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# Clinical Research Protocol
# OPIATE WITHDRAWAL RESPONSES TO INTRANASAL NALOXONE AS AN INDEX OF ALTERED ENDOGENOUS OPIOID ACTIVITY AMONG INDIVIDUALS WITH OBESITY: A FEASIBILITY AND EFFICACY STUDY

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| Protocol Number: | HECHTMASON1 |
| Version Date: | 15 January 2016 |
| Investigational Product: | Naloxone Hydrochloride, administered intranasally (Intranasal Naloxone) |
| IND Number: | Pending |
| Development Phase: | Feasibility |
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| Funding Organization: | National Heart Blood and Lung Institute (NHLBI) |
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## PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Frederick M. Hecht, MD with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: HECHTMASON1

Protocol Title: **OPIATE WITHDRAWAL RESPONSES TO INTRANASAL NALOXONE AS AN INDEX OF ALTERED ENDOGENOUS OPIOID ACTIVITY AMONG INDIVIDUALS WITH OBESITY: A FEASIBILITY AND EFFICACY STUDY**

Protocol Date: 15 January 2016

| | |
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ALT** | Alanine aminotransferase |
| **AST** | Aspartate aminotransferase |
| **BMI** | Body Mass Index |
| **CITI** | Collaborative Institutional Training Initiative |
| **CFR** | Code of Federal Regulations |
| **CHR** | Committee on Human Research (UCSF IRB) |
| **CRF** | Case Report Form |
| **DMC** | Data Monitoring Committee |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **HIPAA** | Health Insurance Portability and Accountability Act of 1996 |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IRB** | Institutional Review Board |
| **IM** | Intramuscular |
| **IN** | Intranasal |
| **IT** | Information Technology |
| **IUD** | Intrauterine Device |
| **IV** | Intravenous |
| **MAD** | Mucosal Atomization Device |
| **OS** | Operating System |
| **PI** | Principal Investigator |
| **SAE** | Serious adverse experience |
| **SID** | Subject Identification Number |
| **SC** | Subcutaneous |
| **SQL** | Structured Query Language |
| **SSL** | Secure socket layer |
| **UCSF** | University of California – San Francisco |
| **VPN** | Virtual private network |

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE** | **OPIATE WITHDRAWAL RESPONSES TO INTRANASAL NALOXONE AS AN INDEX OF ALTERED ENDOGENOUS OPIOID ACTIVITY AMONG WOMEN WITH OBESITY: A FEASIBILITY AND EFFICACY STUDY** |
| **SPONSOR** | Frederick M. Hecht, MD |
| **FUNDING ORGANIZATION** | National Heart Blood and Lung Institute (NHLBI) |
| **NUMBER OF SITES** | 1 |
| **RATIONALE** | Understanding what drives compulsive overeating among individuals with obesity will lead to the development of more effective treatments. A large body of literature implicates the endogenous opioid system in eating behavior. Researchers have published the use of exogenous opioidergic blockade as a method to assess endogenous opioid activity in obesity[1,2]. Data suggest that women are more sensitive to exogenous opioidergic blockade. Our work shows that withdrawal responses, as indexed by nausea following opioidergic antagonism using oral naltrexone, are associated with non-homeostatic eating in obese women[1,2]. To (1) reduce the amount of time needed to investigate associations between eating behavior, obesity, and the endogenous opioid system, thereby reducing subject burden, and (2) take the initial steps toward the development of a cost- and time-effective method to assess endogenous opioid activity in women, we plan to evaluate the use of naloxone hydrochloride administered intranasally (intranasal naloxone). |
| **STUDY DESIGN** | This is a single-center, double-blind, placebo-controlled, randomized, crossover trial design. |
| **PRIMARY OBJECTIVE** | 1. To determine if 2 mg/2 mL intranasal naloxone elicits the withdrawal symptom of nausea (present versus absent) in obese women. |
| **SECONDARY OBJECTIVES** | 1. To determine if 2 mg/2 mL intranasal naloxone elicits other withdrawal symptoms, as measured by subjective opiate withdrawal scales[3] in obese women<br>2. To determine the rate of the cortisol response following 2 mg/2 mL intranasal naloxone in obese women |
| **NUMBER OF SUBJECTS** | 24 women |
| **SUBJECT SELECTION CRITERIA** | <u>Inclusion Criteria</u>:<br>1. Subject must be able to complete written informed consent procedures and be able to comply with the requirements of the study.<br>2. Women aged 18 years or older<br>3. Obese, as defined by BMI greater than or equal to 30 |

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| | 4. Self-reported binge eating as defined in DSM-5, in the last 4 weeks<br>5. If sexually active with men and pre-menopausal, must agree to use birth control (e.g., barrier methods, oral contraceptive)<br>6. Must have negative pregnancy test at visit 1<br><br><u>Exclusion Criteria</u>:<br>1. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the subject or the quality of the data<br>2. Pregnant or breastfeeding<br>3. Known hypersensitivity to naloxone hydrochloride or to any ingredients in naloxone hydrochloride<br>4. Allergies to any ingredients in naloxone hydrochloride<br>5. History of or current alcoholism<br>6. History of or current drug dependence<br>7. Bulimia Nervosa as defined in DSM 5<br>8. Current or past use of opiate-containing medications in the last 30 days<br>9. Plan to use opiate-containing medications during the study days<br>10. Use of opiate medications or drugs, which are contraindicated with naloxone hydrochloride<br>11. Medical conditions that are contraindicated with intranasal procedures: Nasal septal abnormalities, nasal trauma, epistaxis, excessive nasal mucus, and intranasal damage caused by the use of substances (e.g., cocaine)<br>12. Severe hypotension (<90/60 mmHg)<br>13. Recent or current use of vasoconstrictor or vasodilator medications<br>14. Current or history of diabetes |
| **TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION** | 2 mg/2 mL Naloxone Hydrochloride (Intranasal Naloxone)<br>1 mg/1 mL administered per nostril using a nasal mucosal atomization device (MAD) (manufactured by Teleflex, Inc., Research Triangle Park, NC, USA). |
| **CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION** | 2 mL 0.9% sodium chloride (Intranasal Placebo)<br>1 mL administered per nostril using a nasal mucosal atomization device (MAD) (manufactured by Teleflex, Inc., Research Triangle Park, NC, USA). |
| **DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY** | Subjects will be in the study for up to 3 weeks. There will be a period of at least 24 hours between visits 1 and 2.<br>Web-based eligibility: Screening for self-report eligibility criteria, approx. 15 minutes<br>Phone Screen: Phone call to review eligibility and schedule visit 1, planning for visit 1, approx. 15 minutes<br>Visit 1: In-person baseline assessment (screening for pregnancy and |

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| | drug use), approx. & Administration day 1 (approximately 1.5-2 hours)<br>Visit 2: Administration day 2 (approximately 1.5-2 hours)<br>Recruitment and participation are expected to take 6 months |
| **CONCOMITANT MEDICATIONS** | Allowed:<br>1. Medications are permitted with use of naloxone hydrochloride unless listed below under "prohibited"<br>Prohibited:<br>1. Current use of opiate-containing medications<br>2. Current use of vasoconstrictor medication<br>3. Initiation of new medications that are contraindicated with naloxone hydrochloride use during the study period<br>4. Current use of insulin |
| **EFFICACY EVALUATIONS** | 1. Self-reported nausea at 0 minutes (pre-administration), and 10 and 30 minutes following administration of test product or control product<br>2. Self-reported symptoms of withdrawal as measured by the subjective opiate withdrawal scale (SOWS[3]) at 0 minutes (pre-administration), and 10 and 30 minutes following administration of test product or control product<br>3. Salivary cortisol values at 0 minutes (pre-administration) and 20 and 50 minutes following administration of test product or control product |
| ***PRIMARY ENDPOINT*** | **1.** Presence or absence of the self-reported withdrawal symptom of nausea following administration of the test versus control product. |
| ***SECONDARY ENDPOINTS*** | **1.** Scores on self-report Subjective Opiate Withdrawal Scale (SOWS)[3] following administration of the test versus control product.<br>**2.** Rate of the cortisol response, as measured by salivary cortisol, following administration of the test versus control product. |
| **OTHER EVALUATIONS** | N/A |
| **SAFETY EVALUATIONS** | Incidence of unexpected adverse events. Subjects will be monitored for unexpected adverse events and serious adverse events following administration of the test product and control product. |
| **PLANNED INTERIM ANALYSES** | Due to the current study design and safety profile of this test product, no interim analyses are planned. |
| **STATISTICS**<br>**Primary Analysis Plan** | McNemar's tests will be performed to evaluate whether there is a statistically significant difference in nausea response (dichotomously scored as present or absent) across test product (intranasal naloxone) and control product (intranasal placebo) conditions. |

