Study information

Title	Active Surveillance Program for Misuse, Abuse, Addiction, Overdose and Death Attributed to EMBEDA® and Other Oral Extended-Release Morphine
Protocol number	B4541022
Protocol version identifier	Version 1
Date of last version of protocol	14 May 2015
European Union (EU) Post-Authorization Study (PAS) register number	Study not registered
Active substance	OPIOIDS (N02A): Morphine sulfate and naltrexone hydrochloride
Medicinal product	EMBEDA®
Research question and objectives	To quantify the extent of misuse, abuse, addiction, overdose and death believed to be associated with each of two comparison groups -- EMBEDA and other oral ER morphine tablets and capsules -- in the community over time.
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090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

TABLE OF CONTENTS

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CSP	College Survey Program
DAST-10	Drug abuse screening test-10
ER	Extended release
EU	European Union
FDA	Food and Drug Administration
IR	Immediate-release
NIS	Non-interventional study
PASS	Post-authorization safety study
PCP	Poison Center Program
PMR	Post-marketing requirement
RADARS® System	Researched Abuse Diversion and Addiction-Related Surveillance System
ROA	Route of administration
SAP	Statistical analysis plan
SAMHSA	Substance Abuse and Mental Health Services Administration
TCP	Treatment Center Program
WMP	Web Monitoring Program

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2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

3. ABSTRACT

- **Title:** Active Surveillance Program for Misuse, Abuse, Addiction, Overdose and Death Attributed to EMBEDA® and Other Oral Extended-Release Morphine
  Version: 1.0, 14 May 2015 [Kenneth R. Petronis, MPH, PhD; Pfizer Inc.]

- **Rationale and background**
  EMBEDA® capsules contain individual pellets of morphine sulfate with a sequestered naltrexone hydrochloride inner core. When taken as prescribed, morphine is released in an extended-release (ER) profile to provide relief of moderate to severe chronic pain for up to 24 hours. Abuse of prescription opioids, such as morphine, has reached epidemic proportions in recent years in the United States. ER opioid formulations such as EMBEDA are more prone to tampering than immediate-release (IR) formulations, likely due to the larger amount of medication available in the ER dosage units. Tampering releases these larger doses immediately, producing a more intense euphoric effect that is sought by drug abusers. EMBEDA was developed in the context of this public health crisis in an effort to help mitigate abuse of morphine. Tampering with EMBEDA releases the antagonist naltrexone and blocks the action of the morphine, and thereby its euphoric effect. This surveillance is intended to provide quantitative evidence that there is less misuse, abuse, addiction, overdose and death associated with EMBEDA, compared to other oral ER morphine tablets and capsules, in the community.

- **Research question and objectives**
  The objective of this study is to quantify the extent of misuse, abuse, addiction, overdose and death believed to be associated with each of the two comparison groups, EMBEDA and other oral ER morphine tablets and capsules, in the community over time.

- **Study design**
  The methodological approach of active surveillance will be used. Surveillance data will be collected on a quarterly basis. Surveillance will cover the period starting with the first quarter of 2015 and ending with the third quarter of 2019. In addition, data for the comparator, other oral ER morphine tablets and capsules, will be collected for two full quarters before EMBEDA availability (third and fourth quarters of 2014).

- **Population**
  Surveillance populations will be specific to each Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System data source, as described below. The Treatment Center Program surveillance population consists of patients entering substance abuse treatment programs. The Poison Center Program surveillance population consists of exposure cases recorded by poison control centers. The College Survey Program surveillance population consists of students attending a two- or four-year college, university or technical school at least part-time. The Web Monitoring Program surveillance population consists of individuals who post statements related to misuse, abuse, addiction, overdose and death on public social media accounts, online blogs, web forums and other internet sites.

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- **Variables**
  Rates of five endpoints (misuse, abuse, addiction, overdose, and death) will be calculated separately for EMBEDA and other oral ER morphine tablets and capsules.

- **Data sources**
  Four component data sources of the RADARS System will be used: Treatment Center Program, Poison Center Program, College Survey Program, and Web Monitoring Program.

- **Study size**
  Active surveillance is not intended to test a pre-specified statistical hypothesis therefore a pre-determined sample size is not calculated.

- **Data analysis**
  The primary goal of the analyses will be to estimate rates of five safety-related endpoints (misuse, abuse, addiction, overdose, and death) associated with each of the two comparison groups. These rates will be estimated across time and by route of administration. A Poisson regression model with a drug group specific dispersion parameter will be utilized to estimate trends over time in rates for the two comparison groups. Evaluation of data from the Web Monitoring Program will be of a descriptive nature as it does not allow for the calculation of rates.

- **Milestones**
  Surveillance will cover the period from July 2014, seven months prior to first availability of EMBEDA (February 2015), through September 2019. The final report will be delivered in April 2020.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

4. AMENDMENTS AND UPDATES

None.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

5. MILESTONES

Milestone	Planned date
Registration in EU PAS register	15 May 2016
Start of data collection	31 May 2016
End of data collection	30 November 2019
Final study report	30 April 2020

6. RATIONALE AND BACKGROUND

The EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release (ER) capsule formulation was approved by the U.S. Food and Drug Administration (FDA) in August 2009. After a voluntary recall in March 2011, EMBEDA became available again in February 2015. It is indicated for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. EMBEDA capsules contain individual pellets of morphine sulfate with a sequestered opioid antagonist naltrexone hydrochloride inner core. When taken as prescribed (whole capsule or intact pellets sprinkled on apple sauce and consumed without chewing), the extended-release properties of the formulation are maintained to provide analgesic effects of morphine for up to 24 hours while the sequestered core of naltrexone remains intact. The sequestered naltrexone in EMBEDA is intended to have no clinical effect when EMBEDA is taken as directed.

The intended route of administration (ROA) for EMBEDA is swallowing the capsule intact. Alternatively, in patients who cannot swallow capsules, pellets can be sprinkled on apple sauce and consumed without chewing. Unintended ROAs involve tampering with the capsule. Such tampering can release both the morphine and the antagonist naltrexone, essentially creating an immediate- release dosage form of both drugs. EMBEDA is expected to deter abuse by tampering via oral and intranasal ROAs. These unintended ROAs release the antagonist naltrexone and block the action of the morphine. The euphoric effect of morphine typically sought via unintended ROAs is thereby also blocked.

The 2011 Prescription Drug Abuse Prevention Plan states that abuse of prescription opioids such as morphine, the analgesic component of EMBEDA, has reached epidemic proportions in recent years in the United States (Executive Office of the President of the United States, 2011).[12] EMBEDA was developed in the context of this public health crisis in an effort to help mitigate abuse of morphine.

6.1. Overview of Opioid Abuse in the United States

Clinical guidelines for chronic pain recommend that opioids be considered only after an adequate trial of non-opioid options have proven ineffective (Centers for Disease Control and Prevention, 2014; Manchikanti et al., 2012, Chou et al., 2009; Department of Veterans

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

Affairs, 2010; Utah Department of Health, 2009; Medical Board of California, 2014; Washington State Agency, 2010).[4,6,11,24,26,37,39] Nevertheless, opioids remain an important treatment option for the management of chronic pain (Furlan et al., 2006).[15] Opioid availability and use for acute and chronic pain have increased over the past few decades, resulting in improved treatment for many patients (Kelly et al., 2008).[22] Unfortunately, as prescription opioid use increased over the past two decades, a major upswing in societal problems related to prescription opioids has also occurred. These problems include abuse, with 4.5 million persons (1.7%) 12 years of age or older indicating current (within the last month prior to the survey) nonmedical use of prescription pain relievers (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014a);[34] fatal overdoses of prescription opioids in 2013 numbered over 16,000 in the United States (Hedegaard et al., 2015);[18] dependence, with about 1.9 million Americans currently meeting criteria for addiction to prescription opioids (SAMHSA, 2014a)[34] and over 169,868 admissions to substance-abuse treatment centers per year for non-heroin opiate abuse (SAMHSA, 2014b);[35] over 9,000 children exposed to a prescription opioid in a 3.5-year period (Bailey et al., 2008);[2] about 488,000 emergency department visits per year related to nonmedical use of prescription opioids (SAMHSA, 2013);[36] 1 in 10 twelfth-graders reporting recreational use of Vicodin®, and 1 in 20 OxyContin® (Johnston et al., 2009);[20] and over $50 billion in annual societal costs associated with prescription opioid abuse in the United States (Birnbaum, 2010).[1] Drug overdose deaths in the U.S. increased almost four-fold between 1999 and 2011 (Chen et al 2014),[5] with the majority of these deaths associated with misuse of prescription opioid analgesics (Morbidity and Mortality Weekly Report, 2011). The dramatic increase in these opioid-related overdoses has rapidly emerged as a major public health problem in the U.S. (King et al., 2014).[23] More recent data suggest that trends in prescription opioid abuse and diversion since 2010 have begun to decrease (Dart et al., 2015).

