused on improving care for youth in New Mexico with Serious Emotional Disturbances and their families. Dr. Salvador has broad research interests within health and health services including teen pregnancy, diabetes and behavioral health, particularly substance abuse, with a qualitative, ethnographic approach to understand and improve health outcomes and health disparities. She is interested in understanding the feasibility and impact of televideo approaches for building provider capacity to implement evidence-based practices in behavioral health in rural and high need areas. Her research focuses on health services at multiple levels including consumers, direct service providers, state-level leadership and policy makers to improve our understanding of individual, community, systems and policy level factors that impact health disparities in rural and ethnically diverse communities.

Kimberly Page, PhD, Professor and Chief of Epidemiology, Biostatistics and Preventive Medicine, in the Department of Internal Medicine at UNM HSC.
Dr. Kimberly Page is an infectious disease epidemiologist with experience in prospective cohort studies, clinical trials and implementation science. She is a Professor and Chief of Epidemiology, Biostatistics and Preventive Medicine, in the Department of Internal Medicine at UNM HSC. Dr. Page's leads nationally and internationally recognized research on HIV and viral hepatitis prevention in underserved and vulnerable populations, including people who inject drugs (PWID), and women engaged in transactional sex. She likes to say that her 'laboratory' is in the community, and embraces the challenges of working with hard-to-reach populations with her work in the U.S. and internationally. In addition to leading the country's first trial testing a prophylactic HCV vaccine in PWID, she has launched new studies integrating HCV

treatment and prevention in rural and urban New Mexico. She collaborates with leading researchers in the U.S and other countries to better understand and deliver global health knowledge and HIV and HCV prevention and to improve health in underserved populations. Dr. Page has a combined nine years of experience as an IRB member, including two years at UNM and previously as a faculty member at two other institutions

Mikiko Y. Takeda, MS, Pharm.D., assistant professor, Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy
Dr. Takeda is a clinical assistant professor of pharmacy practice focusing on neurological diseases, especially epilepsy and pain. Her current educational program in clinical research and public health at the University of Kansas Medical Center strengthened her research skills. She also has a research background in Japan, where she received a master's degree in pharmaceutical science, evaluating the effects of preservatives in eye drops on a rabbit cornea using electrophysiological methodology. She also initiated a cross-sectional study of disinfectant use at Saga National Hospital as a principal investigator to enhance appropriate disinfectant use in the hospital. As part of her fellowship, she initiated a safety study of Keishibukuryogan (a Japanese herbal medication) among women with epilepsy. Her passion and enthusiasm for clinical research motivates her to carry out the proposed study. She coordinates this clinical study and prepares necessary documents, including the research proposal, informed consent form, and budget sheet. She also analyzes and summarizes the data with SAS.

Other significant study personnel/contributor (alphabetical order)
Amal Alchbli, M.D., Department of Neurosurgery
Role: Research assistant

Monica Moya, M.S., Department of Neurosurgery
Role: Research assistant

Karla Wagner, PhD, Assistant Professor in the School of Community Health Sciences at the University of Nevada, Reno.
Dr. Wagner is an Assistant Professor in the School of Community Health Sciences at the University of Nevada, Reno. She conducts mixed methods research that focuses on the prevention of negative health outcomes associated with injection drug use, especially HIV, viral hepatitis, and fatal overdose. Her current projects use qualitative, quantitative, and social network methods to investigate the social and environmental factors associated with HIV risk, HIV testing, and drug overdose. She also provides technical assistance and conducts evaluation research on the effectiveness of overdose education and naloxone distribution to prevent fatal opioid overdoses.