**Rationale for Number of Subjects**

We do not expect any nausea responses to the control product, just as we typically do not expect side effects from placebos. Under the null hypothesis of no difference between conditions, we would also expect no nausea responses under the alternative hypothesis. In terms of probability, "no responses" implies a probability of 0: In other words, an impossible event. A single nausea response to the test product would decisively refute the null. But nausea responses, under either condition, are not literally impossible. We have therefore powered against the expected value of 0 by using the beta distribution with $r = 0$ as a Bayesian prior, in place of the usual point value. The beta with $r = 0$ is a U-shaped distribution concentrating most of the density on the extreme values. Specifically, for values of $p$ from .01 to .99, in .01 increments, we calculated the ordinate of the beta distribution with trial values of $N$; calculated the one-tailed rejection region (outcomes of fewer than 0 nausea responses were not considered) for that value of $p$ and $N$; calculated the power for that $N$ and an alternative value of $p$ (e.g., .4); then used the corresponding ordinate for each value of $p$ as a weight, and calculated the average across the range from .01 to .99 as our estimate of power. Since nausea responses are not literally impossible, we also explored power with null proportions up to .3, with the alternatives in the below table. For these nonzero values, a standard binomial power analysis would have sufficed, but for consistency we have used the corresponding Bayesian priors. The beta prior with $r = N/10$, for example, will concentrate probability on values near .1, whereas that with $r = 0$ will concentrate it around 0. The latter, approximating the impossible event, of course yields high power, whereas power declines as the binomial becomes more symmetrical. For the values of potential interest to us, an $N$ of 24 will suffice for 80%+ power. (Following from the above rationale, the entries in the table below do not correspond to standard power calculations for the McNemar test. The test for 0% vs. 40%, for example, is a test of whether the percentages for the two populations are both 20%; the power of this test is just 1 of 99 values averaged, with weights from the beta distribution, for the results in the table below).

| % Endorsing Nausea | | Number Needed ($N$) | Power to detect difference |
|---|---|---|---|
| Control Product | Test Product | | |
| 0% | 20% | 20 | .811 |
| 0% | 30% | 12 | .823 |
| 0% | 40% | 9 | .844 |
| 10% | 40% | 16 | .817 |
| 20% | 50% | 21 | .805 |
| 30% | 60% | 24 | .805 |

Reference: Uebersax, J.S. Bayesian unconditional power analysis (2007).

# 1 BACKGROUND

Opioid antagonists, such as intravenously and intranasally delivered naloxone (brand name: Narcan), are used clinically throughout the US to acutely reverse opiate drug overdose[4–6]. A nasal naloxone spray device was recently approved for opioid overdose: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm. Intranasal naloxone administration has been effectively completed by lay people who complete brief training generally led by non-medical trained professionals[7]. Depot naloxone injections, as well as an oral formulation (naltrexone) are used throughout the US as ongoing treatments to promote sobriety among individuals with substance use disorders[8]. Opioid antagonism can induce withdrawal symptoms that are well documented in the literature, such as nausea, sweating, and jitteriness. Associations between the endogenous opioid system and neural factors underlying eating behavior are well-documented[9–12].

The Diagnostic and Statistical Manual (DSM) of Mental Disorders – 5th edition outlines criteria for substance dependence, and several self-report measures have been constructed to diagnose substance use disorders. In the past 10 years, researchers have proposed and begun to investigate food addiction by considering food as other researchers have considered other substances (i.e., illicit drugs, alcohol[13,14]). Food addiction has been proposed as a phenotype in obesity[15,16], and more than 30% of treatment-seeking individuals with obesity endorse compulsive overeating[17,18], defined as the consumption of large amounts of food whilst feeling out of control over one's eating.

The endogenous opioidergic system, specifically, μ-opioid activity, plays a critical role in the neural experience of reward that follows from eating highly palatable food[9,19], especially foods high in sugars[10,20,21]. Eating these foods acutely stimulates the release of endogenous opioids, which, in turn, promotes further eating. Chronic overeating of these highly palatable and possibly addictive foods[21–23] can alter μ-opioid activity in ways that increase susceptibility to, and intensify experiences of, food cravings[24–27]. In short-term experimental studies, rats chronically consuming a highly palatable diet that are then either removed from this diet or administered an μ-opioid antagonist display opioid-withdrawal behavior[10]. Animal studies also show that administration of a μ-opioid antagonist decreases short-term ingestion of highly palatable, sweet food, even using doses of a μ-opioid antagonist that do not impact intake of standard chow[21,28]. One phase II placebo-controlled 24-week study ($N = 138$) of intranasal naloxone for binge eating disorder has been reported in abstract form at the American Psychiatric Association's 166th annual meeting, but has not been published[29]. It involved intranasal naloxone (2 mg) (or intranasal placebo) before binge eating up to 2 times daily (up to 4 mg intranasal naloxone total daily). Eighty-one percent of subjects completed the trial, and there were no serious adverse events. Results indicated that naloxone, relative to placebo, resulted in less time spent binge eating and greater weight loss from weeks 12 to 24. This trial was registered at clinicaltrials.gov (NCT01567670).

We have published data showing that overweight and obese women who report nausea (a common opioid withdrawal symptom[30]) following ingestion of a standard 50 mg dose of the μ-opioid antagonist naltrexone[31] also report greater emotional, reward-driven, and/or binge eating[1,2,32]. Thus, antagonizing the endogenous opioid system is a promising method

by which to test for altered μ-opioid activity related to problematic overeating that does not require expensive imaging procedures. The method that my colleagues and I at UCSF have used involves oral naltrexone[31], which requires several hours of data collection due to a slower mechanism of action. Utilizing intravenous administration, while rapid, would pose additional subject burden and discomfort, as it involves injection by needle. Using intranasally administered naloxone, which is now used clinically throughout the US and is has been fast-tracked for FDA approval for drug overdose, would dramatically reduce subject burden (reduces study period from 4 hours to less than 1 hour), and would obviate the use of needles.

## 1.1 Overview of Non-Clinical Studies

**Naloxone Hydrochloride Injection Package Insert:** See Appendix A.

**From Package Insert: Carcinogenesis, Mutagenesis, and Impairment of Fertility**
Studies in animals to assess the carcinogenic potential of naloxone hydrochloride have not been conducted. Naloxone hydrochloride was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study. Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/ day (when based on surface area or $mg/m^2$), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

**From Package Insert: Use in Pregnancy**
**Teratogenic Effects: Pregnancy Category C:** Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or $mg/m^2$), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

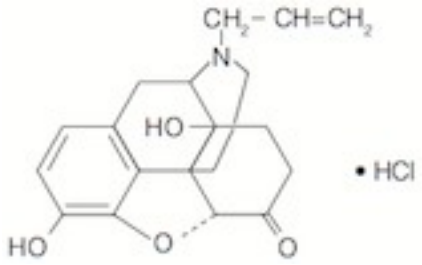
## 1.2 Overview of Clinical Studies

**From Package Insert: Pharmacokinetics: Distribution, Metabolism, and Elimination**
Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent, but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk. Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucoronide as the major metabolite. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours. After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

**From Package Inserts: Clinical Pharmacology**
Naloxone hydrochloride prevents or reverses the effects of opioids including respiratory depression, sedation, and hypotension. It can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine. Naloxone hydrochloride is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Naloxone hydrochloride has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone hydrochloride will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of naloxone hydrochloride administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone hydrochloride and to the degree and type of opioid dependence.

**From Published Research: Route of Administration**
Recent research indicates that intranasal administration (IN) is similar in effectiveness to IM delivery in reversing opioid (heroin) overdose[33]. IN administration is considered an effective option in the treatment of overdose when IV administration is impossible or undesirable[5]. Animal data indicate that the peak plasma levels following intranasal delivery occurs within 3 minutes of administration[34].

**Figure 1**. Structure of naloxone hydrochloride.




## 2 STUDY RATIONALE

More than 30% of individuals who are overweight or obese and seeking treatment for weight loss endorse problems with binge-like, compulsive overeating[17,18]. A large body of research has documented overlaps between the endogenous opioid system and eating behavior[9–12], and in the past decade, food addiction has been proposed as a phenotype in obesity[15,16]. Data show that women are more sensitive to exogenous opioidergic blockade, as defined by experiencing nausea and other withdrawal-like effects more often than men[35,36].

We have published data showing that overweight and obese women who report nausea (a common opioid withdrawal symptom[30]) following ingestion of a standard 50 mg dose of the μ-opioid antagonist naltrexone[31] also report greater emotional, reward-driven, and/or

binge eating[1,2,32]. Our studies have found that women who endorsed nausea responses following naltrexone ingestion had larger reductions in self-reported overeating and greater weight loss when assigned to a weight loss intervention with mindful eating training rather than when assigned to a standard weight loss intervention. Both studies[1,2], however, used oral administration (naltrexone), which required three hours of observation to capture data from the time period involving peak response[31]. Thus, antagonizing the endogenous opioid system is a promising method by which to test for altered μ-opioid activity related to problematic overeating.

Intranasal naloxone has been shown to achieve peak plasma levels in 3 minutes in rodents[34]. Although IV administration would reduce the amount of time needed, this would add a needle stick and therefore increase subject burden. Hence, to (1) reduce the amount of time needed to investigate associations between eating behavior, obesity, and the endogenous opioid system, thereby reducing subject burden, and (2) take the initial steps toward the development of a cost- and time-effective method to assess endogenous opioid activity in women, we plan to evaluate the use of naloxone hydrochloride administered intranasally (intranasal naloxone). This study will provide important preliminary data for future studies investigating treatment matching for weight loss interventions. The development of an intranasal naloxone protocol may contribute to the identification of individuals who may benefit from the incorporation of intervention components traditionally used in substance misuse treatment (e.g., opioid misuse) into their weight-loss intervention program.