6.2. Abuse by Tampering

Tampering, defined as manipulating a dosage form to change its drug delivery in a way not specified by the manufacturer (Katz et al, 2007),[21] is an important part of the prescription opioid abuse problem. Manipulating or altering the pill can include methods such as crushing or dissolving the pill to extract the opioid compound for the purpose of snorting or injecting. Generally, this is done to obtain a better and faster “high” and is seen more commonly with extended-release opioids (Severtson et al, 2013).[30] The most common method of abuse is oral ingestion of either the tampered or intact product, followed by snorting and then injection (SAMHSA, 2014b). Few data in the literature specifically distinguish abuse by swallowing whole versus abuse by chewing or crushing and then swallowing. Nationwide, among individuals entering substance-abuse treatment for prescription opioid abuse, more than half (59%) of primary non-heroin opiate admissions reported oral as the usual route of administration, while 21% reported inhalation and 17% reported injection (SAMHSA, 2014b). Smoking is rare for most products. Extended-release formulations are more prone to tampering than immediate-release formulations, likely due to the larger amount of medication available in the dosage units and the absence of co-formulated analgesics (eg, acetaminophen) that may make snorting or injection less desirable.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

Tampering is worrisome for several reasons, one of which is that this behavior may be associated with accelerated progression along the trajectory of addiction. For example, in one study, approximately 17% of abusers were tampering when they first initiated prescription opioid abuse, but by the time they entered substance-abuse treatment, 78% reported tampering (Hays et al., 2003).[17]

6.3. Abuse Deterrent Formulations

A formulation that addresses any form of prescription opioid abuse is essential to addressing prescription opioid abuse, considered to be a serious public health crisis. Dr. Leonard J. Paulozzi (Medical Epidemiologist, Centers for Disease Control and Prevention), in a statement before the Senate Judiciary Subcommittee on Crime and Drugs (March 12, 2008), indicated that addressing this crisis requires more aggressive measures than have been taken to date including that "drug manufacturers should modify opioid painkillers so that they are more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected" (Paulozzi, 2008).[28] In April 2015, the FDA distributed a guidance document intended to assist sponsors wishing to develop formulation of opioid drug products with potentially abuse-deterrent properties (Food and Drug and Administration, 2015). The document highlights that the FDA considers the development of abuse-deterrent technologies for prescription opioids a high public health priority. According to these recommendations, the goal of post-marketing studies would be to determine whether the marketing of the potentially abuse-deterrent formulation resulted in a significant decrease in population-based and use-based estimates of abuse compared to estimates of abuse from formulations without abuse-deterrent properties.

Early research suggests that reformulating abused prescription opioids to include tamper-resistant properties may be an effective approach to reduce abuse of the specific reformulated products but may not impact overall abuse rates of prescription opioids as a drug class (Cicero et al., 2012; Severtson et al., 2013; and Cassidy et al., 2014).[3,7,30] This research suggests that additional studies will be important to monitor abuse patterns and the public health impact as new abuse-deterrent opioid formulations are developed.

The inclusion of naltrexone in EMBEDA is expected to deter abuse by tampering via oral and intranasal ROAs. This protocol outlines an active surveillance program to informally compare EMBEDA to other ER morphine with respect to the rate of misuse and abuse, and their consequences, addiction, overdose and death, in the community. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the U.S. Food and Drug Administration.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to quantify the extent of misuse, abuse, addiction, overdose and death believed to be associated with each of the two comparison groups -- EMBEDA and other oral ER morphine tablets and capsules -- in the community over time through an active surveillance program. The specific objectives are:

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

- Estimate rates of misuse believed to be associated with EMBEDA and other oral ER morphine tablets and capsules in the community over time;
- Estimate rates of abuse believed to be associated with EMBEDA and other oral ER morphine tablets and capsules in the community over time;
- Estimate rates of addiction believed to be associated with EMBEDA and other oral ER morphine tablets and capsules in the community over time;
- Estimate rates of overdose believed to be associated with EMBEDA and other oral ER morphine tablets and capsules in the community over time;
- Estimate rates of death believed to be associated with EMBEDA and other oral ER morphine tablets and capsules in the community over time.

To the extent possible, rates will also be calculated separately for all intended and unintended ROAs and informally compared. Analyses will exclude morphine solutions, suppositories and injection because these formulations are currently unavailable in an abuse deterrent formulation. This will facilitate use of total number of tablets/capsules dispensed as a denominator of rates of misuse, abuse, addiction, overdose, and death, and the overall market share of morphine. Solutions, suppositories and injections constituted only 8.6% of all morphine prescriptions dispensed in 2014.

A secondary objective is:

- Gather supportive/ancillary information from anecdotal reports in social media regarding misuse, abuse, overdose, addiction and death associated with EMBEDA and other oral ER morphine tablets and capsules.

8. RESEARCH METHODS

The methodological approach of active surveillance will be used to assess for trend in misuse and abuse (and their consequences) of EMBEDA and other oral ER morphine tablets and capsules. Active surveillance allows near-real time evaluation of non-rare adverse drug-related events (U.S. Food and Drug Administration, 2010).[13] An active surveillance *system* involves a systematic process for analyzing *multiple* observational health care data sources to better understand the effects of medical products. It can potentially characterize known side effects, monitor preventable adverse events, and enhance the understanding of safety concerns emerging in the post-market period by supplementing other sources of safety information, such as spontaneous adverse event reporting (Stang et. al., 2010).[33]

Misuse and abuse of prescription opioids involve illicit activities that could result in legal sanctions if discovered. They therefore tend to be conducted covertly and only become detectable when the actor is "revealed" and forced to interact with society at large. Encounters in which opioid misuse and abuse, and their consequences, are revealed include acute health events, encounters with the criminal justice system and drug treatment facilities, and avenues for anonymous communication. The RADARS System capitalizes on such encounters to obtain uniformly-collected, timely and reliable information on prescription drug misuse and abuse in the community (Dart et al, 2015).[10]

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

The RADARS System was originated by Purdue Pharma L.P. in the wake of increasing reports of OxyContin® misuse and abuse in the late 1990s (Cicero et. al., 2007a).[9] Since 2006 it has been operated by Denver Health and Hospital Authority, a public, not-for-profit healthcare system. The specific goal of the RADARS System is to measure, in a timely, proactive and geographically-sensitive manner, trends in the rates of misuse, abuse and diversion of prescription and illegal drugs. It has been successfully employed to monitor for trends in misuse and abuse of prescription opioids (Cicero et. al., 2007a and 2007b; Inciardi et. al, 2009; Schneider et. al., 2009; Spiller et. al., 2009, Dart et. al. 2015).[9,10,29,32] The various data sources in the RADARS System draw from populations at different stages along the drug abuse pathway, from first time experimenters to experienced addicted individuals. No single data collection program adequately captures this breadth of experience with drug abuse. The data sources largely record self-reported data, which make them subject to inherent biases and weaknesses. However, each data source is intended to assess *trends* in misuse and abuse over time. They are not biased with respect to trend assessment because each data source is uniformly-collected over time. There is no reason to expect that the biases in these data sources will change.

The EMBEDA active surveillance program will be implemented using four RADARS System data sources, each of which records information during different types of encounters in which opioid abuse and misuse are revealed. These data sources obtain this information from different persons, repeatedly over time, at different points in the drug abuse pathway and in different settings, making them appropriate for "data triangulation" (Thurmond, 2001).[38]

Data triangulation is the use of multiple data sources to corroborate findings. Any weaknesses in one data source can be compensated for by the strengths of others, thereby increasing the reliability and validity of results. The approach has been used in many fields of research and is especially useful in the study of hard to reach or hidden populations, such as prescription drug abusers. It is not typically possible to create sampling frames for such populations, so standard sampling methods cannot be implemented. Instead, social science researchers often rely on multiple convenience samples, each obtained from a different perspective on the hidden population being studied. No single data source is expected to provide complete and representative information about the group but, considered together, multiple data sources strengthen the credibility of findings, reduce the risk of false interpretations and provide a more complete and comprehensive perspective on the behaviors of the covert group. Triangulating from a range of data types and sources has also been used to monitor epidemics among hidden populations, such as human immunodeficiency virus infection, and to assess the effect of interventions designed to mitigate them (Hales, 2010).[16] Similarly, the EMBEDA active surveillance program will employ data triangulation to assess the effect of an intervention, the EMBEDA tamper-resistant ER morphine formulation, on the misuse and abuse of oral ER morphine tablets and capsules.

In summary, by triangulating four RADARS System data sources, the EMBEDA active surveillance program will provide a timely, sensitive, and reliable assessment of trends in misuse and abuse (and their consequences) over time among the hard to reach population of oral ER morphine tablet and capsule abusers.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

8.1. Study design

The methodological approach of active surveillance will be used. The surveillance design is specific to each of the four RADARS System data sources that will be used: Treatment Center Program; Poison Center Program; College Survey Program; and Web Monitoring Program. A full description of these programs can be found in Section 8.4. Additional details about the Treatment Center Program, Poison Center Program and College Survey Program can be found in the online supplement to a recent publication (Dart et al., 2015).[10] Schematics depicting subject identification relative to EMBEDA exposure and the five surveillance endpoints can also be found in Section 8.4.

Surveillance data will be collected on a quarterly basis. Surveillance will cover the period starting with the first quarter of 2015 and ending with the third quarter of 2019. In addition, data for the comparator, other oral ER morphine tablets and capsules, will be collected for two full quarters before EMBEDA availability (third and fourth quarters of 2014).

8.2. Setting

The surveillance population will be specific to each RADARS System data source, as described below.

Treatment Center Program

The surveillance population consists of patients entering substance abuse treatment programs.

Poison Center Program

The surveillance population consists of exposure cases recorded by poison control centers in 46 states covering over 282 million people in urban, suburban, and rural regions (91.5% of total 2010 US population).

College Survey Program

The surveillance population consists of students attending a two- or four-year college, university or technical school at least part-time.

Web Monitoring Program

The Web Monitoring Program surveillance population consists of individuals who post statements related to misuse, abuse, addiction, overdose and death on public social media accounts, online blogs, web forums and other internet sites.

8.2.1. Inclusion criteria

Treatment Center Program

Subjects must meet all of the following inclusion criteria to be eligible for inclusion in the surveillance:

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

1. Completed the survey.
2. Age 18 years or older.
3. Provided a valid three digit zip code.
4. Reported past month use of any oral ER morphine tablet or capsule to get high.

Poison Center Program

Cases must meet all of the following inclusion criteria to be eligible for inclusion in the surveillance:

1. Report of intentional human exposure to oral ER morphine tablets.

College Survey Program

Subjects must meet all of the following inclusion criteria to be eligible for inclusion in the surveillance:

1. Indicates consent before providing any responses to the questionnaire.
2. Age 18 years or older.
3. Indicates is enrolled in a two- or four-year college, university or technical school at least part-time.
4. Reports non-medical use of any oral ER morphine tablet or capsule in the past 3 months.