Students

10.Prior Approvals

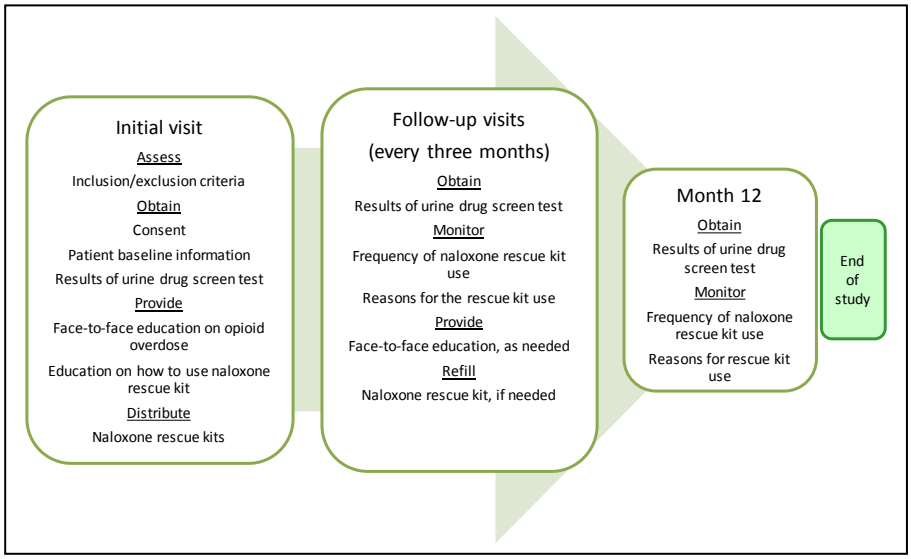
Similar study using intranasal naloxone for patients with chronic opioid therapy at the UNM Pain Center (IRB study ID: 13-630). It was approved in April 2014 (current study status: continued) (see Appendix 1 – initial approval letter).

11.Multi-Site Research

The study site is UNM ASAP only.

12.Study Procedures

Investigators at UNM ASAP will distribute naloxone rescue kits to all study subjects. Naloxone is a prescription medication administered intravenously, subcutaneously or intramuscularly. In this study, the research team will use the naloxone auto-injector which is the only product FDA approved and labeled for use by family members or caregivers for emergency therapy wherever opioids are present. The research team will distribute the kits at the initial visit and provide education on drug overdose and rescue method from an overdose (education materials: see Appendix 2: A Patient's Guide to Evzio and Appendix 9: Opioid Overdose Toolkit) upon receiving informed consent. The education material covers education on opioid overdose and how to use the auto-injector. Education will be provided not only for patients but also, if the patient agrees, their bystander (bystander is defined as a caregiver, such as family member, friend, etc.) at initial visit and follow-up visits. According to the New Mexico Good Samaritan Law, any bystanders of patient are able to provide naloxone when drug overdose occurs. Thus, we will educate patients and their bystanders on the signs and symptoms of drug overdose due to opioids, drug overdose deaths and its risks (Appendix 9), how to use naloxone auto-injector (Appendix 2). If the patient would like to be enrolled in the study without a bystander present, he/she will be educated on the use of intramuscular naloxone and asked that they educate their friends and/or family. The subjects will return to UNM ASAP every three months after the initial visit for a follow-up. The following figure describes the procedures the investigator will carry out during each visit.



Initial Visit: Assess inclusion/exclusion criteria, obtain consent, results of urine drug screening test, and baseline information, provide face to face opioid education (individual or group education – up to 6 people in a group) and how to use naloxone auto-injector, and distribute one naloxone auto-injector carton prior to the next study visit (there are 2

naloxone auto-injector per carton).

Follow-up Visit (every three months): Obtain results of urine drug screening test, monitor frequency of naloxone auto-injector use, reason for naloxone auto-injector use, provide face to face education, as needed and refill naloxone auto-injector kit as needed. When patients report opioid overdose at these follow-up visits, we will obtain further information on the overdose via patient interview. The information will include date, time, and dose of naloxone use, clinical outcome [i.e., successful opioid reversal, death, and utilization of healthcare institution (e.g., EMS, emergency room, hospitalization)], to whom the kits were used, causality [i.e., type(s) of opioid], and call 911 after utilization of the kit. We will confirm the record by accessing PowerChart, only if patients used UNM Hospital for treatment.

Month 12 (1 Year): End of study visit: Obtain results of urine drug screening test, continue to ask same questions as in Follow-up visit.