### 2.1 Risk / Benefit Assessment

The most significant potential benefit of this study is to contribute to the development of an inexpensive, non-invasive method for assessing endogenous opioidergic activity in obesity. This study will generate key preliminary data for investigating this method, which may prove useful in identifying individuals with obesity who engage in binge-like, compulsive overeating ("opioid-mediated eating") that requires treatment modalities traditionally used to treat substance dependence disorders.

Intranasal Naloxone-related risks

Intranasal naloxone is known to reverse (and is used for the purpose of reversing) opioid overdose and can reverse the analgesic effects of an opioid analgesic being taken chronically (e.g., for pain)[4–6,37]. Intranasal naloxone has minimal dug interaction potential[5]. Intranasal naloxone is not used as a continuous medication and is used in acute situations involving overdose, meaning that individuals receiving intranasal naloxone are not tested for the use of other medications prior to receiving it. See Appendix A for package insert.

## 3 STUDY OBJECTIVES

### 3.1 Primary Objective

1. To determine if 2 mg/2 mL intranasal naloxone (1 mg/1 mL per nostril) elicits the withdrawal symptom of nausea (present versus absent) in obese women (compared to intranasal placebo).

### 3.2 Secondary Objectives

1. To determine if 2 mg/2 mL intranasal naloxone (1 mg/1 mL per nostril) elicits other withdrawal symptoms, as measured by subjective opiate withdrawal scales[3] in obese women (compared to intranasal placebo).
2. To determine the rate of the salivary cortisol response following intranasal naloxone administration in obese women (compared to intranasal placebo).

## 4 STUDY DESIGN

### 4.1 Study Overview

This is a single center, double-blind, placebo-controlled, randomized, crossover trial that will include 24 subjects. Subjects will be in the study for up to 3 weeks. Total time involved will be approximately 5-6 hours. There will be a period of at least 24 hours between study Visits 1 and 2.

### 4.2 Total Study Duration:

Total duration of subject participation will be up to 3 weeks, with one session of web-based screening, one session involving a telephone screening call to confirm eligibility and introduce the subject to the study and two lab sessions involving administration of test and control products (first lab session includes urine screen). Total duration of the study, including recruitment and subject study completion, is expected to be 6 months.

## 5 CRITERIA FOR EVALUATION

### 5.1 Primary Efficacy Endpoint

Presence or absence of the self-reported withdrawal symptom of nausea following administration of test product (intranasal naloxone) versus following administration of the control product (intranasal placebo). We will assess for presence of nausea (before and) following administration of each the test and the control products.

### 5.2 Secondary Efficacy Endpoints

1. Scores on self-report Subjective Opiate Withdrawal Scale (SOWS)[3] following administration of the test versus control products. A complete score that captures the full range of withdrawal responses my reveal a withdrawal syndrome that occurs, in addition to, or in the absence of, nausea.
2. Rate of the cortisol response following administration of the test versus control products as measured by salivary cortisol. Cortisol increases following opioidergic blockade may index the degree to which an individual's opioid system controls the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for physiologic stress responses.

### 5.3 Safety Evaluations

Incidence of unexpected adverse events.

# 6 SUBJECT SELECTION

## 6.1 Study Population

Subjects with a diagnosis of obesity using BMI criteria who meet the inclusion and exclusion criteria will be eligible for participation in this study.

## 6.2 Inclusion Criteria

1. Subject must be able to complete written informed consent procedures and be able to comply with the requirements of the study
2. Women aged 18 years or older
3. Obese as defined by BMI greater than or equal to 30
4. Self-reported binge eating as defined in DSM-5, in the last 4 weeks
5. If sexually active with men and pre-menopausal, must agree to use an acceptable form of birth control (e.g., barrier methods, oral contraceptive)
6. Must have negative pregnancy test at visit 1

## 6.3 Exclusion Criteria

1. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the subject or the quality of the data
2. Pregnant or breastfeeding
3. Known hypersensitivity to naloxone hydrochloride (intranasal naloxone) or to any ingredients in naloxone hydrochloride
4. Allergies to any ingredients in naloxone hydrochloride
5. History of or current alcoholism
6. History of or current drug dependence
7. Bulimia Nervosa as defined in DSM 5
8. Current or use of opiate-containing medications in the last 30 days
9. Plans to use opiate-containing medications during the study days
10. Use of opiate medications or drugs, which are contraindicated with naloxone hydrochloride
11. Medical conditions that are contraindicated with intranasal administrations: Nasal septal abnormalities, nasal trauma, epistaxis, excessive nasal mucus, and intranasal damage caused by the use of substances (e.g., cocaine)
12. Severe hypotension (<90/60 mmHg)
13. Recent or current use of vasoconstrictor or vasodilator medications
14. Current or history of diabetes

# 7 CONCURRENT MEDICATIONS

## 7.1 Allowed Medications and Treatments

Medications are allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

1. Medications permitted with use of naloxone hydrochloride are allowed.

### 7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

1. Subjects may not use opiate-containing medications during the study period. This is because they are contraindicated with naloxone hydrochloride use.
2. Subjects may not use vasoconstrictor medications during the study period. This is because they are contraindicated with naloxone hydrochloride use.
3. Subjects may not initiate new medications that are contraindicated with naloxone hydrochloride use during the study period.
4. Subjects may not be using insulin.

## 8 STUDY TEST AND CONTROL PRODUCTS

### 8.1 Method of Assigning Subjects to Treatment Groups

Twenty-four eligible subjects will be randomly assigned to receive the test product (intranasal naloxone) or control product (intranasal placebo) first (on visit 1 versus on visit 2) in a 1:1 ratio using a SAS-based computer-generated randomization table computed by Scott Fields, PharmD, of the UCSF Research Pharmacy Staff.

### 8.2 Blinding

Due to the objectives of the study, the identity of the test product and control product will be unknown to investigators, study staff, and subjects, excepting two study staff, who will prepare study syringes (see **8.4.3 Preparation of Study Syringes**). The following study procedures will be in place to ensure double-blind administration of the test product and control product:

Access to the randomization table will be strictly controlled and available only to the UCSF Research Pharmacy staff who create it and the two unblinded study staff who will prepare study syringes at each subject visit.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the subject's condition (control or text product) is necessary for further subject management. When possible, the Investigator will discuss the emergency with the Medical Monitor, Frederick M. Hecht, MD, prior to unblinding.

### 8.3 Formulation of Test and Control Products

Though nasal administration of naloxone was recently FDA approved and is available in a pre-loaded device from Adapt Pharmaceuticals as shown in Figure 2a, below (http://www.narcannasalspray.com/), the proposed study will use a Mucosal Atomization Device (MAD) with a standard syringe attached, as shown in Figure 2b, below (http://intranasal.net/OpiateOverdose/default.htm). This is because the proposed study requires a blinded control condition (intranasal placebo). To date, published literature has used the method depicted in Figure 2b with a 2 mg dose of naloxone to test the

effectiveness of intranasal administration against intramuscular administration in reversing opioid overdose and found this dose to be clinically effective[5].

**Figure 2a (left):** Adapt Pharmaceuticals NARCAN Naloxone Nasal Spray 4 mg/0.1 mL
**Figure 2b (right):** Mucosal Atomization Device (MAD), manufactured by Teleflex, Inc. (Research Triangle Park, NC) affixed to 2 mg/2 mL naloxone syringe


### 8.3.1 Formulation of Test Product

Naloxone hydrochloride is a clear solution that requires no reconstitution (see Table 2 for formulation) and is manufactured by International Medication Systems, a subsidiary of Amphastar Pharmaceuticals (http://www.amphastar.com/our-products.html). The intranasal mucosal atomization device (MAD) is manufactured by Teleflex (http://www.lmana.com/pwpcontrol.php?pwpID=6359). Intranasal naloxone was developed for acute reversal of opioid overdose when intravenous and intramuscular methods are not available or desirable[4].

Table 2: Formulation and Measured pH of Naloxone Hydrochloride

| | **Naloxone Hydrochloride (Per 1 mL)** |
|---|---|
| Active Ingredient, mg | Naloxone Hydrochloride, 1 mg |
| Other ingredient, mg | Sodium Chloride, 8.35 mg |
| Other ingredient | Hydrochloric acid (to adjust pH) |
| pH | Range: 3.0 to 4.0 |

### 8.3.2 Formulation of Control Product

The 10 mL, single-use vials of 0.9% sodium chloride is manufactured by Hospira (http://www.hospira.com/en/products_and_services/drugs/SODIUM_CHLORIDE_INJECTION_09).