Web Monitoring Program

1. Online posts originating in the United States which mention EMBEDA or other oral ER morphine tablets or capsules are eligible for inclusion in the surveillance.

8.2.2. Exclusion criteria

There are no exclusion criteria for subjects in the Treatment Center Program, the Poison Center Program or the Web Monitoring Program.

Respondents in the College Survey Program meeting any of the following criteria will not be included in the surveillance:

1. Answers affirmatively to any question about any use (past 3 months) of a non-existent drug.
2. Answers affirmatively to every question about frequency (more than 10 days per month) of illegal drug use.
3. Answers affirmatively to every question about any use (past 3 months) of prescription opioids and stimulants.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

4. Three or more text field responses contain irregularities (eg, long strings of a single character, comment unrelated to the question).

8.3. Variables

The variables to be used in the EMBEDA active surveillance program are identified in Table 1 below with respect to their role in the analysis and the data sources from which they will be derived. Operational definitions will be included in the Statistical Analysis Plan (SAP). Detailed definitions of the five surveillance endpoints, by data source, are provided in Annex 2.

Table 1 Variables in the EMBEDA Active Surveillance Program

Variable	Role	Data source(s)[§]
Abuse	endpoint	TCP, PCP, CSP, WMP*
Misuse	endpoint	PCP, CSP, WMP*
Overdose	endpoint	PCP, WMP*
Addiction	endpoint	CSP, WMP*
Death	endpoint	PCP, WMP*
Covered population	denominator	Census
Units dispensed	denominator	IMS Health
Prescriptions dispensed	denominator	IMS Health
ROA[a]: swallowing intact	sub-group identifier	TCP, PCP, CSP, WMP*
ROA: chewing then swallowing	sub-group identifier	PCP, CSP, WMP*
ROA: dissolving in mouth then swallowing	sub-group identifier	CSP, WMP*
ROA: intranasal	sub-group identifier	PCP, CSP, WMP*
ROA: injection	sub-group identifier	TCP, PCP, CSP, WMP*
Age	potential confounder & sub-group identifier	TCP, PCP, CSP
Sex	potential confounder & sub-group identifier	TCP, PCP, CSP
Race/Hispanic ethnicity	potential confounder & sub-group identifier	TCP, CSP

[a]ROA = route of administration
[§]TCP = Treatment Center Program; PCP = Poison Center Program; CSP = College Survey Program; WMP = Web Monitoring Program

Note: Operational definitions for all variables will be included in the Statistical Analysis Plan. Detailed descriptions of the endpoints are provided in Annex 2.

* The Web Monitoring Program will collect descriptive information regarding all five endpoints and all ROAs. It will be used to provide context that will assist in interpreting data collected by the other three data sources; it will not be used to calculate any rates.

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8.4. Data sources

Four component data sources of the RADARS System will be used, as described below. In addition, units dispensed and prescriptions dispensed will be obtained from IMS Health.

8.4.1. Treatment Center Program

The RADARS System Treatment Center Program combines two complementary national data sources: the Opioid Treatment Program and the Survey of Key Informants' Patients. The Opioid Treatment Program collects data from patients entering methadone maintenance treatment programs and the Survey of Key Informants' Patients collects data from patients entering other substance abuse treatment programs (ie, excluding methadone maintenance facilities). The same data collection tool is used by both programs, allowing their data to be combined. Combining these two data sources provides a comprehensive data source on patients entering the full spectrum of treatment programs available nationally.

The American Association for the Treatment of Opioid Dependence and the National Development and Research Institutes work in collaboration with the RADARS System to manage the Opioid Treatment Program. This program seeks to determine the past 30 day use of prescription opioid products among patients admitted to methadone maintenance treatment programs nationally. All patients enrolling in participating methadone programs are recruited for the study and voluntarily complete a standardized, self-administered questionnaire on product specific prescription drugs used to get high in the past 30 days.

A second treatment program, Survey of Key Informants' Patients, is conducted at Washington University in St. Louis, Missouri. Like the Opioid Treatment Program, the Survey of Key Informants' Patients Program collects data from patients entering substance abuse treatment programs other than methadone treatment programs. Each newly admitted patient to the Survey of Key Informants' Patients program is offered the opportunity to complete a standardized self-administered questionnaire that solicits information on product specific prescription drugs used to get high in the past 30 days.

In 2014, the Treatment Center Program (Opioid Treatment Program and Survey of Key Informants' Patients programs combined) collected a total of 10,030 patient surveys. The median age was 32 years with an interquartile range of 27 to 41. Of those surveyed, 5,364 (53.5%) of respondents were male and 4,508 (45.0%) were female, the remaining 158 (1.5%) did not indicate their sex. Figure 1 displays the 2014 coverage area of the Treatment Center Program.

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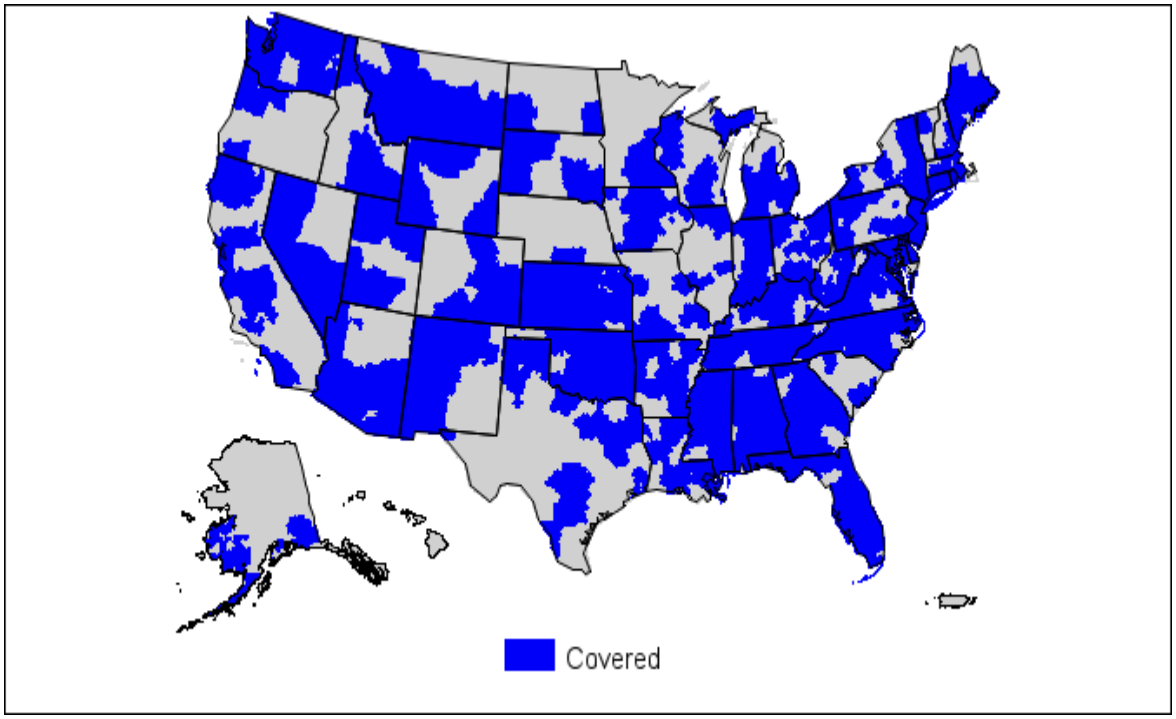
Figure 1. Three Digit ZIP Codes of Patients and Program Locations in the RADARS System Treatment Center Program in 2014



In general, Opioid Treatment Program sites are publicly funded and Survey of Key Informants' Patients program sites are primarily privately funded. Combining these two programs enables surveillance of a broad spectrum of individuals seeking prescription drug abuse treatment for addiction.

The questionnaire used by the Opioid Treatment Program and Survey of Key Informants' Patients Programs includes basic demographic items, 3-digit ZIP code of patient's residence, primary opioid of abuse, opioids used to get high (past month) and whether they were injected (past month)[1]. Subjects are recruited to complete the questionnaire within the first week of admission, typically on the first or second day. In the current questionnaire, patients are asked to indicate which drugs they have used to get high in the past month by checking boxes next to product names.

The definition of the comparison groups to be identified in this surveillance is depicted in Figure 2 below. Note that it is possible for a single patient to be included in both comparison groups, as indicated by the curved arrows at the bottom of the figure. Patients reporting use of both EMBEDA and other oral ER morphine tablets or capsules are included in the EMBEDA comparison group and also in the other oral ER morphine tablet or capsule comparison group.

[1] The OTP questionnaire is reviewed every quarter and revised to reflect the current opioid market.