If a patient uses the naloxone prior to the scheduled clinic visit, the study team will distribute one naloxone auto-injector carton prior to the next study visit. The study team will inquire about the circumstances for the use of the naloxone auto-injector.

Optional qualitative sub-study: If a study subject is selected as a potential candidate for the qualitative study, they may be contacted by phone or in person during one of their clinic visits and have the optional sub-study consent explained to them. If the person agrees to be interviewed, this will be done at a private consult room at ASAP. This visit may take 30-45 min at the end of which they will receive a $20 gift card.

13.Data Analysis

Statistical Analysis

Statistical analysis will be performed usingSTATA (College Station Texas) and SAS version 9.3 (Cary, NC, United States).
The research team will collect the data and will use a descriptive analysis for demographic, social status, medical history, physical examinations, including vital signs (normal vs. abnormal findings), number of concomitant medications, scores of RIOSORD, and outcome related parameters listed in Section 12.

The team will compare the monitoring parameters listed above to identify demographic data, epidemiological data, and correlations with the use of naloxone rescue kits. Differences between ASAP in categorical variables (utilization of naloxone auto-injector, utilization of EMX-run and emergency room visit during study period, gender, race, ethnicity, education level, marital status, results of physical examination [normal vs. abnormal], presence of substance abuse) will be tested by Chi Square test or Fisher exact test where appropriate. Differences in continuous variables (e.g., age, RIOSORD scores) will be tested by independent two samples, Student's *t* test, or Wilcoxon Rank Sum test, where appropriate. *P* values of less than 0.05 were considered statistically significant.

14.Provisions to Monitor the Data to Ensure the Safety of Subjects

In accordance with the IRB at UNM HSC, the investigators commit that the data will be used only for the research purpose. The data will be disclosed to all study investigators. The investigators will use PowerChart to obtain necessary information, such as past medical history, family history, and concomitant medications. The investigator will keep a patient log ("log book", Appendix 7) to track patients' consequent clinic visits. The investigators will use paper- and electronic-based data collection during their face-to-face interviews. All data will be transferred to REDCap system. The paper-based data and the log book will be stored in a locked cabinet in physician's office (Dr. Bhatt) at UNM ASAP. The paper- and electronic-based database and Excel file will be destroyed upon completion of data analysis. The study medication is stored in another locked cabinet of the same office. This room is also locked and only a few employees (charge nurse, study coordinator, PI, medical director) have access to open the room each day.
Reported adverse reactions from naloxone for opioid overdose were tremor and hyperventilation associated with an abrupt return to consciousness.[16] We will ask if study subjects experience withdrawal symptoms at their clinic visits. The frequency of these adverse reactions is unknown. These adverse reactions are not life-threatening, and hyperventilation will be managed with rescue breathing. This topic is included in patients' education in this study.

Only deidentified health related information will be shared with the study sponsor. However, the following agencies will be contacted for specific circumstances: CYFD for child abuse; NM Department of Health for reportable communicable disease (e.g., measles, varicella, rubella); and UNM security or Albuquerque Police Department for subject's threat of violence to self or others. The study related data may be audited by federal agencies, such as the U.S. Department of Health & Human Services or the Food and Drug Administration (FDA). You have a right to request in writing the disclosure of any identifying information.

Data Safety Monitoring Board Meeting
The study team has periodical Data Safety Monitoring Board meeting. We plan to have this meeting every three months to objectively monitor unanticipated problems related to the study. When an unexpected adverse reaction is identified, we will schedule a meeting immediately. The board members are:

- Edwin M Nemoto, PhD, FAHA, Research Professor, Dir. Research, Department of Neurosurgery
- William E. Rivers, D.O., Assistant Professor, Department of Neurosurgery
- Andrew P Carlson, M.D., Assistant Professor, Department of Neurosurgery

15. Withdrawal of Subjects

Any subject can withdraw from this clinical study at any time during the study period. The investigators will explain the withdrawal opportunity before a study subject signs the consent form. The investigators may ask the reason for the withdrawal.