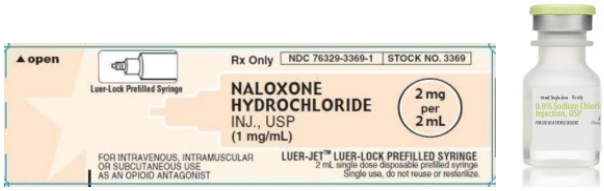
### 8.3.3 Packaging and Labeling

*Packaging:* The control product (intranasal placebo; 0.9% sodium chloride) will be received from Hospira in 10 mL, single-use vials. The test product (intranasal naloxone; naloxone hydrochloride) will be received from International Medication Systems in 2 mL, single-use syringes.

For full pictorial description of syringe assembly, see Appendix B or http://www.lmana.com/files/lma_623_mad_nasal_procedure_guide.pdf?PHPSESSID=5ac33303fd1793f2edb171ce0958f3dd

*Labeling:* Vials containing the control product (intranasal placebo) are manufactured with clear labeling as such. Syringes containing the test product (intranasal naloxone) are manufactured with clear labeling as such. See Figure 3.

**Figure 3.** Packaging for test product (left) and control product (r ight).




## 8.4 Supply of Test and Control Products at the Site

The PI (or designee) will collect (in person) the box with the label depicted in Figure 4 that contains thirty 10 mL vials of the control product and thirty 2 mg/2 mL syringes of the test product and transport it to the UCSF Osher Center for Integrative Medicine at the UCSF Mount Zion Campus, 1545 Divisadero Street, 3rd Floor, Suite 301, San Francisco, California, 94115. The test and control products will be collected by the PI (or designee) only after site activation.

**Figure 4:** Label that UCSF Research Pharmacy Staff will place on the box containing syringes of the test product and vials of the control product.

UCSF Research Pharmacy
505 Parnassus Avenue, Room M39C
San Francisco, CA, 94143
(415) 353 1798

Study protocol: HECHTMASON1
Date dispensed: _____
Institutional Review Board (IRB) Approval #: _____

Frederick M. Hecht MD
Ashley E. Mason, PhD

30 vials 10 mL 0.9% sodium chloride solution (saline), Lot # _____
30 syringes 2 mg/2 mL naloxone hydrochloride (naloxone), Lot # _____
**"Caution: Limited by Federal (or United States) law to Investigational Use."**

### 8.4.1 Dosage/Dosage Regimen

All subjects receive the control product and test product at different study visits (visits 1 and 2, which occur on different days). There will be a period of at least 24 hours between visits 1 and 2, as the period of time between each administration day does not impact analyses assessing primary or secondary outcomes. Subjects will be administered the test product (intranasal naloxone), 1 mg/1 mL per nostril, on one of their two visit days. Subjects will be administered the control product (intranasal placebo), 1 mL per nostril, on one of their two visit days.

### 8.4.2 Dispensing

Scott Fields, PharmD, of the UCSF Research Pharmacy, will order the test and control products from their manufacturers listed in 8.3.1 Formulation of the Test Product and 8.3.2 Formulation of the Control Product. Unblinded study staff will prepare the syringes and affix them to the mucosal atomization device (MAD; see section 8.4.3 Preparation of Study Syringes). Ashley E. Mason, PhD, will administer the prepared test and control products to subjects. Ashley E. Mason, PhD and Frederick Hecht, MD (Medical Monitor) have carefully reviewed the documents prepared by the Massachusetts Department of Public Health (http://www.mass.gov/eohhs/docs/dph/substance-abuse/core-competencies-for-naloxone-pilot-participants.pdf), which include intranasal naloxone administration instructions in the context of training potential overdose responders to recognize and respond to an opioid overdose. They have also reviewed a step-by-step video that demonstrates assembly of the MAD (https://www.youtube.com/watch?v=Uq6AxrEY3Vk) that was developed and produced to train individuals seeking core competencies in intranasal naloxone administration. Dr. Hecht will supervise Dr. Mason in trial runs of completing intranasal administration using the MAD prior to subject enrollment. Dr.

Mason will document all training related to this study in a Study Training Log, and Dr. Hecht will review and initial each entry (Appendix C).

### 8.4.3 Preparation of Study Syringes

Study syringes will be prepared by two unblinded study staff who have completed all UCSF training required to conduct research with human subjects as detailed by the UCSF Institutional Review Board (IRB; http://www.research.ucsf.edu/chr/Train/chrTrain.asp). UCSF requires completion of the Collaborative Institutional Training Initiative (CITI) Course in the Protection of Human Research Subjects (https://www.citiprogram.org/) and HIPAA Training (http://www.research.ucsf.edu/chr/HIPAA/chrHIPAAtrng.asp). Documentation of successful completion of this training (and any additional training stipulated by the UCSF IRB) will be reviewed by Dr. Mason and this documentation will be stored with study documents as described in 8.4.4 Storage.

The unblinded study staff will review the Massachusetts Department of Public Health materials (document and video linked in section 8.4.2 Dispensing). These study staff will also complete a UCSF Learning Module on aseptic techniques (portal to training: https://learningcenter.ucsfmedicalcenter.org/) entitled, Sterile Technique: Key Concepts and Practices." Frederick M. Hecht, MD, the Medical Monitor and Sponsor of this proposal, who is a practicing physician with privileges at UCSF, will (1) verify their completion of this course, and (2) provide them with hands-on training in aseptic techniques and syringe preparation.

Prior to each study visit, the unblinded study staff will consult the randomization table that was generated by the UCSF Research Pharmacy Staff to determine which of the following two procedures to follow:

1. For the control product (intranasal placebo), the unblinded study staff will draw 2 mL of the 0.9% sodium chloride from the original 10 mL vial into a standard 3 mL syringe, and then affix this to a nasal mucosal atomization device (MAD; see Figure 2b).
2. For the test product (intranasal placebo), the unblinded study staff will draw 2 mL of the naloxone hydrochloride from the original 2 mL syringe into a standard 3 mL syringe, and then affix this to a MAD (see Figure 2b).

The study staff will then log which product she has prepared in the (paper) Test and Control Product Accountability Log (Appendix D) and then will provide Dr. Mason with the prepared MAD.

### 8.4.4 Storage

The test and control products (as well as all other study materials) will be stored at the study site for visits 1 and 2 (UCSF Osher Center for Integrative Medicine at the UCSF Mount Zion Campus, 1545 Divisadero Street, 3rd Floor, San Francisco, California, 94115) in Suite 301. Suite 301 requires a numeric passcode for entry and houses a room that requires badge entry (and tracks all entries), wherein materials will be stored. This room maintains a controlled temperature range of 15 to 30ºC (59 to 86ºF). All materials will be stored in one of three study-specific locked cabinets (includes 1 locked file cabinet), which will maintain cool and dry environments. In the event that the temperature of the

room (in Suite 301 of the aforementioned address) in which the test and control products are stored or at the UCSF Research Pharmacy exceeds or falls below this range, this will be reported to the Sponsor.

### 8.5 Test and Control Product Accountability

An accurate and current accounting of the dispensing of the test and control products will be maintained on an ongoing basis by the unblinded study staff. Specifically, the number of doses of the test and control products dispensed will be recorded on the Test and Control Product Accountability Log (see Appendix D), which will be stored in the locked cabinets described in 8.4.4 Storage.

### 8.6 Measures of Treatment Compliance

N/A

## 9 STUDY PROCEDURES AND GUIDELINES

A 'Schedule of Events by Study Visit' representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix E. All subject visits will be documented in the Subject Tracking Log (Appendix F). See 16 Data Collection, Retention, and Monitoring, for details.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

Subjects will be compensated for their time and travel expenditures, up to $200 total. Subjects will be paid up to $50 for completion of each study visit, and up to an additional $50 upon completion of all study visits.

### 9.1 Clinical Assessments

All clinical assessment information will be collected on study-specific forms.

#### 9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented during the Phone Screen, and re-confirmed at lab visits.

#### 9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded during the Phone Screen and confirmed at visit 1.

#### 9.1.3 Medical History

Relevant medical history, including history of or current disease and other pertinent medical history will be recorded at the Phone Screen.

#### 9.1.4 Physical Examination

Height and weight will be measured at visit 1.

### 9.1.5 Vital Signs

Blood pressure will be measured at visit 1.

### 9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity, outcome, treatment and relation to study drug will be recorded on case report forms (CRFs).

## 9.2 Clinical Laboratory Measurements

### 9.2.1 Pregnancy Test

A urine pregnancy test will be obtained from all subjects at visit 1.

### 9.2.2 Urinalysis

Urine will be obtained for pregnancy testing and testing for opioid drug/medication use at visit 1.

### 9.2.3 Salivary Cortisol Measurements

Saliva collected for determination of cortisol levels will be collected at both visits 1 and 2. Specimens will be collected prior to receiving the control or test product, as well as 20 and 50 minutes after receiving the control or test product, using the passive drool technique, which involves subjects drooling into a collection tube. All specimen collections will be documented on the Specimen Accountability Log (Appendix G). The passive drool technique protocol is located on page 6 of the following manual:
https://www.salimetrics.com/assets/documents/Saliva_Collection_Handbook.pdf
Materials for this procedure are detailed here:
https://www.salimetrics.com/collection-systems
These tubes will be labeled with the subject ID number, visit number, and date, and stored in the study freezer. Once all samples are collected, all samples will be shipped on dry ice for batch processing at the Hellhammer Laboratory. The Sponsor and PI have an existing collaborative relationship with this laboratory and maintain ongoing e-correspondence.