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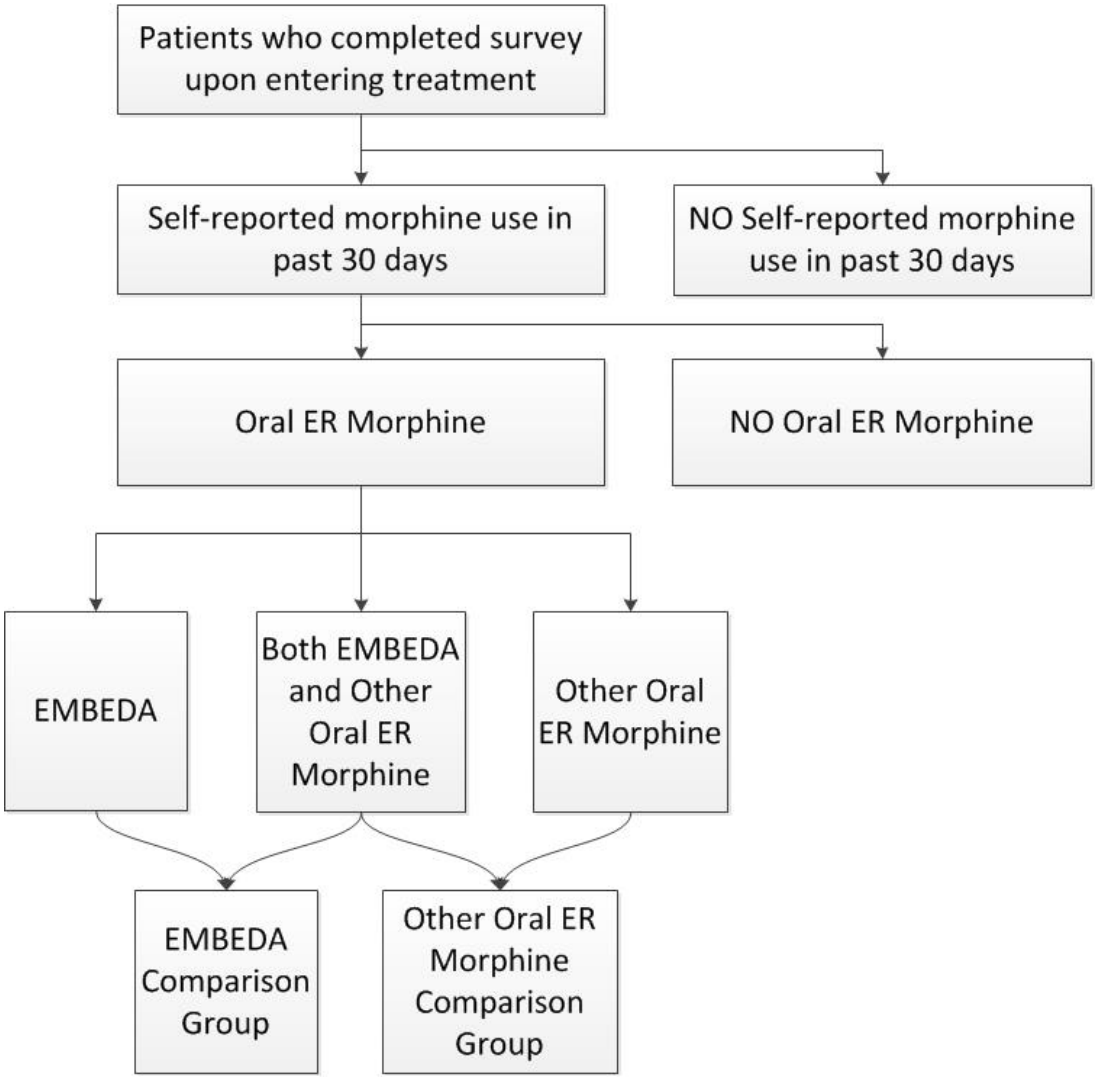
Figure 2. Comparison Groups in Treatment Center Program Surveillance



8.4.2. Poison Center Program

Currently, there are 55 United States poison centers that collectively receive over 2.2 million exposure calls per year from the general population and health care providers seeking advice following an exposure to a potentially toxic substance, including prescription drugs. In 2014, the RADARS System Poison Center Program gathered data from 48 of these 55 regional United States poison centers in 46 states, covering over 286 million people in urban, suburban, and rural regions (91.5% of total 2010 US population). The median age of exposure cases in 2014 was 28 years with an interquartile range of 14 to 47, 35,170 (46.1%) of respondents were male, 41,002 (53.7%) were female, and the remaining 156 (0.2%) did not indicate their sex. A map of the three digit zip codes covered by the Poison Center program appears as Figure 3 below.

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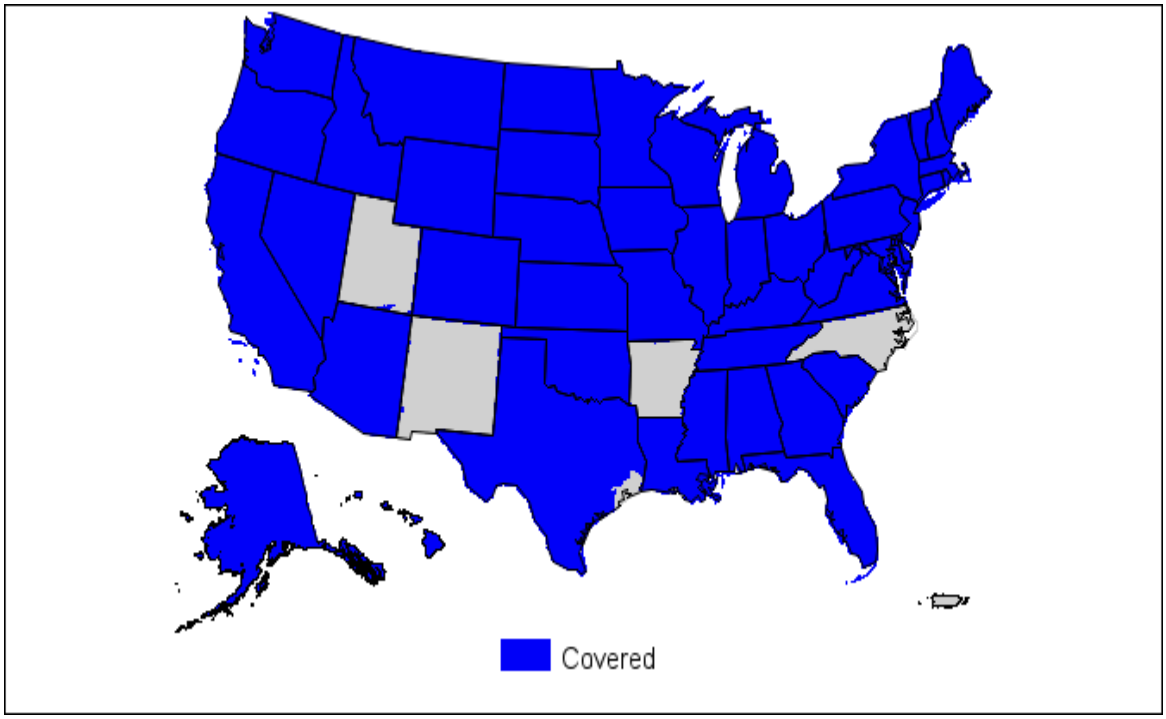
Figure 3. Three Digit ZIP Codes Covered by the RADARS System Poison Center Program in 2014



Investigators at each participating poison center collect data using a nationally standardized electronic health record. Case reports are accompanied with detailed notes and are submitted to the RADARS System for review and quality assurance. RADARS System staff review every poison center case to verify the coding of case characteristics including reason for exposure, products involved, route of exposure, and medical outcome. This quality control process ensures accurate product-specific data are collected to monitor prescription drug exposures.

Poison centers assign cases a reason for exposure and classify them as either intentional or unintentional exposures. Intentional exposures are assigned to subcategories including abuse, misuse, suicide and unknown. For purposes of this surveillance, all intentional exposures will be considered a general measure of overdose. As part of standard procedures, poison centers follow cases and document a categorical medical outcome. Death is one of the possible medical outcome categories.

All poison centers utilize an interactive tool that includes photographs of opioids. Micromedex® (Truven Health Analytics Inc) assists poison center staff in accurately identifying the opioid(s) mentioned during a call. Micromedex is a drug inventory that includes identifying characteristics such as size, shape, color and imprint, as well as photographs of most products. This shared drug lexicon allows for standardized coding of product name, formulation and dosage strength. Route of exposure (ingestion, inhalation or

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parenteral) is also captured for each product. Ingestion is further categorized into three routes of administration by RADARS System staff upon review of the case notes: swallowing intact; chewing then swallowing; transmucosal (ie, dissolving in mouth then swallowing) and other.

Micromedex is an interactive tool and can be searched by name, active ingredient, imprint code, color and shape. The RADARS System provides targeted education to the poison centers when new opioid products are introduced to the market and when systematic errors are recognized during its rigorous quality control process. These targeted education campaigns will continue and will include a campaign specifically addressing ascertainment between EMBEDA and other oral ER morphine tablets and capsules.

The definition of the comparison groups to be identified in this surveillance is depicted in Figure 4 below. Note that it is possible for a single case to be included in both comparison groups, as indicated by the curved arrows at the bottom of the figure. Cases in which use of both EMBEDA and other oral ER morphine tablets or capsules is reported are included in the EMBEDA comparison group and also in the other oral ER morphine tablet/capsule comparison group.