16. Data Management/Confidentiality

Monitoring Parameters

1. Outcome related parameters (Appendix 3, 4; self-report).
    a. Number of naloxone auto-injector dispensed.
    b. Reason for dispensing the naloxone rescue kit.
    c. Circumstances surrounding the use of the naloxone rescue kit.
        - Including use of other substances such as heroin, cocaine, benzodiazepine, alcohol, or methamphetamine/amphetamine.
    d. Opiate reversals.
    e. Opioid prescription data through Prescription Monitoring Program (or PMP; available through New Mexico State Board of Pharmacy) and actual patient's opioid use
2. Demographic (at initial visit only, Appendix 3: National Institute of Neurological Disorders and Stroke [NINDS] data collection format, modified).[17]
    a. Age.
    b. Gender.
    c. Ethnicity and race (self, maternal, paternal).
    d. County of residence
3. Social status (at initial visit only, Appendix 3: NINDS data collection format, modified).[17]
    a. Education level.
    b. Marital status.
4. Medical history (at initial visit only, Appendix 3: NINDS data collection format, modified).[17]
    - Past and current medical history.
5. Behavioral history (at initial visit only, Appendix 3: NINDS data collection format, modified).[17]
    - Smoking, alcohol, and illicit drug use
6. Family history (at initial visit only).[17]
    - Will only ask addiction-related diseases (i.e., history of alcohol abuse, substance abuse [prescription drug and illicit drug], and tobacco use)
7. Vital signs (heart rate, blood pressure, respiratory rate, temperature, weight, height, Likert Pain Scale (0-10), Appendix 3, 4: NINDS data collection format, modified).[17]
8. Concomitant medications (Appendix 3: NINDS data collection format, modified).[17]
9. Urine toxicology screening test
    - Patients have urine toxicology screening test at each clinic visit (every week or every 2 or 3 months, which is dependent on patient's treatment regimen), as urine toxicology screening test is a part of standard care at UNM ASAP. If a patient does not have urine toxicology screening test done within 1 week prior to follow-up study visit, the research team will order the test.
10. Risk index for overdose or serious opioid-induced respiratory depression (RIOSORD,[20] Appendix 5)

Certificate of Confidentiality

This study has a certificate of confidentiality issued by the NIH that protects study

subject's privacy.

Location of data storage
All paper-based study data will be kept in a locked cabinet at UNM ASAP. Electronic data will be kept in a secured computer system in Dr. Takeda's office (UNM College of Pharmacy, Room B21B) and Dr. Joanna Katzman's office (Clinical Neuroscience Center or CNC). The computers are in their personal office behind a locked door, and the computer requires a password to open. The password for the office computer will not be shared with other people; thus, the data will be safely stored in PI's office at CNC and UNMCOP. Access to study databases is restricted to an as-needed basis. The investigators will use paper-based and electronic-based data collection when seeing the study subjects.

Duration of data storage
The data will be kept safely for 5 years, at which time Dr. Bhatt at ASAP will destroy all paper-based patient-relevant information with a shredder or put it in a confidential disposal box. The electronic data will be destroyed at the completion of data analysis.

Data access
Dr. Takeda, Ms Moya and Ms Greenberg will be responsible for data storage and will share the data with other IRB-approved investigators on an as needed basis. Dr. Takeda and Ms. Moya may share the data with a biostatistician at the Clinical Translational Science Center for the purpose of data analysis. The biostatistician will follow HIPAA regulations and keep the data in accordance with the data storage policy at CTSC.

17. Data and Specimen Banking
In accordance with the IRB at the UNM Health Science Center (UNM HSC), the investigators commit that the data will be used only for the research purpose and not to identify individual study subjects. The investigators will use minimum identifiers (e.g., date of birth, last clinic visit) to protect the identity of the participants.

18. Risks to Subjects
The research team assumes the following risks during the study: adverse reactions from naloxone and loss of confidentiality.