Hellhammer Laboratory shipping address:

Biochemisches Labor, Unversitaet Trier
FB 1, Biol. und Klin. Psychologie
Frau Fritzen/Frau Reinert/Frau Scholtes
Karl-Marxstr. 94-96
54290 Trier
Germany

# 10 EVALUATIONS BY VISIT

Table 1. Study events, description, and length of time involved

| Event | Description | Length |
|---|---|---|
| Web-based eligibility | Screening for self-report eligibility (inclusion and exclusion) criteria | <15 minutes |

| | | |
|---|---|---|
| screening | | |
| Phone Screen | Confirm eligibility criteria<br>Schedule baseline assessment<br>Review food buffet menu options | <15 minutes |
| Visit 1 | Screening for specimen-based exclusion criteria<br>Self-report measures of eating behavior<br>Computerized cognitive tasks<br>Test or control product administration day 1 | 1.5 to 2 hours |
| Visit 2 | Test or control product administration day 2 | 1.5 to 2 hours |

**Web-based eligibility screening:**

- Subjects who meet all inclusion criteria and who have none of the exclusion criteria on the UCSF-hosted web-based eligibility screening website (wherein they provide their phone number) will be called by study staff to complete the Phone Screen.

**Phone Screen:**

- *Verify Eligibility:* Review inclusion and exclusion criteria with subject to ensure eligibility, including relevant medications, demographics, and medical history.
- *Review Protocol:* Review study protocol to ensure subject's willingness to partake in each component of the study, including the time commitment and locations of visits 1 and 2, as well as self-report measures, a urine screen for pregnancy and opiate drug/medication use, eating pre-selected foods from a "buffet" of preferred foods at two study visits, receiving the intranasal naloxone and intranasal placebo, and providing saliva samples.
- *Schedule Visits 1 and 2*: Schedule subject's visits 1 and 2. There will be a period of at least 24 hours between visits 1 and 2, and, as the period of time between each administration day does not impact analyses assessing primary or secondary outcomes, the amount of time between administrations will vary according to the subject's schedules so as to reduce subject burden.

**Visits 1 and 2: Control Product and Test Product Administration Visits:**

- *Location*: Subjects will present to the UCSF Mount Zion Campus, 1545 Divisadero Street, 3rd Floor, Suite 301, San Francisco, California, 94115.
- *Clinical Assessments Conducted by Study Staff:*
    - *Objective Weight and Height Measures:* Staff will collect the subject's height and weight.
    - *Blood pressure:* Staff will collect blood pressure.
    - *Pregnancy and Opiate Drug/Medication Screen*: Staff will collect a urine sample to test for pregnancy and use of opioid drugs/medications.
- *Randomization*: Dr. Mason will report the subject's ID number and eligibility status to the unblinded study staff, who will consult the randomization table generated by the UCSF Research Pharmacy staff (which will dictate the ordering in which the subject will receive the test and control products at each visit).
- *Taste Test Procedure:* At visits 1 and 2, subjects will eat for 10 minutes from a food buffet that includes foods that they selected during visit 1 (different foods will be provided at each visits 1 and 2 so as not to repeat foods). All foods will be served in

large bowls and in large quantities, factors that are known to non-consciously increase intake[40]. Bowls of food will be weighed before and after the "taste test" period and this information will be documented (Appendix H). As commonly done in studies involving hedonic eating, subjects will indicate (on paper forms) how much they liked each food on paper questionnaires after tasting each food, as done in prior studies examining the role of opioid involvement in liking of foods[41,42].

- *Administration of Test Product (Intranasal Naloxone) or Control Product (Intranasal Placebo):* Subjects will receive each the test product (intranasal naloxone) (2 mg/ 2 mL, 1 mg/1 mL per nostril) and control product (intranasal placebo, 1 mL per nostril) via a nasal mucosal atomization device (MAD; See 8.4.3 Syringe Assembly) in a randomized order (per the randomization table generated by the UCSF Research Pharmacy and accessible only to unblinded study staff) on visits 1 and 2, immediately following the food buffet procedure.
- *Self-Report Measures*: Subjects will self-report their level of nausea (present versus absent) in the context of completing the SOWS[3] prior to receiving either the test or control product, as well as 10 and 30 minutes after receiving the test or control product.
- *Saliva Samples (Salivary Cortisol):* Subjects will provide saliva samples prior to receiving the test and control products, as well as 20 and 50 minutes after receiving the test or control products.

# 11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

## 11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the Adverse Event Accountability Log (Appendix I) and in the subject's CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

### AE Severity

The guidelines shown in Table below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

**Table 3. AE Severity Grading**

| Severity (Toxicity Grade) | Description |
|---|---|
| Mild (1) | Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well. |
| Moderate (2) | Mild to moderate limitation in activity, no or minimal medical intervention/therapy required. |
| Severe (3) | Marked limitation in activity, medical intervention/therapy required, hospitalizations possible. |
| Life-threatening (4) | The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe. |

**AE Relationship to Study Drug**

The relationship of an AE to the study agent should be assessed using the following the guidelines in Table .

**Table 4. AE Relationship to Study Drug**

| Relationship to Drug | Comment |
|---|---|
| Definitely | Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis. |
| Probably | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions. |
| Possibly | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors. |
| Unrelated | An event that can be determined with certainty to have no relationship to the study drug. |

### 11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

1. death
2. a life-threatening adverse experience
3. inpatient hospitalization or prolongation of existing hospitalization
4. a persistent or significant disability/incapacity
5. a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

### 11.2.1 Serious Adverse Experience Reporting

All SAEs that occur (whether or not related to study drug) will be documented per UCSF CHR (IRB) Guidelines (http://www.research.ucsf.edu/chr/guide/Violation_Incident_Guidelines.asp). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit (visit 2) have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

## 11.3 Medical Monitoring

Frederick M. Hecht, MD, is the Medical Monitor for this study and should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (415) 476-4082 extension #431
Pager: (415) 443-1599

Frederick M. Hecht, MD will be the primary person responsible for study adverse event monitoring and will report adverse events and unanticipated problems to the UCSF IRB. All subjects will be monitored for possible adverse events and unanticipated problems throughout the study period.

# 12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue his or her participation
- Protocol violation requiring discontinuation of study protocol
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test at visit 1 or self-reported pregnancy at visits 2 or 3

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the Subject Tracking Log (Appendix F) and the subject's CRF.

### 12.1 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. This will be documented in the Subject Tracking Log (Appendix F) and the subject's CRF.

### 12.2 Replacement of Subjects

Subjects who withdraw from the study will be replaced.

## 13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, research assistant(s), investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication or drug

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be completed on the online UCSF CHR (IRB) portal (this form is reproduced in Appendix J). As requested by the UCSF CHR (IRB), the Sponsor and Principal Investigator will consult with the UCSF Privacy Office (http://hipaa.ucsf.edu/) when completing this form. This form will be electronically signed by the Principal Investigator. A printed copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

## 14 DATA SAFETY MONITORING

N/A

## 15 STATISTICAL METHODS AND CONSIDERATIONS

### 15.1 Data Sets Analyzed

All eligible subjects who are randomized into the study and complete, at a minimum, visit 2, will be included in analyses. Michael Acree, PhD, a statistician at the UCSF Osher Center for Integrative Medicine, will perform the data analysis for this study.

### 15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, age, height and weight.

### 15.3 Analysis of Primary Endpoint

McNemar's tests will be performed to evaluate whether there is a statistically significant difference in nausea response (dichotomously scored as present or absent) across the test product (intranasal naloxone) and control product (intranasal placebo) conditions.

### 15.4 Analysis of Secondary Endpoints

Linear mixed effects regression modeling will be performed to assess differences across conditions in rate of cortisol change over the course of all assessments (baseline and 20 and 50 minutes post-administration).

### 15.5 Sample Size and Randomization

We do not expect any nausea responses to the control product. Under the null hypothesis of no difference between conditions, we would also expect no nausea responses under the alternative. In terms of probability, "no responses" implies a probability of 0: In other words, an impossible event. A single nausea response to intranasal naloxone would decisively refute the null. But nausea responses, under either condition, are not literally impossible. We have therefore powered against the expected value of 0 by using the beta distribution with $r = 0$ as a Bayesian prior, in place of the usual point value. The beta with $r = 0$ is a U-shaped distribution concentrating most of the density on the extreme values. Specifically, for values of $p$ from .01 to .99, in .01 increments, we calculated the ordinate of the beta distribution with trial values of $N$; calculated the one-tailed rejection region (outcomes of fewer than 0 nausea responses were not considered) for that value of $p$ and $N$; calculated the power for that $N$ and an alternative value of $p$ (e.g., .4); then used the corresponding ordinate for each value of $p$ as a weight, and calculated the average across the range from .01 to .99 as our estimate of power. Since nausea responses are not literally impossible, we also explored power with null proportions up to .3, with the alternatives in the below table. For these nonzero values, a standard binomial power analysis would have sufficed, but for consistency we have used the corresponding Bayesian priors. The beta prior with $r = N/10$, for example, will concentrate probability on values near .1, whereas that with $r = 0$ will concentrate it around 0. The latter, approximating the impossible event, of course yields high power, whereas power declines as the binomial becomes more symmetrical. For the values of potential interest to us, an $N$ of 24 will suffice for 80%+ power. (Following from the above rationale, the entries in the table below do not correspond to standard power calculations for the McNemar test. The test for 0% vs. 40%, for example, is a test of whether the percentages for the two populations are both 20%; the power of this test is just 1 of 99 values averaged, with weights from the beta distribution, for the results in the table below).

| % Endorsing Nausea | | Number Needed ($N$) | Power to detect difference |
|---|---|---|---|
| Control Product | Test Product | | |
| 0% | 20% | 20 | .811 |
| 0% | 30% | 12 | .823 |
| 0% | 40% | 9 | .844 |
| 10% | 40% | 16 | .817 |

| | | | |
|---|---|---|---|
| 20% | 50% | 21 | .805 |
| 30% | 60% | 24 | .805 |

Reference: Uebersax, J.S. Bayesian unconditional power analysis (2007).