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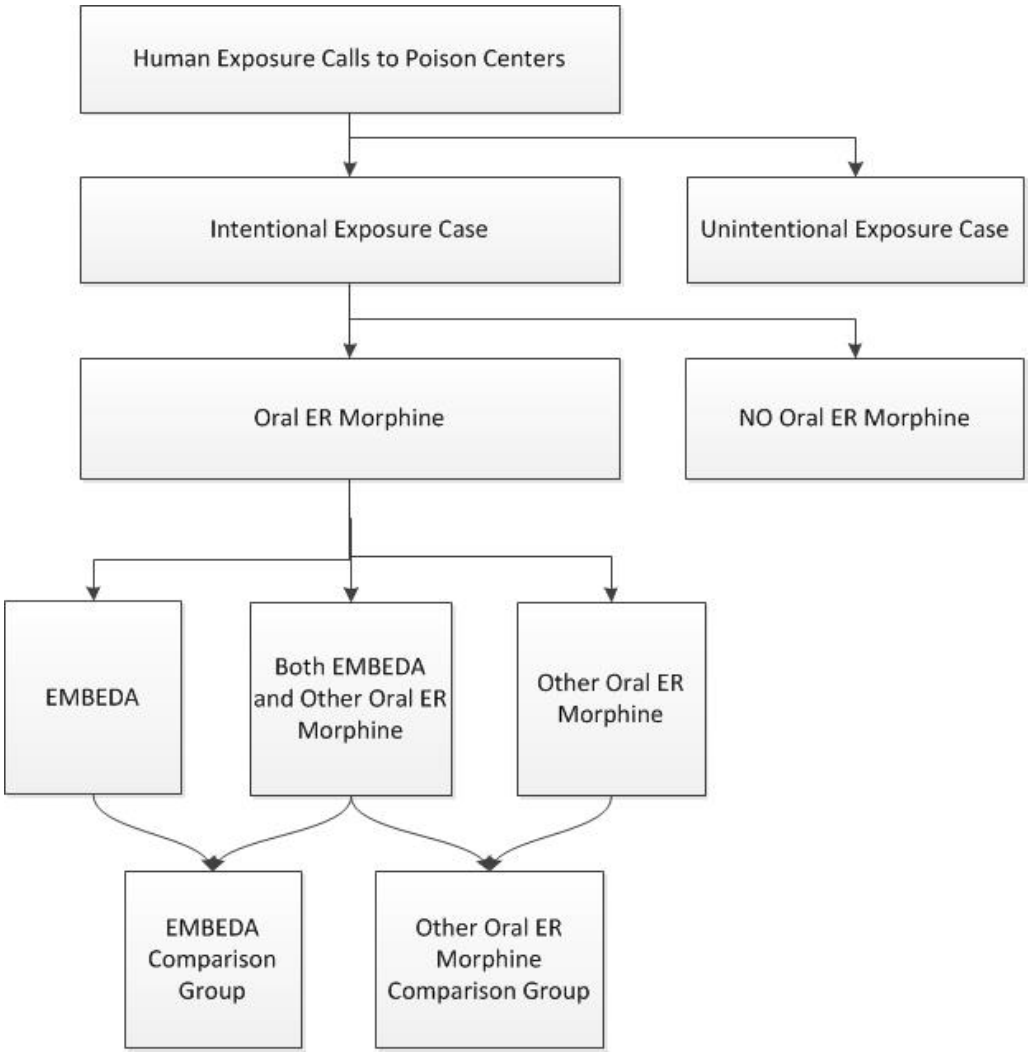
Figure 4. Comparison Groups in Poison Center Program Surveillance



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8.4.3. College Survey Program

The College Survey Program is under the direction of Richard C. Dart, MD, PhD (Principal Investigator) of Rocky Mountain Poison and Drug Center. The program aims to estimate the scope of prescription drug use for nonmedical reasons among college students in the United States. The College Survey Program consists of an online questionnaire collecting data from self-identified students attending a two- or four-year college, university or technical school at least part-time during the specified sampling period. A nationwide panel company is utilized to target college students age 18 years or older. For each survey, an email invitation is sent to a pool of individuals who sign up to complete a variety of surveys in exchange for points which can be redeemed for modest compensation. Self-identified college students who complete the RADARS System College Survey earn points worth approximately $4.00. Data on nonmedical use of specific prescription drugs are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. A target of 2,000 surveys are completed three times per year with enrollment stratified equally into the four US census regions (West, Midwest, South, Northeast), thus helping to ensure a nationwide distribution of respondents.

The questionnaire consists of basic demographic items (including age, sex, race, and Hispanic origin), 3-digit ZIP code where respondents report living during the specified sampling period, grade point average, reason for use, non-medical prescription drug use (including opioids) during the past three months, route of administration (swallowed intact; chewed then swallowed; dissolved in mouth then swallowed; inhaled; injected; dermal and other) and Drug Abuse Screening Test – 10 (DAST-10) score[2] (Skinner, 1982).[31] The online questionnaire for the College Survey Program includes photographs of opioid products.

Respondents are asked at the beginning of the questionnaire if they understand their answers will be kept confidential and anonymous. Respondents who do not answer affirmatively to this question are prevented from completing the survey.[3]

Through 2014, there have been 35,665 participants in the College Survey Program. Of all respondents, 14,672 (41.1%) were male, and 20,993 (58.9 %) were female. The median age was 23 years with an interquartile range of 20 to 28. Three digit zip codes of college survey respondents for the year 2014 are shown in Figure 5 below.

[2] The Drug Abuse Screening Test (DAST-10) is a self-reported instrument consisting of ten questions regarding a respondent's involvement with drugs. Each question can be answered yes or no and the number of yes responses constitutes the DAST-10 score. The higher the score, the greater the respondent's level of involvement with drugs (McCabe et al, 2007).[25]

[3] The College Survey Program questionnaire is reviewed every quarter and revised to reflect the current opioid product market and nomenclature.

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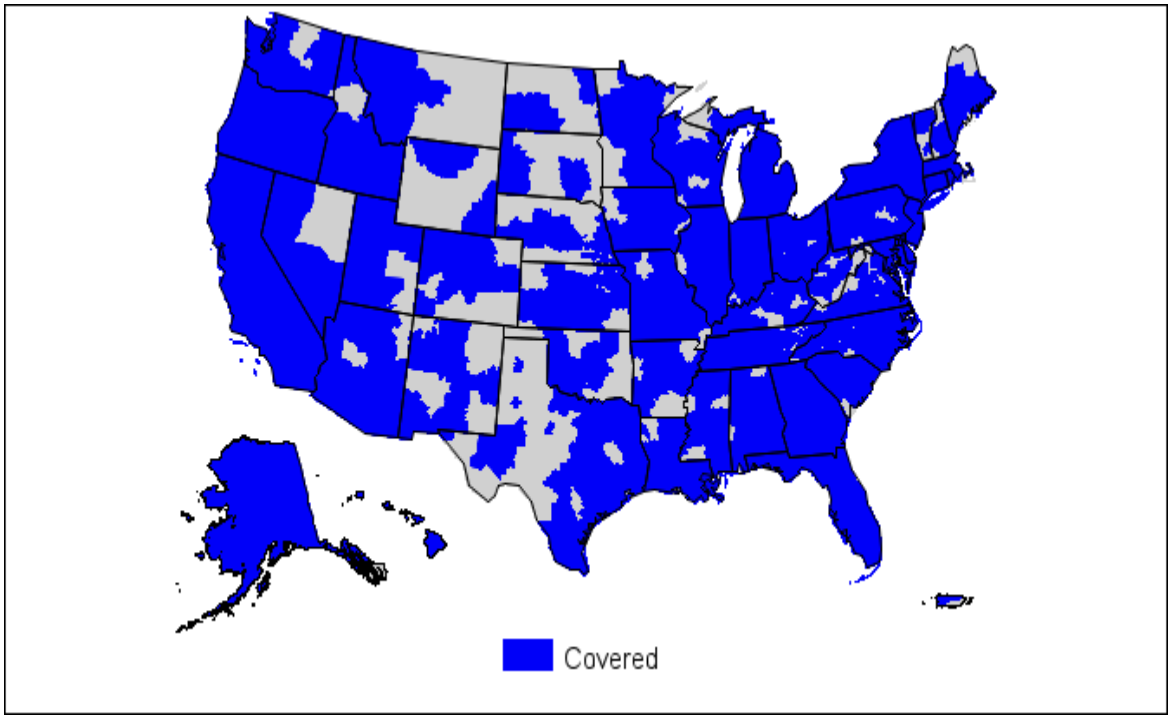
Figure 5. Three Digit ZIP Codes of Participants in the RADARS System College Survey Program in 2014



The definition of the comparison groups to be identified in this surveillance is depicted in Figure 6 below. Note that it is possible for a single respondent to be included in both comparison groups, as indicated by the curved arrows at the bottom of the figure. Respondents reporting use of both EMBEDA and other oral ER morphine tablets or capsules are included in the EMBEDA comparison group and also in the other oral ER morphine tablet/capsule comparison group.

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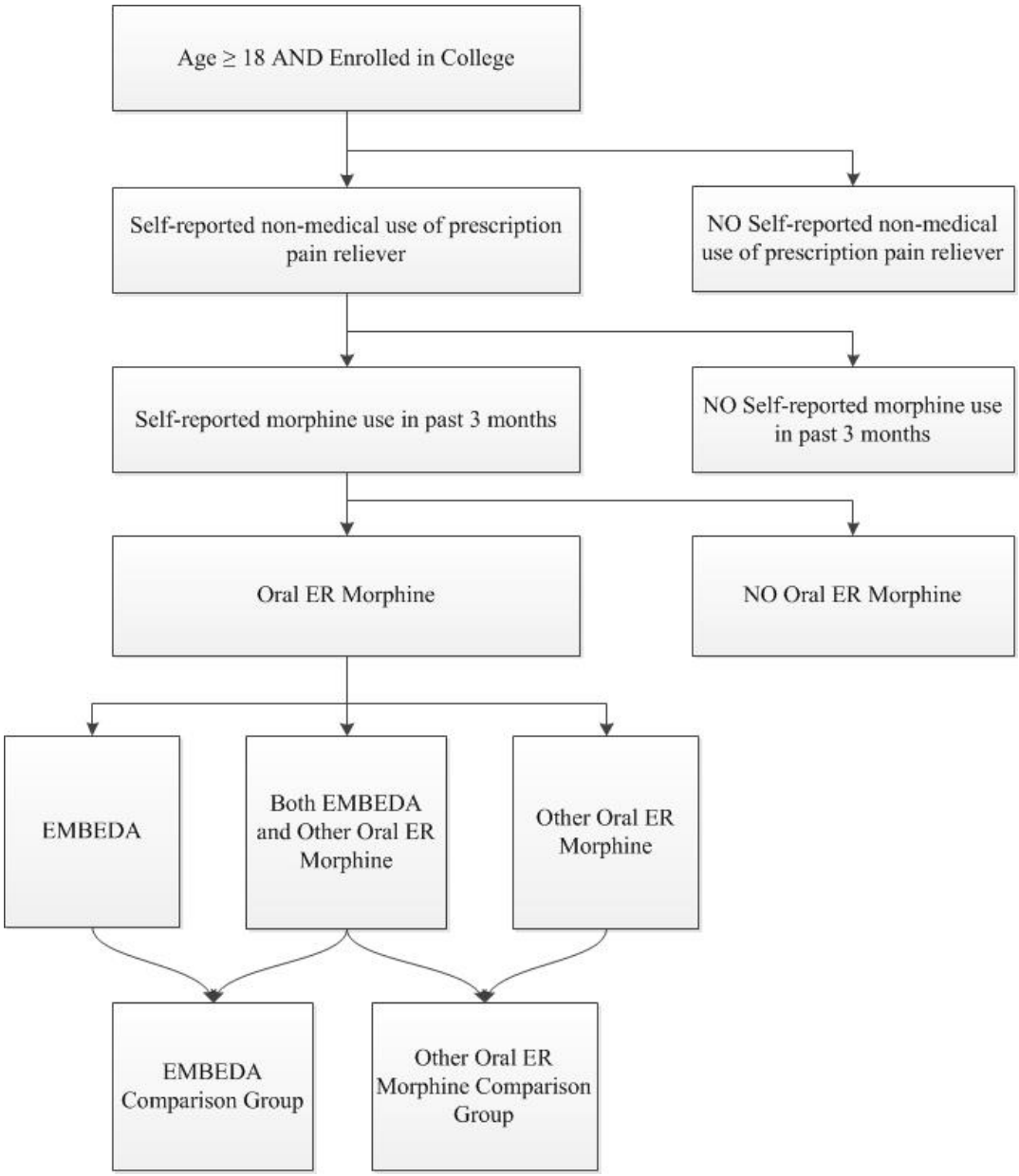
Figure 6. Comparison Groups in College Survey Program Surveillance



