NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Evaluation of the Misuse and Abuse of Pregabalin using RADARS® System Programs in the United States and the European Union
Protocol number	A0081363
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Medicinal product	Lyrica® (pregabalin)
Product reference	EMEA/H/C/000546
Procedure number	Not yet assigned
Marketing Authorisation Holder (MAH)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
Joint PASS	No
Research question and objectives	The primary objectives of this evaluation: 1) Summarize misuse and abuse data for pregabalin and each comparator within each country for each data source 2) Perform a statistical analysis of trends over time for pregabalin and each comparator to assess changes in misuse and abuse within each country and data source
Country(-ies) of study	United States France Germany Italy
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AAPCC	American Association of Poison Control Centers
AE	Adverse event
API	Active pharmaceutical ingredient
AU-CNS	Associazione per l'Utilizzo delle Conoscenze Neuroscientifiche a fini Sociali
COMIRB	Colorado Multiple Institutional Review Board
DAST-10	Drug abuse screening test-10
EUROPAD	European Opiate Addiction Treatment Association
EUROPAD Program	European Opioid Treatment Patient Survey Program
FTP	File transfer protocol
GTNet Program	Global Toxicosurveillance Network Program
IEC	Independent ethics committee
IRB	Institutional review board
MAH	Marketing Authorisation Holder
N/A	Not applicable
NI	Non-interventional study
NMURxP	Survey of Non-Medical Use of Prescription Drugs Program
NPDS	National Poison Data System
NUTS	Nomenclature of Territorial Units
OTC	Over-the-counter
PASS	Post-authorization safety study
RADARS® System	Researched Abuse, Diversion and Addiction-Related Surveillance System
RMPDC	Rocky Mountain Poison & Drug Center
SAP	Statistical analysis plan
TCPC	Treatment Center Programs Combined
WMP	Web Monitoring Program
WUSTL	Washington University at St. Louis

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

- **Title:** Evaluation of the Misuse and Abuse of Pregabalin using RADARS® System Programs in the United States and the European Union

  Version 1.0, 04 June 2018 [Kofi Asomaning, PhD; Pfizer Inc.]

- **Rationale and background**

  Alpha-2-delta (α(2)δ) Ligands (e.g. pregabalin and gabapentin) are widely used in neurology, psychiatry, and primary healthcare but are increasingly being reported globally as possessing a potential for misuse and abuse. These drugs are primarily prescribed as anticonvulsants, for the treatment of neuropathic pain as well as for the treatment of generalized anxiety disorders. Numerous international guidelines recommend pregabalin and gabapentin as first-line treatments for neuropathic pain. There has been a large increase in prescriptions of these drugs over the last decade. In the United States, pregabalin is listed as one of the 30 most prescribed medications as of 2011. Although pregabalin and gabapentin are prescribed for several approved therapeutic indications, there may be alternative motives for taking these drugs. There are reports of abuse of pregabalin and gabapentin from the European Union, from the US and globally. Abuse occurs at supra-therapeutic doses and is more prevalent among those with a current or past opioid use disorder. At dosages exceeding the therapeutic dosages, both drugs have anecdotally been reported by users to produce both sedative and dissociative/psychedelic effects. Reported pregabalin abuse among an addiction services population in Ireland suggests that pregabalin is an attractive drug to opioid dependent drug users. Further, concomitant opioid and gabapentin exposure has been found to be associated with a 49% higher risk of opioid-related death. Both pregabalin and gabapentin may also be used off label to treat substance use disorders.

- **Research question and objectives**

  The primary objectives of this evaluation:

  1. Summarize misuse and abuse data for pregabalin and each comparator within each country using the following data sources:
     a. France, Germany, Italy:
        i. Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System European Opioid Treatment Patient Survey (EUROPAD) Program
        ii. RADARS System Global Toxicosurveillance Network (GTNet) Program
        iii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program
     b. United States:
        i. RADARS System Treatment Center Programs Combined

ii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program

iii. RADARS System Web Monitoring Program

iv. American Association of Poison Control Centers' (AAPCC's) National Poison Data System (NPDS)

2. Perform a statistical analysis of trends over time for pregabalin and each comparator to assess changes in misuse and abuse within each country and data source.

- **Study design**

Objective 1: Summarize misuse and abuse data for pregabalin and each comparator

The MAH will estimate rates or prevalence estimates for each of the outcomes (non-medical use, misuse, abuse, intentional exposures) by program for pregabalin and comparators within each country using descriptive statistics. No rates will be calculated in the evaluation of data from the Web Monitoring Program.