# 16 DATA COLLECTION, RETENTION, AND MONITORING

## 16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific paper Case Report Form (CRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a four-digit subject identification number (SID). All paper documents will be kept in study-specific locked cabinets described in 8.4.4 Storage.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data, and initial and date the change.

The PI is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the PI. A copy of the CRF will remain at the PI's site at the completion of the study.

## 16.2 Data Management Procedures

The data will be entered into an electronic database that will be managed by Michael Coccia, MA, who will serve as a study Database Manager. His office is located at 3333 California Street, 4th Floor, Center for Health and Community, San Francisco, CA. Michael Coccia, MA, works as a Database Manager and statistician for Dr. Epel's and others' ongoing trials. The Database Manager will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

The UCSF Departments of Medicine and Psychiatry comply with federal, state, University, and campus electronic information security requirements through a combination of physical, technical, procedural, and management controls. At the procedural level, all researchers working with human subjects undergo security awareness training for HIPAA and the handling of sensitive data. All employees of the University of California, San Francisco are required to obtain Security Awareness Training and implement appropriate security measures.

The Osher Center for Integrative Medicine has a password-protected computer network that is connected into the greater UCSF system and network file servers, with high-speed Internet access. A HIPAA-compliant server is dedicated to research data storage. Access to this server is restricted to persons on the UCSF network, and requires network log-on authentication for access. Access to digital research data is further restricted to particular study staff and investigators working on projects, and access to research files is logged so

that there is a record of which individuals have accessed files. Daily back-up is performed on network servers. Extensive information technology (IT) support is provided for all computer operations through the UCSF IT Service.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

### 16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

### 16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. The Database Manager backs up databases in conjunction with any updates or changes to the database.

Study data will be stored on a HIPAA-compliant encrypted server managed by UCSF IT services that is privately maintained and hardware firewalled. Website communications are encrypted using a Secure Socket Layer (SSL) certificate and server access is restricted to research personnel working on campus or through the university Virtual Private Network (VPN). Access to study data will be restricted to approved study staff. File access is logged and audited by UCSF IT. UCSF IT performs daily backup of network servers. Laptop computers used for data collection or analysis are configured with full-disk encryption and antivirus software. UCSF IT is reachable 24/7 by telephone for any technological issues, including servers or critical data center equipment issues.

### 16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to authorized representatives of the Sponsor, IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (subject files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

### 16.6 Monitoring

Monitoring will be conducted by the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6).

### 16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a Subject Identification Number (SID) will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

## 17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by SID only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a SID will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

### 17.1 Protocol Amendments

The study investigators will write any amendment to the protocol. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRBs are notified within five working days.

### 17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to

the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

### 17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will place IRB/IEC-approved copy of the Informed Consent Form in the locked study file cabinet.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

### 17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

### 17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and make changes only after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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# 18 APPENDIX A: NALOXONE HYDROCHLORIDE PACKAGE INSERT

BARCODE 3 OF 9

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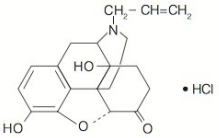
## NALOXONE HYDROCHLORIDE INJECTION, USP
## Opioid Antagonist

Rx Only

**DESCRIPTION**

Naloxone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride




Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Naloxone Hydrochloride Injection is available as a sterile solution for intravenous, intramuscular and subcutaneous administration in 1 mg/mL concentration. pH is adjusted to 3.5 ± 0.5 with hydrochloric acid. Each mL also contains 8.35 mg of sodium chloride. Naloxone Hydrochloride Injection is preservative-free.

**CLINICAL PHARMACOLOGY**

**Complete or Partial Reversal of Opioid Depression**

Naloxone hydrochloride prevents or reverses the effects of opioids including respiratory depression, sedation, and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonist such as pentazocine.

Naloxone hydrochloride is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

Naloxone hydrochloride has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone hydrochloride will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of naloxone hydrochloride administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone hydrochloride and to the degree and type of opioid dependence.

While the mechanism of action of naloxone hydrochloride is not fully understood, *in vitro* evidence suggests that naloxone hydrochloride antagonizes opioid effects by competing for the μ, κ and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptor.

When naloxone hydrochloride is administered intravenously (I.V.), the onset of action is generally apparent within two minutes. The onset of action is slightly less rapid when it is administered subcutaneously (S.C.) or intramuscularly (I.M.). The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride. Intramuscular administration produces a more prolonged effect than intravenous administration. Since the duration of action of naloxone hydrochloride may be shorter than that of some opiates, the effect of the opiate may return as the effects of naloxone hydrochloride dissipates. The requirement for repeat doses of naloxone hydrochloride will also be dependent upon the amount, type and route of administration of the opioid being antagonized.

**Adjunctive Use in Septic Shock**

Naloxone hydrochloride has been shown in some cases of septic shock to produce a rise in blood pressure that may last up to several hours; however, this pressor response has not been demonstrated to improve patient survival. In some studies, treatment with naloxone hydrochloride in the setting of septic shock has been associated with adverse effects, including agitation, nausea and vomiting, pulmonary edema, hypotension, cardiac arrhythmias, and seizures. The decision to use naloxone hydrochloride in septic shock should be exercised with caution, particularly in patients who may have underlying pain or have previously received opioid therapy and may have developed opioid tolerance.

Because of the limited number of patients who have been treated, optimal dosage and treatment regimens have not been established.

**PHARMACOKINETICS**

**Distribution**

Following parenteral administration, naloxone hydrochloride is rapidly distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

**Metabolism and Elimination**

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucoronide as the major metabolite. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours. After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

**INDICATIONS AND USAGE**

Naloxone hydrochloride injection is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids including, propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine and butorphanol and cyclazocine. Naloxone hydrochloride is also indicated for the diagnosis of suspected or known acute opioid overdosage.

Naloxone hydrochloride injection may be useful as an adjunctive agent to increase blood pressure in the management of septic shock. **(see CLINICAL PHARMACOLOGY; Adjunctive Use in Septic Shock).**

**CONTRAINDICATIONS**

Naloxone hydrochloride injection is contraindicated in patients known to be hypersensitive to it or to any of the other ingredients in naloxone hydrochloride.

## WARNINGS

### Drug Dependence

Naloxone hydrochloride should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

### Repeat Administration

The patient who has satisfactorily responded to naloxone hydrochloride should be kept under continued surveillance and repeated doses of naloxone hydrochloride should be administered, as necessary, since the duration of action of some opioids may exceed that of naloxone hydrochloride.

### Respiratory Depression due to Other Drugs

Naloxone hydrochloride is not effective against respiratory depression due to non-opioid drugs and in the management of acute toxicity caused by levopropoxyphene. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone. If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated.

## PRECAUTIONS

### General

In addition to naloxone hydrochloride, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.
Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death. Excessive doses of naloxone hydrochloride in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**; **Usage in Adults-Postoperative Opioid Depression**).

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had preexisting cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, naloxone hydrochloride should be used with caution in patients with preexisting cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

### Drug Interactions

Large doses of naloxone are required to antagonize buprenorphine since the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression. The barbiturate methohexital appears to block the acute onset of withdrawal symptoms induced by naloxone in opiate addicts.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to assess the carcinogenic potential of naloxone hydrochloride have not been conducted. Naloxone hydrochloride was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study.

Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/$m^2$), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

### Use in Pregnancy

**Teratogenic Effects: Pregnancy Category C:** Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/$m^2$), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

**Non-teratogenic Effects:** Risk-benefit must be considered before naloxone hydrochloride is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the mother. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored as severe hypertension may occur.

### Use in Labor and Delivery

It is not known if naloxone hydrochloride affects the duration of labor and/or delivery. However, published reports indicated that administration of naloxone during labor did not adversely affect maternal or neonatal status.

**Nursing Mothers:** It is not known whether naloxone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naloxone is administered to a nursing woman.