8.4.4. Web Monitoring Program

The Web Monitoring Program is under the direction of Jody L. Green, PhD (Principal Investigator) of the Rocky Mountain Poison and Drug Center. The aim of this program is to gather qualitative information regarding misuse, abuse, addiction, overdose and death as reported via the internet. The program will use commercially available social media monitoring software[4] to identify online posts related to EMBEDA or other oral ER morphine

[4] Radian6, salesforce.com, inc., http://www.exacttarget.com/products/social-media-marketing/radian6

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tablet/capsule products on public social media accounts (eg, Facebook, Twitter, Tumblr, Instagram), online blogs and web forums (eg, Opiophile, Bluelight, Erowid) and other internet sites. The monitoring software allows for active real-time monitoring of social media.

The Web Monitoring Program will identify relevant posts using search parameters that evolve over time. The initial search parameters will include terms to identify EMBEDA and other oral ER morphine tablets/capsules, including known slang terms and common misspellings. When new terms are discovered, they will be incorporated into the search parameters. While data are collected in real-time, searches will be conducted on a monthly basis and the results will be manually categorized by a team of RADARS System staff trained as coders.

RADARS System staff will manually review and code the posts with respect to endpoint (abuse, misuse, addiction, overdose and death) and comparison group. If a post mentions morphine without specifying the formulation (ie, IR or ER) it will be categorized as "unknown" (see Figure 7). If a post mentions ER morphine without specifying the brand or generic status, it will be categorized as "unknown" (see Figure 7). Further, they will categorize posts based on salient themes (eg, diversion, abuse deterrent formulations, drug information, route of administration, source of drug acquisition, co-ingestions, etc.) and sentiment of the posts regarding those themes (positive, negative, or neutral). If the number of relevant posts identified is larger than is feasible to manually code, a random subset of the posts will be coded. Redacted posts will be provided where both EMBEDA and tampering are mentioned.

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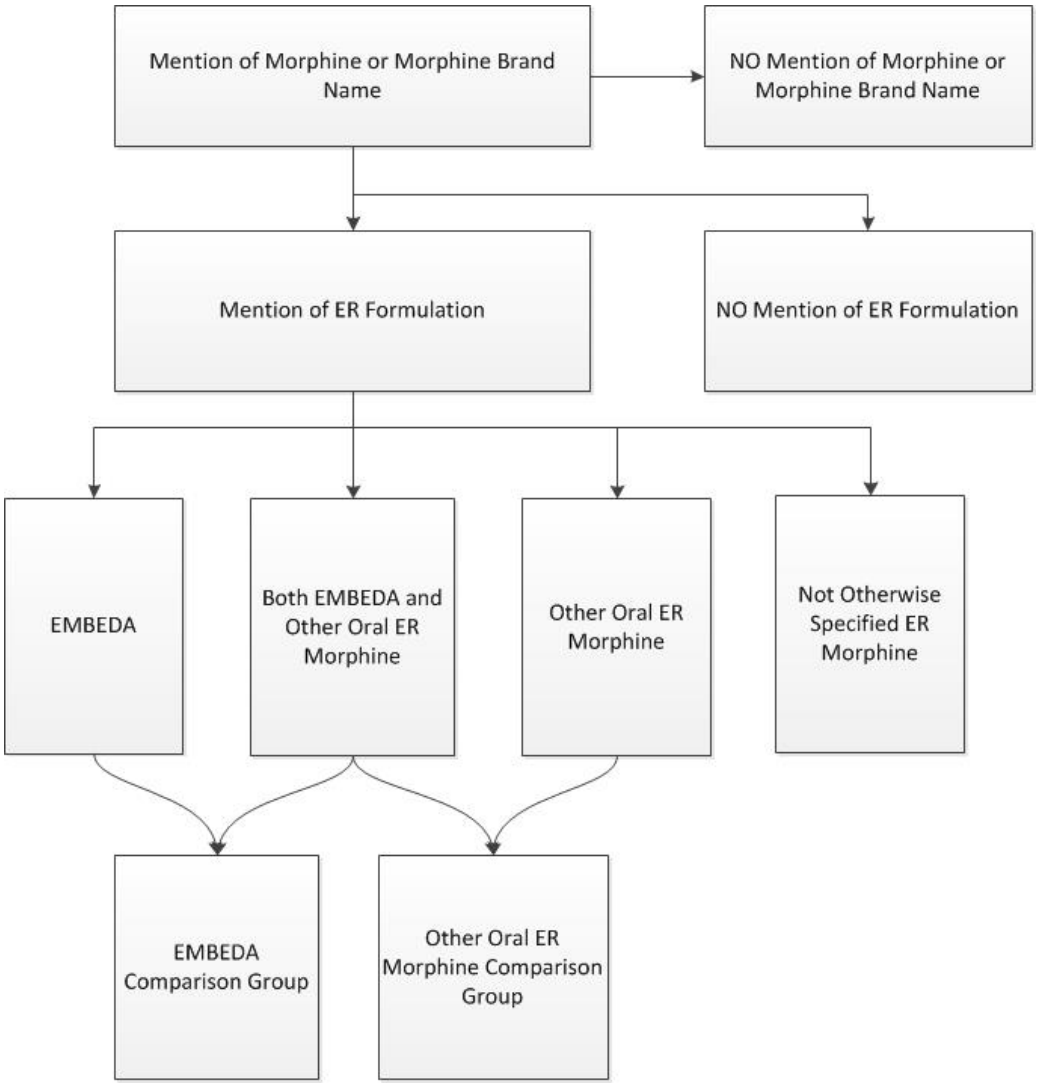
Figure 7. Comparison Groups in Web Monitoring Program Surveillance



8.5. Study size

Active surveillance is not intended to test a pre-specified statistical hypothesis. It is intended to detect events among a target population; therefore a pre-determined sample size is not calculated. The number of individuals who will take EMBEDA or experience any other oral ER morphine tablet/capsule-related endpoint in the future is unknown.

8.6. Data management

Data from each RADARS System data source will be imported into SAS. SAS databases will be created from delimited text files exported from the Central SQL Database.

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8.6.1. Data Cleaning

The data are retrieved from four RADARS System data sources which clean the data according to their respective protocols, as described below.

Treatment Center Program

The operator conducts a manual review to ensure the data are accurately recognized by the Teleform software application. On a quarterly basis, RADARS System Quality Assurance personnel perform a Database Quality Audit, following statistically valid sampling schemes, to ensure that data in the final dataset match the source data (faxed images of the questionnaires). An error percentage is calculated based on the number of errors detected divided by the total number of fields audited. An evaluation of the source and type of errors, and impact on the data analysis, is performed if the error percentage exceeds the established action limit of 1%.

In the Survey of Key Informant Patients program, all data entry is verified by an independent team member and verified surveys undergo random sampling for accuracy checks by the project Quality Assurance Administrator. Data listings are prepared through the Survey of Key Informants' Patients Central Database and reviewed by the Database Administrator and Project Quality Assurance Administrator to identify potential discrepancies on the final data prior to upload to Denver Health. Data validation steps are performed to ensure the accuracy of the data uploaded to the Central Database. On a quarterly basis, RADARS System Quality Assurance personnel perform a Database Quality Audit following statistically valid sampling schemes to ensure that data entered into and uploaded to the Central Database match the source data (questionnaires). An error percentage is calculated based on the number of errors detected, divided by the total number of fields audited. An action limit is established whereby an evaluation of the source and type of errors, and impact on the data analysis, is performed if the error rate exceeds the established action limit of 1%.

Poison Center Program

RADARS System staff perform initial and final quality reviews of all data received from participating poison centers to ensure that databases are properly created and managed and that cases are properly coded. RADARS System staff review these databases for inconsistencies. If inconsistencies are found, the site is notified and asked to rectify the queries. Each case is then reviewed to determine the accuracy of the reason code used. RADARS System staff determines from the notes field if each case is an information case or an intentional or unintentional exposure case. RADARS System staff will again review the cases and may remove more case or identifying information before the database is considered ready for analysis.

College Survey Program

RADARS System staff initiate a Database Quality Audit on the final cleaned data set at the completion of every launch. All variables are reviewed for 10% of the cases. A population list is compiled of all questionnaires received during the relevant quarter. The population list

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

is used to generate a 10% random sample plan using SAS. A manual comparison between the online questionnaire results and the data listings for each questionnaire is then conducted. The number of errors (if any) is then documented and an error rate is calculated. If the error rate exceeds 1%, an evaluation is conducted, taking into consideration the error type and source, and the impact to the data is then determined.