1. Adverse reactions from naloxone

Reported adverse reactions from naloxone for opioid overdose were tremor and hyperventilation associated with an abrupt return to consciousness.[16] According to the package insert, the abrupt reversal was described as follows: "Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated signs and symptoms of opioid withdrawal including: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia." The frequency of these adverse reactions is unknown. These adverse reactions are not life-threatening, and hyperventilation will be managed

with rescue breathing. This topic is included in patients' education in this study.
The research coordinator and clinician will discuss the signs and symptoms of a near fatal overdose (slowed breathing, pallor, lack of responsiveness, inability to follow directions, etc). We provide validated materials to the patients from kaléo (Appendix 2) and Substance Abuse and Mental Health Services Administration (Appendix 9) related to opioid overdose which they can take home and study as well. A "practice" naloxone autoinjector is then used in the clinic so that the patient and his/her bystander can understand how it might be used in an emergency and life threatening situation. In the event of emergency Naloxone use, the autoinjector speaks to the patient through the procedure so it can help with the delivery of the medication.
Distribution of the naloxone rescue kits and providing appropriate education on drug overdoses will potentially save lives of patients in New Mexico who took opioids. Naloxone auto-injector enables patients and their bystanders to provide naloxone immediately without the utilization of healthcare institution for the administration of intravenous naloxone. Additionally, the intramuscular administration route is an easy and effective way to deliver medication with minimum drug degradation.

2. Loss of confidentiality

The research team will make efforts to protect patient-related information as much as possible. The research team collects patient information, such as demographic information, use of opioids, and use of illegal drugs. The research team will not use a patient's name or any information that might reveal the identity of the patient. The research team will create a specific ID (i.e., first letter of study site, enrollment number (3-digit); e.g., A001) for each patient to minimize using a patient's name.
Additionally, as stated in Section 26, all paper-based study data will be kept in a locked cabinet at UNM ASAP. Electronic data will be kept in a secured computer system in Dr. Takeda's office (UNM College of Pharmacy, Room B21B) and Dr. Joanna Kaztman's office (Clinical Neuroscience Center).

The team will handle sensitive information regarding illegal drug use of a patient and of his/her bystanders. The study team wants to emphasize that the information obtained for the study will not be reported to law enforcement authorities. The Certificate of Confidentiality, which insures patient's privacy, was issued by the National Institute of Health for UNM Pain Center and UNM ASAP.

19. Potential Benefits to Subjects

Because New Mexico has led the country in unintentional opioid overdose deaths and opioid misuse, finding appropriate prevention for drug overdose is critical. Distribution of the naloxone rescue kits and providing appropriate education on drug overdoses will potentially save lives of patients in New Mexico who now have an opioid substance use disorder. Intramuscular naloxone enables patients and their bystanders to provide naloxone immediately without the utilization of healthcare institution for the administration of intravenous naloxone. Additionally, the intramuscular administration route is an easy and effective way to deliver medication through the muscle with minimum drug degradation. Moreover, appropriate education will help study subjects identify symptoms of drug overdose and will manage associated symptoms, such as rescue breathing. In our patient education, we will emphasize that naloxone is to be used

for opioid overdose as an antidote for patients with chronic opioid therapy but not to be used as a means of rescue method for recreational opioid use.

By utilizing a "Universal Precautions" approach in this study, where any patient on chronic opioid therapy is given an intramuscular naloxone kit, the stigma attached to the use of intramuscular naloxone may be diminished. Additionally, this approach may have an impact on the prescribing of chronic opiate medication, to the point that any patient being prescribed chronic opiate medications will routinely be given a naloxone auto-injector --Much the same as any patient prescribed insulin receives glucose tablets and/or a glucagon pen. This would have the potential to dramatically increase the safety when opiate medications are misused.

20.Recruitment Methods

Study recruitment will occur at UNM ASAP. Healthcare providers at the UNM ASAP will identify a potential study candidate or naloxone posters will be posted in the private methadone dispensing room and in the patient rooms. The patient can ask ASAP staff in a private setting about obtaining naloxone autoinjectors The candidates will be asked by ASAP staff if they are interested in taking part in the study, then they will be referred to a study coordinator on the team. The study coordinator will explain the clinical study and answer questions, such as about risks and benefits from the study candidates. After the candidate understands the study and agrees to sign an informed consent form, the candidate becomes a study subject and receives naloxone rescue kits.