### Pediatric Use

Naloxone hydrochloride injection, USP may be administered intravenously, intramuscularly or subcutaneously in children and neonates to reverse the effects of opiates. The American Academy of Pediatrics, however, does not endorse subcutaneous or intramuscular administration in opiate intoxication since absorption may be erratic or delayed. Although the opiate-intoxicated child responds dramatically to naloxone hydrochloride, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

When naloxone hydrochloride is given to the mother shortly before delivery, the duration of its effect lasts only for the first two hours of neonatal life. It is preferable to administer naloxone hydrochloride directly to the neonate if needed after delivery. Naloxone hydrochloride has no apparent benefit as an additional method of resuscitation in the newly born infant with intrauterine asphyxia which is not related to opioid use.

***Usage in Pediatric Patients and Neonates for Septic Shock:*** The safety and effectiveness of naloxone hydrochloride in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established. One study of two neonates in septic shock reported a positive pressor response; however, one patient subsequently died after intractable seizures.

**Geriatric Use**

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Renal Insufficiency/Failure**

The safety and effectiveness of naloxone hydrochloride in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when naloxone hydrochloride is administered to this patient population.

**Liver Disease**

The safety and effectiveness of naloxone hydrochloride in patients with liver disease have not been established in well-controlled clinical trials. Caution should be exercised when naloxone hydrochloride is administered to patients with liver disease.

**ADVERSE REACTIONS**

**Postoperative**

The following adverse events have been associated with the use of naloxone hydrochloride in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults-Postoperative Opioid Depression**).

**Opioid Depression**

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death (see **PRECAUTIONS**).

**Opioid Dependence**

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the following signs and symptoms: 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. In the neonate, opioid withdrawal may also include: convulsions; excessive crying; hyperactive reflexes (see **WARNINGS**).

Adverse events associated with the postoperative use of naloxone hydrochloride are listed by organ system and in decreasing order of frequency as follows:

***Cardiac Disorders:*** pulmonary edema, cardiac arrest or failure, tachycardia, ventricular fibrillation, and ventricular tachycardia. Death, coma, and encephalopathy have been reported as sequelae of these events.

***Gastrointestinal Disorders:*** vomiting, nausea

***Nervous System Disorders:*** convulsions, paraesthesia, grand mal convulsion

***Psychiatric Disorders:*** agitation, hallucination, tremulousness

***Respiratory, Thoracic and Mediastinal Disorders:*** dyspnea, respiratory depression, hypoxia

***Skin and Subcutaneous Tissue Disorders:*** nonspecific injection site reactions, sweating

***Vascular Disorders:*** hypertension, hypotension, hot flushes or flushing.

See also **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults; Postoperative Opioid Depression**.

**DRUG ABUSE AND DEPENDENCE**

Naloxone hydrochloride is an opioid antagonist. Physical dependence associated with the use of naloxone hydrochloride has not been reported. Tolerance to the opioid antagonist effect of naloxone hydrochloride is not known to occur.

**OVERDOSAGE**

There is limited clinical experience with naloxone hydrochloride overdosage in humans.

**Adult Patients**

In one small study, volunteers who received 24 mg/70 kg did not demonstrate toxicity. In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m$^2$/min) of naloxone hydrochloride followed immediately by 2 mg/kg/hr for 24 hours. Twenty-three patients experienced adverse events associated with naloxone use, and naloxone was discontinued in seven patients because of adverse effects. The most serious adverse events were: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, cognitive impairment and behavioral symptoms, including irritability, anxiety, tension, suspiciousness, sadness, difficulty concentrating, and lack of appetite have been reported. In addition, somatic symptoms, including dizziness, heaviness, sweating, nausea, and stomachaches were also reported. Although complete information is not available, behavioral symptoms were reported to often persist for 2-3 days.

**Pediatric Patients**

Up to 11 doses of 0.2 mg of naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2-1/2 year-old child who inadvertently received a dose of 20 mg of naloxone for treatment of respiratory depression following overdose with diphenoxylate hydrochloride with atropine sulfate. The child responded well and recovered without adverse sequelae. There is also a report of a 4-1/2 year-old child who received 11 doses during a 12-hour period, with no adverse sequelae.

**Patient Management**

Patients who experience a naloxone hydrochloride overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date patient management information.

**DOSAGE AND ADMINISTRATION**

Naloxone hydrochloride injection may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, which is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of naloxone, the patient should be kept under continued surveillance. Repeated doses of naloxone should be administered, as necessary.

**Intravenous Infusion**

Naloxone hydrochloride injection may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of naloxone in 500 mL of either solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused mixture must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Naloxone hydrochloride injection should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone hydrochloride injection unless its effect on the chemical and physical stability of the solution has first been established.

**General**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

**Usage in Adults**

**Opioid Overdose—Known or Suspected:** An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two-to-three-minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

**Postoperative Opioid Depression:** For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of naloxone hydrochloride are usually sufficient. The dose of naloxone hydrochloride should be titrated according to the patient's response. For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.1 to 0.2 mg intravenously at two-to three-minute intervals to the desired degree of reversal—i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating, or circulatory stress.
Repeat doses of naloxone may be required within one- to two-hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.
***Septic Shock:*** The optimal dosage of naloxone hydrochloride or duration of therapy for the treatment of hypotension in septic shock patients has not been established (see **CLINICAL PHARMACOLOGY**).

**Usage in Children**

***Opioid Overdose—Known or Suspected:*** The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.
***Postoperative Opioid Depression:*** Follow the recommendations and cautions under **Adult Postoperative Depression**. For the initial reversal of respiratory depression naloxone hydrochloride should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

**Usage in Neonates**

***Opioid-Induced Depression:*** The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M., or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative opioid depression.

**HOW SUPPLIED**

1 mg/mL naloxone hydrochloride injection USP, for intravenous, intramuscular and subcutaneous administration.
Available as follows:

**1 mg/mL**

2 mL single dose disposable prefilled syringes, in the MIN-I-JET® system with 21 G. x 11/2" needle. Shrink Wrapped Packages of 10.
NDC 76329-1469-1 Stock No. 1469 (contains no preservative)

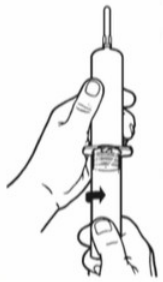
2 mL single dose disposable Luer-Jet™ Luer-Lock Prefilled Syringe. Shrink Wrapped Packages of 10.
NDC 76329-3369-1 Stock No. 3369 (contains no preservative)

**Syringe Assembly Directions:**

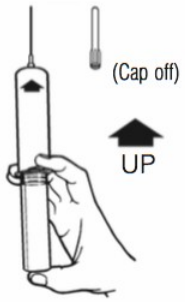
The MIN-I-JET® syringe with needle, illustrated below, is the basic unit upon which all the other syringe systems are built; slight adaptations and/ or additional auxiliary parts create the other syringe systems. Assembly directions remain essentially the same.

**USE ASEPTIC TECHNIQUE**
**Do not assemble until ready to use.**

**Remove protective caps. Align vial such that the injector needle is centered on the stopper.**



**Thread vial into injector 3 half turns, or until needle penetrates stopper.* DO NOT PUSH VIAL INTO INJECTOR; THIS MAY CAUSE MISALIGNMENT.**




**Remove needle cap and expel air before injection.**

*CAUTION: IMPROPER ENGAGING MAY CAUSE GLASS BREAKAGE AND SUBSEQUENT INJURY.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]
Protect from light.
Store in carton until contents have been used.

INTERNATIONAL MEDICATION SYSTEMS, LIMITED
SO. EL MONTE, CA 91733, U.S.A.
An Amphastar Pharmaceuticals Company

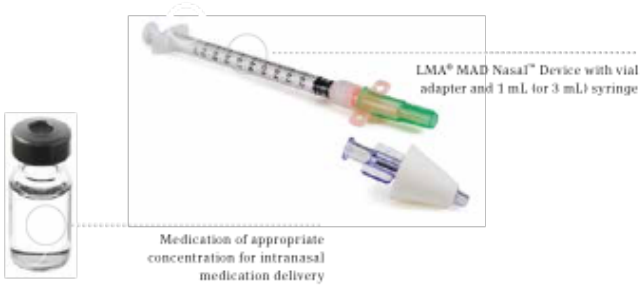
REV. 11-13

# 19 APPENDIX B: SYRINGE ASSEMBLY

## Using the LMA® MAD Nasal™ Intranasal Mucosal Atomization Device

LMA® MAD Nasal™ INTRANASAL MUCOSAL ATOMIZATION DEVICE

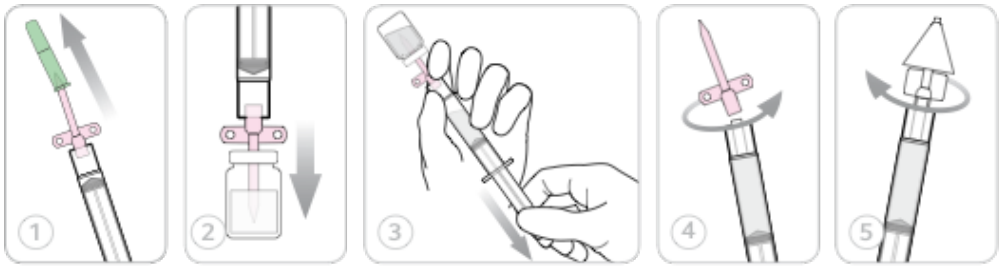
### MATERIALS




### TIPS TO IMPROVE SUCCESS

1. Minimize volume, maximize concentration
   - 1/3 mL per nostril is ideal, 1 mL is maximum
   - Use the appropriately concentrated drug
2. Maximize total mucosal absorptive surface area
   - Atomize the drug (rather than drip it in) to cover broad surface area
   - Use BOTH nostrils to double the absorptive surface area
   - Aim slightly up and outwards to cover the turbinates and olfactory mucosa
3. Beware of abnormal mucosal characteristics
   - Mucous, blood and vasoconstrictors reduce absorption
   - Suction nostrils or consider alternate drug delivery method in these situations