Web Monitoring Program

RADARS System staff will manually review the identified posts and select those that are in alignment with the inclusion criteria. During manual review, they will also code the posts with respect to endpoint (abuse, misuse, addiction, overdose and death). Further, they will categorize posts based on salient themes (eg, diversion, abuse deterrent formulations, drug information, route of administration, etc.) and sentiment of the posts regarding those themes (positive, negative, or neutral). A percentage of coded posts will be verified by an independent team member and inter-rater reliability will be calculated to assess consistency of categorization by the coders. If the inter-rater reliability score is below a determined threshold, further evaluation of the differences and the impact on data analysis will be performed. Additionally, on a biannual basis, RADARS System Quality Assurance personnel will perform a Database Quality Audit to ensure that the number of mentions in the final dataset match the source data (mentions obtained from a web monitoring platform). The number of errors (if any) is documented and an error rate is calculated. An evaluation of the source and type of errors, and impact on the data analysis, is performed if the total error percentage exceeds an established action limit of 1%. Finally, edit checks will be performed to ensure that all posts were reviewed and coded.

8.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. An overview of the expected analyses follows.

The primary goal of the analyses for the Treatment Center Program, Poison Center Program and College Survey Program will be to estimate rates of five safety-related endpoints (abuse, misuse, overdose, addiction and death) believed to be associated with each of the two comparison groups -- EMBEDA and other oral ER morphine tablets/capsules. These rates will be estimated across time and by ROA. For the Web Monitoring Program the primary analysis will be to count mentions of EMBEDA and other oral ER morphine tablets/capsules over time for each of the five endpoints.

As there is no assurance of statistical power, no statistical testing will be conducted. Ninety-five percent confidence intervals will be calculated around all estimated rates and regression coefficients to provide an assessment of their statistical variability. Rates and trends will only be informally compared. As depicted in the first example shell table in Annex 3, rates of each endpoint will be calculated for every combination of data source and denominator, facilitating a comparison of EMBEDA to other oral ER morphine tablets/capsules. The first example shell table also facilitates comparison of rates for each endpoint by data source and by denominator.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

Analyses of other oral ER Morphine will be conducted for two full quarters prior to market release of EMBEDA. This will provide two baseline prevalence points for the five endpoints prior to the introduction of EMBEDA.

Rate Estimation

Three different rates of two types will be calculated. One of the rates is a population rate, which will give an indication of the extent of the drug abuse and misuse problem in a region such as the US. The other two rates are drug availability rates, which adjust the population rate for drug availability and are therefore often considered to reflect drug likeability ratings.

Rates will be computed for each of the five endpoints using data from the Treatment Center Program, Poison Center Program and College Survey Program. First, rates per population will be computed as the total number of cases experiencing an event in a given year/quarter divided by the covered population[5] that year/quarter as denoted below. The rates will then be scaled to yield rates per 100,000 population, as shown below:

$$\text{Rate per 100,000 Population} = (\text{total cases} * 100{,}000) / \text{Total Population}$$

Secondly, rates per prescriptions dispensed will be computed each year/quarter. Prescription data represent the number of prescriptions dispensed and is thereby also a measure of prescription drug availability from legitimate distribution methods. Analyses have been restricted to tablets and capsules. Rates per prescriptions dispensed will be scaled to yield rates per 1,000 prescriptions dispensed. Data on dispensed prescriptions will be obtained from IMS Health. The formula for the rate per prescriptions dispensed is shown below:

$$\text{Rate per 1,000 Prescriptions} = (\text{total cases} * 1{,}000) / \text{Total Prescriptions}$$

Third, rates per dosing units dispensed will be computed each year/quarter. Dosing unit data represent the number of tablets or capsules dispensed and are thereby also a measure of prescription drug availability from legitimate distribution methods. Analyses have been restricted to tablets and capsules (pill counts). Rates per dosing units will be scaled to yield rates per 1,000 dosing units dispensed. Dosing unit data will be obtained from IMS Health. The formula for the rate per dosing units is shown below:

$$\text{Rate per 1,000 Dosing Units} = (\text{total cases} * 1{,}000) / \text{Total Dosing Units}$$

Sensitivity Analysis

The population rate will give an estimate of the extent of the abuse, misuse, overdose, addiction or death believed to be associated with each of the two comparison groups on a national level. Rates per prescriptions dispensed provide a measure of the extent of the abuse, misuse, overdose, addiction, or death believed to be associated with each of the two comparison groups.

[5] The covered population is the US Census population residing in the catchment area of the respective RADARS System program.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

Use of drug availability rates provides important information on the public health impact of the abuse of EMBEDA and other oral ER morphine tablets/capsules. Rates of abuse per population provide an estimate of the scope of abuse in the US population. However, recently introduced products like EMBEDA may have few prescriptions written and filled. Rates per prescriptions dispensed and units dispensed will therefore also be computed as they estimate the extent of misuse and abuse adjusting for the availability of the drug.

As coverage may differ across time, sensitivity analyses will be repeated on the subset of Treatment Centers that contributed at least one subject during at least 80% of the surveillance period, and the subset of poison centers that contributed at least one subject during the entire surveillance period.

Time Trend Estimation

A Poisson regression model with a drug group specific dispersion parameter will be utilized to estimate trends over time in rates for EMBEDA and the comparator opioid (other oral ER morphine tablets/capsules). The independent variables in the model will include a categorical variable for drug group, a linear trend over time, and the interaction of drug group and time. The model thereby fits separate regression lines for each of the two comparison groups -- EMBEDA and other oral ER morphine tablets/capsules.

Intercepts and slopes of the two trend lines will be informally compared to assess whether rates of abuse, misuse, overdose, addiction or death for EMBEDA appear to be lower than the corresponding rates for other oral ER morphine tablets/capsules. They will also be informally compared to assess whether any apparent differences in rates vary across time. Ninety-five percent confidence intervals for the slopes and intercepts will be computed. If suggested by the time series plots additional polynomial terms (quadratic or cubic may be included) or quarter may be modeled as a categorical variable. As data are time series data, adjustment for serial correlation will be considered Akaike's information criteria (AIC) will be used to choose terms to add to the model in a stepwise manner.

Stratification by ROA

Five ROAs will be examined. The intended ROA, swallowing intact capsules/tablets, and four unintended ROAs: chewing then swallowing; dissolving in mouth then swallowing; intranasal; injection. Rates will be calculated separately for intended and unintended ROAs and informally compared. In particular, for each comparison group, rates of abuse, misuse, overdose, addiction and death will be calculated for the intended ROA and informally compared to unintended ROAs as a group. If data allow, further analyses by individual unintended ROAs will be conducted.

A time trend will again be estimated via a Poisson regression model with group specific dispersion parameters. In this model, the rate data will be a function of comparison group, ROA, a time trend and all two and three way interactions of group, ROA and time.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

Adjustment for Potential Confounders

Information on potential confounders varies by RADARS System data source, but is generally limited. When warranted, secondary analyses adjusting for the confounding variables of median age and percent male will be performed. Adjustment for confounding variables is important when the potential confounding variable is related to both the outcome variable of interest and the predictor variable. These relationships need not be causal. Considerations for adjustment will include whether or not any of the five endpoints differ by age and sex, and whether or not the confounder is related to either of the predictor variables: comparison group (EMBEDA versus other oral ER morphine tablets/capsules) and time.

An important unmeasured confounding factor cannot be incorporated into quantitative analyses as described above. It is likely that EMBEDA will be prescribed more often than other oral ER morphine tablets/capsules to patients more likely to abuse morphine. This tendency is expected because EMBEDA is intended to deter use by routes of administration favored by abusers: intranasal use and injection.

Selected examples of table shells expected to be populated with the results of the analyses described above are presented in Annex 3. The SAP will specify all tables and figures to be produced. The SAP will include equations for all regression models.

8.8. Quality control

To ensure quality of data used in this surveillance, each SAS program used to conduct analyses will be written by a biostatistician or statistical research specialist trained in SAS programming and with training in relevant statistical analyses. Programmers will also have knowledge of RADARS System databases. These programs will be validated by another biostatistician or statistical research specialist with a similar level of training. Any inconsistencies will be resolved by the director of biostatistics.

8.9. Strengths and limitations of the research methods

8.9.1. Limitations

The limitations of the research methods are largely related to the quality of the data sources used.

The limitations of the RADARS System Treatment Center Program include:

- Voluntary participation may result in sampling bias.

The limitations of the RADARS System Poison Center Program include:

- Poison centers collect data on spontaneous reports which are subject to reporting bias.
- Calls to poison centers result from a medical concern regarding an exposure, therefore actual frequencies may underestimate true incidence of exposures and death.

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- Underreporting is not likely product or geographic specific, therefore comparisons across drug products and geographic regions likely reflect true differences in abuse, misuse, overdose and deaths rates across products.

- There is currently no other program that can provide timely data regarding the outcome of death, particularly death accompanied by product and geographic specificity.

The limitations of the RADARS System College Survey Program include:

- Voluntary, self-selected population may result in sampling bias.

- Estimates of rarely used products may not be detected in any given quarter due to a relatively small quarterly sample size and may need to be measured on an annual basis.

The limitations of the RADARS System Web Monitoring Program include:

- Voluntary posts may result in bias.

- Information contained in posts to social media cannot be validated.

8.9.2. Strengths

The strengths of the research methods are largely related to the quality of the data sources used.

The strengths of the RADARS System Treatment Center Program include:

- Coverage is broad in terms of the total United States population and geographic distribution, particularly in high risk regions.

- Data are available within 3 months of data capture.

- Geographic specificity of patient's residence is captured at a 3-digit ZIP code level.

- Product and route of administration are recorded.

- Opioid Treatment Program and Survey of Key Informants' Patients by definition treat an addicted population.

The strengths of the RADARS System Poison Center Program include:

- Coverage is extensive in terms of the total United States population and geographic distribution.