21.Provisions to Protect the Privacy Interests of Subjects

Subjects will be notified by their clinic providers of this clinical study. Then the provider will obtain patients' consent. Patient's personal information will be obtained via PowerChart and/or interview, and pharmacy students and pharmacy residents will transfer the data to Excel spread sheet, which is stored in a shared drive. Any information on study subjects, such as demographic information and history of drug abuse, will be confidential.

A subject will be able to call his/her provider and ask any study-related questions before, during, and after the clinical study. The investigators will never start the study if a subject has any concerns about the study. A patient's provider will discuss with an investigator or subject's physician as needed any issues related to a subjects' health condition.

22.Economic Burden to Subjects

No cost is needed for all study participants for naloxone rescue kits and clinic visit for the study purpose.

23.Compensation

We will provide a $20 retail department store gift card for patients who participate in the qualitative study. The gift card will be paid upon completion of the interview.

24.Compensation for Research-Related Injury

Because naloxone is an antidote of opioids and only minor adverse reactions were reported in the similar clinical studies, the investigators will not anticipate serious adverse reactions. The research team will encourage all study subjects to report any adverse reactions from naloxone at each visit, if a subject uses the rescue kit. The research team will examine the causality and severity of the adverse reaction with the Naranjo algorithm and Common Terminology Criteria for Adverse Events (CTCAE) v4.0. If a serious adverse reaction occurs and the reaction is related to naloxone, the study team will compensate the patient for the cost of an emergency room visit and necessary patient's care (primary care physician's visit, medications, etc.).

25.Consent Process

The research team will obtain consent from all study subjects. The consent process will take place at the ASAP. The research team will provide enough time for a potential study candidate to understand the clinical study and to ask any study-related questions of the research team and study coordinator until all concerns are resolved. The research team also will explain that participation in the study will not affect the quality of a subject's primary care, whether or not the subject agrees with the participation. As described in Section 24 in this protocol, healthcare providers at the ASAP will identify potential study candidates. The candidates will be asked if they are interested in taking part in the study. Then the candidate will be referred to an investigator on the team. The investigator will explain the clinical study and answer questions, such as about risks and benefits, from the study candidates. After the candidate understands the study and agrees to sign the informed consent form (ICF), the candidate becomes a study subject and will receive naloxone rescue kits. The research team will follow "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

We will not recruit patients who are not able to speak and understand English. According to the latest census data, 47% of the population of New Mexico is Hispanic or Latino (2012).[10] Although the statistics shows that the major ethnicity in NM is Hispanic or Latino, the majority of the patient population at ASAP is English speaking, with only 2% of the patients are Spanish speakers. Currently there is a lack of personnel and resources available to translate all relevant materials into Spanish, should the patient population change then an effort will be made to include Spanish consent and a translator.

Subjects who are not yet adults (infants, children, teenagers)

The research team will not recruit infants, children, and teenagers 17 or younger in this study.

Cognitively Impaired Adults

The research team will not recruit cognitively impaired adults in this study.

Adults Unable to Consent

The research team will not recruit adults unable to consent in this study.

26.Documentation of Consent

The research team will follow "SOP: Written Documentation of Consent (HRP-091)."

27.Study Test Results/Incidental Findings

We will not share the study test results with study participants during the study period. However, the research team will publish the data to addiction psychiatry-related or pain management-related journal. Once the article become available in public, then we will share the article with the participants.

28.Sharing Study Progress or Results with Subjects

The results will not be shared with the study subjects. The investigator will not share any identified patient health related information with the study sponsor.

29.Inclusion of Vulnerable Populations

- The research team will not recruit infants, children, and teenagers 17 or younger in this study.
- The research team will recruit pregnant and breast feeding women. Benefits from naloxone auto-injector outweighs the risks of opioid overdose death rather than the risk of congenital malformation due to naloxone. Additionally, pregnancy risk category of the naloxone is B.[21,22] See definition below. Data on the excretion of naloxone in breast milk is unknown.
    - **Pregnancy category B**:
        - Animal reproduction studies show no evidence of impaired fertility or harm to the fetus; however, no adequate and well-controlled studies have been conducted in pregnant women.