### PROCEDURE



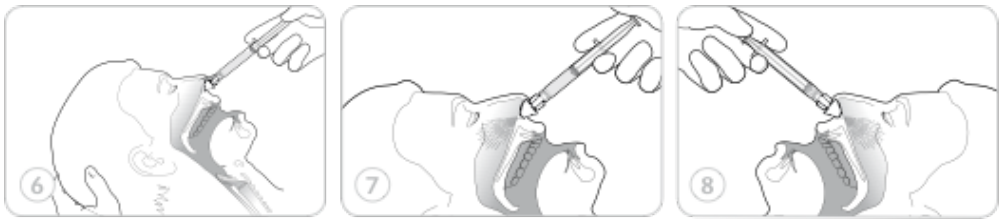

**STEP 1:** Remove and discard the green vial adapter cap.

**STEP 2:** Pierce the medication vial with the syringe vial adapter.

**STEP 3:** Aspirate the proper volume of medication required to treat the patient (an extra 0.1 mL of medication should be drawn up to account for the dead space in the device).

**STEP 4:** Remove (twist off) the syringe from the vial adapter.

**STEP 5:** Attach the MAD Nasal™ Device to the syringe via the luer lock connector.




**STEP 6:** Using the free hand to hold the occiput of the head stable, place the tip of the MAD Nasal™ Device snugly against the nostril aiming slightly up and outward (toward the top of the ear).

**STEP 7:** Briskly compress the syringe plunger to deliver half of the medication into the nostril.

**STEP 8:** Move the device over to the opposite nostril and, repeating steps 6 and 7, administer the remaining medication into the nostril if indicated.

For use with drugs approved for intranasal delivery.

TO ORDER, CALL 1.866.246.6990 OR VISIT OUR WEBSITE WWW.LMANA.COM



Teleflex®

# 20 APPENDIX C: STUDY TRAINING LOG

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

**STUDY TRAINING LOG**

| Name of Person Receiving Training | Training Completed (Aseptic Techniques, Syringe/MAD Assembly, etc.) | Date of Training | Initials of Study Sponsor: Frederick M. Hecht, MD |
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# 21 APPENDIX D: TEST AND CONTROL PRODUCT ACCOUNTABILITY LOG

| **Test and Control Product Accountability Log** | PAGE NO. |
|---|---|
| Name of Institution: University of California San Francisco | Protocol Number: HECHTMASON1 |
| Test Product: Naloxone Hydrochloride 2 mg/2 mL syringes | Control Product: 0.9% Sodium Chloride, 10 mL vials |
| Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study | Dispensing Area: Room 343, 344, or 345, 1545 Divisadero, 3rd Floor, San Francisco, CA, 94115 |
| Investigator Name: Ashley E. Mason, PhD | Sponsor Name: Frederick M. Hecht, MD |

| Line No. | Date | Subject's Initials | Subject's ID No. | Product (Test or Control) | Quantity Dispensed Or Received | Balance Forward | Lot Number | Rcpt / Disp Recorded By | [redacted] | Date Returned | Qty Returned | Recorder's Initials |
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# 22 APPENDIX E: SCHEDULE OF EVENTS BY STUDY VISIT

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

| | VISIT 1 | VISIT 2[a] |
|---|---|---|
| Informed Consent | **X** | |
| Medical History | **X** | |
| Height | **X** | |
| Weight | **X** | |
| Demographics | **X** | |
| Pregnancy Test (Urine) | **X** | |
| Drug Screen (Urine) | **X** | |
| Measures of Eating Behavior (Self-Report) | **X** | |
| Randomization | **X** | |
| Food Buffet Menu Selection | **X** | |
| Vital Signs (Pulse Rate, Temperature, Blood Pressure | **X** | |
| Taste Test Procedure | **X** | **X** |
| Administration of Control Product or Test Product | **X** | **X** |
| Self-report Measures of Nausea (SOWS) | **X** | **X** |
| Saliva | **X** | **X** |
| Adverse Experiences | **X** | **X** |
| Concomitant Medication Review | **X** | **X** |

[a] At least 24 hours after Visit 1

## 23 APPENDIX F: SUBJECT TRACKING LOG

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

| **Subject Study ID #** | **Projected or Actual** | **24 PHONE SCREEN**<br>**25 DATE** | **Visit #1 Date** | **26 VISIT #2**<br>**27 DATE** | **28 DATE AND REASON IF EARLY TERMINATION**<br>(please initial) |
|---|---|---|---|---|---|
| | Projected: | | | | |
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# 29 APPENDIX G: SPECIMEN ACCOUNTABILITY LOG

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

| Subject ID # | Visit Number | Saliva Specimen # | Date and Time of Collection | Storage Location | Initials of Person Collecting Sample | Date and Time of Shipping/ Release |
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## 30 APPENXIX H: TASTE TEST ACCOUNTABILITY

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

| **Subject ID#** | **Visit #** | **Date** | **Food Item Name** | **Bowl # (Label on bottom of bowl)** | **Empty Bowl Weight** | **Filled Bowl Weight (Pre-eating)** | **Filled Bowl Weight (Post-eating)** |
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# 31 APPENDIX I: ADVERSE EVENT ACCOUNTABILITY LOG

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

| | **Subject ID #** | **Start Date of Event** | ***Date Event Resolved** | **Description of Event** | **Severity of Event** | **Nature of Event** | **Relationship of Event** | **Action with study drug** 1- No Action 2- Interrupted 3- Discontinued | **Is this an unanticipated problem involving risks to subjects or others?** | ****Date Report Sent to IRB** |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | | | | | | | | | | |
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* All events should be resolved or noted as unresolved at the time of subject's discontinuation in the study (i.e. study complete or subject withdrawal)
** Report all adverse events in accordance with UCSF CHR (IRB) Guidelines (http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.asp - 2)

# 32 APPENDIX J: PROTOCOL VIOLATION / INCIDENT REPORTING FORM

Protocol Institutional Review Board #: _____
Protocol Title: Opiate withdrawal responses to intranasal naloxone as an index of altered endogenous opioid activity among individuals with obesity: A feasibility and efficacy study
Principal Investigator: Ashley E. Mason PhD
Sponsor: Frederick M. Hecht, MD

Date of First Awareness of Violation or Incident: _____

Participant ID (or number of affected participants if more than one): _____

Report to the CHR within 10 working days of awareness:

Change in protocol necessary to immediately protect research participants or others

Report to the CHR within 10 working days of awareness:

Major Protocol Violation

- Incorrect research treatment or intervention given
- Enrollment of participant ineligible per CHR protocol
- Procedure/lab required by protocol not done
- Procedure/lab done outside the required window

Major Research-Related Incident

- Problem with the informed consent or recruitment process
- Significant concern or complaint received
- Lapse in study approval
- Loss of adequate resources
- Unauthorized disclosure of private information (e.g., stolen or lost research data, privacy incident)
- Other type of Major Protocol violation or Incident

If Other, explain:

What happened and how did it happen:

What are the consequences or possible consequences of the event:

What you have done in response to the event:

What you have done to prevent recurrence of this type of event:

Explain whether the event has been resolved:

Is a modification needed

- Yes
- No

If YES, specify what will be modified:

Protocol

Consent form(s)

Other

Specify Other:

If YES, explain when the modification will be submitted. If NO explain why a modification is not needed:

Actions Taken: Check all that apply

Participant has been withdrawn from further study participation

Study treatment for all subjects has been stopped (temporarily)

Study treatment for all subjects has been stopped (permanently)

Approved study data analysis plan modified

Sponsor has been notified

Other

If Other, please explain:

Did this event involve a definite or possible subject injury:

Yes
No

This report involves a SF VA Medical Center patient, tissue, or data:

Yes
No

Late Submissions: If this report is being submitted late [after 10 working days from first awareness, per the above], please explain 1) why this report is late, and 2) how late submissions will be avoided in the future:

Breach of Confidentiality Questions (section applies only if section 1.0 indicates a breach of confidentiality.

The Breach of Confidentiality involves:

Social security number(s)

Electronic PHI

Non-Electronic PHI

Notification of the UCSF HIPAA Office

Do you plan to inform subjects of the breach:

Yes
No

If YES, describe your plan for informing subjects of the breach. If NO, explain why not.

The PI and Sponsor will consult the UCSF Privacy Office at 415 353-2750 or affiliate Privacy Office when devising this plan.