- Data are available within 3 months of data capture.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

- Geographic specificity is captured at a 3-digit ZIP code level.
- Product specific information is recorded for cases of abuse, misuse, overdose and death.
- Standardized definitions and data fields are used across poison centers.
- Quality review of all case notes ensures proper product identification, reason for exposure, route of administration and medical outcome.
- Changes in rates over time have been shown to be sensitive indicators of interventions or product formulation changes.

The strengths of the RADARS System College Survey Program include:

- Coverage is extensive in terms of the total United States population and geographic distribution.
- Respondent demographics are representative of United States college students.
- Data are available within 3 months of data capture.
- Geographic specificity is captured at a 3-digit ZIP code level.
- Product specific information is recorded for cases of abuse, misuse and addiction.
- Use of an established scale (DAST-10; Skinner, 1982)[31] can be used as a surrogate measure of addiction.

The strengths of the RADARS System Web Monitoring Program include:

- Coverage is extensive in terms of the total United States population and geographic distribution.
- Product-specific information is recorded when available.
- Data are available in real-time and provide early signals of emerging trends.
- Discovery of emerging perceptions, attitudes and behaviors.

8.10. Other aspects

Not applicable.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The data are being collected under existing RADARS System protocols. For this reason, patient information and consent is not applicable because there is no direct contact with human subjects.

9.2. Patient withdrawal

Not Applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This protocol is part of the research being conducted under the protocols for the four RADARS data sources. Those protocols have already been reviewed and approved by IRBs as described below. The approvals allow for unlimited analysis of data. Further, the work in this protocol involves no interaction with human subjects. A separate IRB review of this protocol is therefore not necessary.

Treatment Center Program

The Opioid Treatment Program protocol was last reviewed and received expedited approval from the IRB of the Principal Investigator, National Development and Research Institutes Inc. on 06 June 2014. The Survey of Key Informants' Patients study protocol was last reviewed and received expedited approval from the IRB of Washington University in St. Louis, the home institution of the Principal Investigator, on 15 April 2014.

Poison Center Program

The Poison Center Program study protocol was last reviewed and received approval from the Colorado Multiple Institutional Review Board (COMIRB) on 16 January 2014. In addition, the study protocol was reviewed and approved by the IRB of each participating poison center.

College Survey Program

The College Survey Program study protocol was last reviewed and approved by COMIRB on 05 April 2014.

Web Monitoring Program

The Web Monitoring Program study protocol was determined to be non-human subject research by COMIRB on September 18, 2013.

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9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Treatment Center Program, Poison Center Program and College Survey Program

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event (AE) reports.

Web Monitoring Program

If RADARS System staff become aware of an AE in the execution of the Web Monitoring Program and the reporter of the AE is identifiable, the report will be considered valid and will be reported to Pfizer. A reporter is considered identifiable if s/he is privately contactable (ie, it is possible to communicate directly with the reporter using a mailing address, an email address, or a phone number, without the need to post questions to a public forum/environment to obtain more information).

If the reporter is identifiable, the following safety events must be reported on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure (all reportable, regardless of whether associated with an AE), when associated with the use of a Pfizer product. RADARS System staff must complete the NIS AEM Report Form and submit it to Pfizer within 24 hours of becoming aware of the safety event.

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RADARS System staff will complete AE reporting requirements training. This training will be provided by Pfizer prior to commencement of the study. A "Confirmation of Training Certificate" (for signature by the trainee) will be included as a record of completion of the training, which must be kept in a retrievable format. RADARS will also provide copies of all signed training certificates to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Pfizer will submit a final study report to FDA by 30 April 2020. The final results will be summarized in a manuscript and submitted to a peer-reviewed journal for publication.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

090177e18682a70a\Approved\Approved On: 18-May-2015 08:22

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

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ANNEX 2. ENDPOINT DEFINITIONS

Abuse

Definition for Treatment Center Program
Patients are asked to report the prescription drugs they have taken "to get high" during the month before entering treatment. A report of use of EMBEDA or other oral ER morphine will be considered a case of abuse of EMBEDA and/or other oral ER morphine tablets/capsules, respectively.

Definition for Poison Center Program
Abuse cases will be defined as those Poison Center cases with a reason for exposure of abuse. According to Bronstein (2008), abuse is defined as: an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect.

Definition for College Survey Program
Abuse cases will be defined as any survey respondent endorsing nonmedical use of a drug. Non-medical use is defined as "use without a doctor's prescription or for any reason other than what was recommended by *your* prescribing doctor".

Definition for Web Monitoring Program
Abuse cases will be defined as those posts reporting a drug exposure where the likely reason was attempting to gain a psychotropic effect (eg, high, euphoria).

Misuse

Definition for Poison Center Program
Misuse cases will be defined as those Poison Center cases with a reason for exposure of misuse. According to Bronstein (2008), misuse is defined as an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect.

Definition for College Survey Program
Misuse is defined as any respondent who indicates use of a drug to relieve pain without a doctor's prescription or in a way other than what was indicated by the prescribing doctor.

Definition for Web Monitoring Program
Misuse is defined as an exposure resulting from the intentional or unintentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.

Overdose

Definition for Poison Center Program
This endpoint will be defined in two ways. First, since Poison Centers are typically only called for a medical concern, a general measure of overdose is all cases with a reason for exposure considered intentional. This consists of all cases with reasons of abuse, misuse, suicide, withdrawal, or unknown intentional. Note informational calls are excluded. A

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second endpoint of deliberate overdose will be defined as any case with a reason for exposure of suspected suicide. Suspected suicides are defined as exposures resulting from the inappropriate use of a substance for self-destructive or manipulative reasons.

Definition for Web Monitoring Program
Overdose is defined as a post that mentions the accidental or intentional overdose of a drug. The post contains information about using a dangerous amount of a drug (ie, a quantity greater than recommended or generally practiced) which may result in a medical intervention.

Addiction

Definition for Treatment Center Program
By nature of their entering a treatment program, all Opioid Treatment Program and Survey of Key Informants' Patient will be considered addicted. Patients who indicate their primary drug is a prescription opioid will be considered addicted to a prescription opioid(s). The prescription opioid to which they are addicted cannot be definitely determined but can be inferred from the specific opioid(s) they indicated they used in the 30 days prior to entering treatment. Hence, patients who indicate their primary drug is a prescription opioid and who report use of EMBEDA or other oral ER morphine tablets/capsules "to get high" during the month prior to entering treatment will be considered addicted to EMBEDA and/or other oral ER morphine tablets/capsules, respectively.

Definition for College Survey Program
Addiction is defined by identifying the subset of respondents who report using a substance and have a DAST-10 score of 6 or above.

Definition for Web Monitoring Program
A post that mentions information one or more of the following: 1) physical or psychological dependence; 2) tolerance; or 3) withdrawal effects.

Death

Definition for Poison Center Program
Deaths will be defined as those Poison Center Program cases with a medical outcome of death. The endpoint of death is defined as a patient who died as the result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication.

Definition for Web Monitoring Program
Death will be defined as any statement that indicates a death has occurred in relation to a drug.

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ANNEX 3. SHELL TABLES

Table x.x.x
The RADARS® System XXX Program
XXX Rates over Time by Drug Group
XXX Quarter 20XX through XXX Quarter 20XX

	Intercept				Slope			
Drug Group	**Rate (95% CI)**	**p-value**	**Rate Ratio (95% CI)**	**p-value for difference**	**Percent Quarterly Change (95% CI)**	**p-value**	**% difference (95% CI)**	**p-value for difference**
Rate per 100,000 Population								
EMBEDA	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx, x.xxxx)	x.xx		.
Other ER Morphine Tablets/Capsules	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx, x.xxxx)	x.xx	x.xxxx(x.xxxx,x.xxxx)	x.xx
Rate per 1,000 Prescriptions								
EMBEDA	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx, x.xxxx)	x.xx		.
Other ER Morphine Tablets/Capsules	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx, x.xxxx)	x.xx	x.xxxx(x.xxxx,x.xxxx)	x.xx
Rate per 1,000 Dosing Units								
EMBEDA	x.xxxx(x.xxxx,x.xxxx)	x.xxxx		.	x.xxxx(x.xxxx, x.xxxx)	x.xx		.
Other ER Morphine Tablets/Capsules	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx,x.xxxx)	x.xxxx	x.xxxx(x.xxxx, x.xxxx)	x.xx	x.xxxx(x.xxxx,x.xxxx)	x.xx

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Table XXX
The RADARS® System Treatment Center Programs
XXX Rates by Quarter and Drug Group
From X Quarter 20XX through <current quarter>

Drug	Year/Quarter	Number of Mentions	Population Covered	Treatment Centers Covered	Rate per 100,000 Population (95% CI)	Rate per 1,000 Prescriptions Dispensed (95% CI)	Rate per 1,000 Units Dispensed (95% CI)
EMBEDA	xQ2014						
	…						
	1Q2015						
	2Q2015						
	…						
	xQ2017						
Other ER Morphine Tablets/Capsules	xQ2014						
	…						
	1Q2015						
	2Q2015						
	…						
	xQ2017						

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Table XXX
The RADARS® System Treatment Center Programs
XXX Response Percentages by Quarter and Drug Group
From X Quarter 20XX through <current quarter>

Year/Quarter	Number of Surveys Distributed	Number of Surveys Returned	% Returned
xQ2014			
…			
1Q2015			
2Q2015			
…			
xQ2017			

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Table X
The RADARS® System Poison Center Program
XXX Rates by Quarter and Drug Group
From X Quarter 20XX through <current quarter>

Drug	Year/Quarter	Number of Mentions	Population Covered	Poison Centers Covered	Rate per 100,000 Population (95% CI)	Rate per 1,000 Prescriptions Dispensed (95% CI)	Rate per 1,000 Units Dispensed (95% CI)
EMBEDA	xQ2014						
	…						
	1Q2015						
	2Q2015						
	…						
	xQ2017						
Other ER Morphine Tablets/Capsules	xQ2014						
	…						
	1Q2015						
	2Q2015						
	…						
	xQ2017						

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