30.Community-Based Participatory Research

Not applicable.

31.Research Involving American Indian/Native Populations

We do recruit Native Americans but this research is not intended to target American Indian/Native populations nor is it conducted on tribal lands. While participants may be of these populations we are not seeking out these participants. We have a wealth of experience with persons of tribal descent and therefore we are sensitive to the local population in terms of tribal regulations, applicable laws and standards of professional conduct and practice.

32.Transnational Research

Not applicable

33.Drugs or Devices

Drug[23]

- Generic name: Naloxone hydrochloride injection, USP
- Brand name: EVZIO

- Strength: 0.4 mg/0.4 mL in each kit[21] and 2 mg/0.4 mL in each kit[22]
- NDC number
  - 0.4 mg kit: 60842-030-01[21]
  - 2 mg kit: 60842-051-01[22]
- Manufacturer:
  Kaleo
  Richmond, VA 23219
- Pharmacology[24]
  - Naloxone is an antidote of opioids and has been used frequently for patients whose condition is opioid intoxication or for patients with respiratory depression with therapeutic opioid doses. Several formulations are available: intravenous, intramuscular, and subcutaneous injections are commonly used administration routes. However, adverse events due to opioid overdose can occur at any time. Thus, a convenient drug formulation of naloxone is necessary to administer naloxone to prevent drug overdose deaths, regardless of a patient's knowledge.
- Pharmacokinetics
  - Time to peak: 15 minutes
  - Maximum serum concentration 1.24 ng/mL
  - Time to maximum concentration: 20 minutes
  - Metabolism:
    - Primarily metabolism route: liver via glucuronidation
  - Elimination half-life: 1.36 hours
  - Excretion: Urine (as metabolites)
- Indications[24]
  - Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
    - Immediate administration as emergency therapy in settings where opioids may be present.
- Necessity of Investigational New Drug (IND) application
  - No. This product has an FDA approval in 2014.

- Drug storage
  - Naloxone auto-injector is stored at 15-25°C (59-77°F).[21] Access to the naloxone auto-injector should be limited to the investigators at UNM ASAP.
  - The naloxone auto-injectors are stored in a secure area in the medication room in UNM ASAP. A pharmacist at UNM Investigational Pharmacy will maintain logs to track who the naloxone autoinjectors are dispensed for regulatory requirements (Appendix 7 and 8).[17]

- Drug destruction
  - At the end of the clinical trial, all unused naloxone kits will be

transferred to Dr. Takeda. She will contact the Safety Office at the University of New Mexico, and will follow the direction for drug destruction accordingly. She will also create a detail report to explain following items upon destruction:

- Numbers of kit remaining at the end of the study
- Expiration date and lot number of naloxone
- Reason for the destruction

Dr. Takeda will keep the document at least 5 years from the end of the study.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

1. Describe the data source that you need to review (e.g., medical records):
   Medical record (PowerChart)

2. Describe the purpose for the review (e.g., screening):
   Screening

3. Describe who will conducting the reviews (e.g., investigators, research staff):
   Investigators and research coordinator

4. Do all persons who will be conducting the reviews already have permitted access to the data source?
   ☒ Yes
   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:
   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.
      ☒ True
      ☐ Other justification:
   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).
      ☒ True
      ☐ Other justification:
   c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.
      ☒ True
      ☐ Other justification:
   d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the*

subjects will be provided with additional pertinent information after participation.)
☒ True
☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment

1. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☒ Yes. Describe:
   A review of the medical records of current patients at the UNM ASAP is required to identify potential study subjects. This requires the use of the medical record number to review the medical record for eligibility requirements.
   ☐ No

If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

The data will be kept until all data analysis is completed, the use of PHI for screening involves no more than minimal risk as we already have access to this information for clinical care of these patients. PHI that may be used/viewed for screening will not be retained in any way after the consent process has been completed. If the patient is determined to not be an eligible participant or declines consent all PHI that may have been collected during screening will be destroyed immediately and will not be retained in any way. If the patient is determined to be eligible the patient will be consented and will sign a HIPAA authorization at that time. Any PHI collected for screening purposes will be destroyed at the earliest time possible and will not be disclosed or re-used.

2. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
   ☒ True
   ☐ False

B. Waiver of Documentation of Consent – not applicable for our study

1. Are you requesting a waiver of documentation of consent for some or all subjects?
   ☐ All
   ☐ Some. Explain:

2. Provide justification for one of the following:
    a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

    b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?
    ☐ Yes. Please attach a copy to your submission in Click.
    ☐ No

C. Alteration of Consent – not applicable for our study

Note: FDA-regulated research is not eligible for an alteration of consent.

1. Which element(s) of consent do you wish to eliminate and why?

2. Which element(s) of consent do you wish to alter and why?

3. Provide justification for each of the following regulatory criteria:
    a) The research involves no more than minimal risk to the subjects:

    b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

    c) The research could not practicably be carried out without the waiver or alteration:

    d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission – not applicable for our study

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
    ☐ All
    ☐ Some. Explain:
2. Provide justification for each of the following regulatory criteria:
    a) The research involves no more than minimal risk to the subjects:

b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs) – not applicable for our study

1. Are you requesting a waiver for some or all subjects?
   ☐ All
   ☐ Some. Explain:
2. Provide justification for each of the following regulatory criteria:
   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization – not applicable for our study

1. Are you requesting a waiver of authorization for some or all subjects?
   ☐ All
   ☐ Some. Explain:
2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under

the Privacy Rule.
☐ True
☐ False

G. Other Waiver Types – not applicable for our study

II. Vulnerable Populations

A. Adults with Cognitive Impairments – not applicable for our study

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.
2. Describe how capacity to consent will be evaluated.
3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.
4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.
5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.
6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.
7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.
8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children – not applicable for our study

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.
   - ☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*
   - ☐ Research involving greater than minimal risk but presenting the

prospect of direct benefit to the individual subjects.
Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
   The research team will recruit pregnant and breast feeding women. Benefits from naloxone auto-injector outweighs the risks of opioid overdose death rather than the risk of congenital malformation due to naloxone. Additionally, pregnancy risk category of the naloxone is B.[21] See definition below. Data on the excretion of naloxone in breast milk is unknown.
   - **Pregnancy category B**:
     Animal reproduction studies show no evidence of impaired fertility or harm to the fetus; however, no adequate and well-controlled studies have been conducted in pregnant women.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
   Naloxone hydrochloride was administered during organogenesis to mice.

These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride. But benefits from naloxone auto-injector outweighs the risks of opioid overdose death rather than the risk of congenital malformation due to naloxone.

3. Any risk is the least possible for achieving the objectives of the research. Naloxone is only recommended for use during pregnancy when there are no alternatives and benefit outweighs risk. But, again, benefits from naloxone auto-injector outweighs the risks of opioid overdose death rather than the risk of congenital malformation due to naloxone.

D. Neonates of Uncertain Viability or Nonviable Neonates – not applicable for our study

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates – not applicable for our study

Complete this checklist if the subject population will include nonviable neonates.
Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained
   - ☐ True
   - ☐ False
6. The research will not terminate the heartbeat or respiration of the neonate
   - ☐ True
   - ☐ False
7. There will be no added risk to the neonate resulting from the research
   - ☐ True
   - ☐ False

F. Biomedical and Behavioral Research Involving Prisoners – not applicable for our study

1. Select and justify which allowable category of research involving prisoners this research falls within:
   - ☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects
   - ☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects
   - ☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)
   - ☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject
   - ☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.
2. Provide justification for each of the following regulatory criteria:
   a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III. Medical Devices – not applicable for our study

A. Device Name:
B. Manufacturer:
C. Does the research involve a Significant Risk Device under an IDE?
   - ☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*
   - ☐ No

D. Is the research IDE-exempt?
   - ☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.
   - ☐ No

E. Does the research involve a Non-Significant Risk (NSR) Device?
   - ☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.
   - ☐ No

* This FDA guidance includes a description for when a device study is exempt from the

IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf
**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

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