Objective 2: Perform a statistical analysis of trends over time for pregabalin and each comparator

Trend analysis will be performed for each drug and comparator for each of the outcomes by program within each country when continuous coverage for at least five year-quarters of data is available. Five continuous year-quarters of data allow for a more accurate trend line to be fit; less than five continuous year-quarters of data are not as stable and have the potential for more variability. Trends will be modeled using the rates of misuse and abuse.

This evaluation will compare pregabalin at the active pharmaceutical ingredient level (API; all branded and generic products combined) to the comparison groups in each country as presented below. The comparator drugs represent other central nervous system compounds that are known to be misused and abused, limited to the data available in each program in each country. No formal hypothesis tests will be conducted between pregabalin and comparators.

Germany, Italy, and France:

1. EUROPAD Program:
    a. Gabapentin (branded and generic products with gabapentin as an API)
    b. Benzodiazepines (total drug class level [drug substances rollup; data on individual APIs are not collected])
    c. Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    d. Buprenorphine (branded and generic products with buprenorphine as an API)
    e. Methadone (branded and generic products with methadone as an API)
    f. Tramadol (branded and generic products with tramadol as an API)
    g. Heroin (all heroin mentions, regardless of form)

2. GTNet Program
    a. Gabapentin (branded and generic products with gabapentin as an API)
    b. Benzodiazepines (branded and generic products with identified benzodiazepines as an API, combined into a single comparator group)
    c. Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    d. Buprenorphine (branded and generic products with buprenorphine as an API)
    e. Methadone (branded and generic products with methadone as an API)
    f. Tramadol (France and Germany only) (branded and generic products with tramadol as an API)
3. Survey of Non-Medical Use of Prescriptions Drug Program
    a. Gabapentin (branded and generic products with gabapentin as an API)
    b. Baclofen (branded and generic products with baclofen as an API)
    c. Benzodiazepines (total drug class level [drug substances rollup; data on individual APIs are not collected])
    d. Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    e. Buprenorphine (branded and generic products with buprenorphine as an API)
    f. Methadone (branded and generic products with methadone as an API)
    g. Tramadol (branded and generic products with tramadol as an API)
    h. Heroin (all heroin mentions, regardless of form)

United States:

1. Treatment Center Programs Combined:
    a. Gabapentin (branded and generic products with gabapentin as an API)
    b. Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    c. Buprenorphine (branded and generic products with buprenorphine as an API)
    d. Methadone (branded and generic products with methadone as an API)
    e. Tramadol (branded and generic products with tramadol as an API)
    f. Heroin (all heroin mentions, regardless of form)
2. AAPCC's NPDS
    a. Gabapentin (cases coded to the Micromedex® Poisindex® generic code for gabapentin)

b. Baclofen (cases coded to the Micromedex Poisindex generic code for baclofen)

c. Benzodiazepines (cases coded to the Micromedex Poisindex generic code for benzodiazepines [individual APIs are not assigned separate Micromedex Poisindex generic codes])

d. Opioid analgesics (cases coded to the Micromedex Poisindex generic code for identified opioids, combined into a single comparator group)

e. Tramadol (cases coded to the Micromedex Poisindex generic code for tramadol)

f. Heroin (cases coded to the Micromedex Poisindex generic code for heroin)

3. Survey of Non-Medical Use of Prescriptions Drug Program

a. Gabapentin (branded and generic products with gabapentin as an API)

b. Baclofen (branded and generic products with baclofen as an API)

c. Benzodiazepines (total drug class level [drug substances rollup; data on individual APIs are not collected])

d. Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)

e. Buprenorphine (branded and generic products with buprenorphine as an API)

f. Methadone (branded and generic products with methadone as an API)

g. Tramadol (branded and generic products with tramadol as an API)

h. Heroin (all heroin mentions, regardless of form)

4. Web Monitoring Program

a. Gabapentin (branded and generic products with gabapentin as an API)

b. Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)

Surveillance periods for the evaluation will include each RADARS System data source for the period when pregabalin data collection began in that program in each country and will include the last five years for NPDS.

a. France:

i. RADARS System EUROPAD Program: 1st quarter 2015 – 4th quarter 2017

ii. RADARS System GTNet Program: 1st quarter 2012 – 4th quarter 2016

iii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program: 2nd quarter 2017, 4th quarter 2017

b. Germany:

i. RADARS System EUROPAD Program: 4th quarter 2014 – 4th quarter 2017

ii. RADARS System GTNet Program: 1st quarter 2012 – 2nd quarter 2017

iii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program: 4th quarter 2017

c. Italy:

i. RADARS System EUROPAD Program: 4th quarter 2014 – 4th quarter 2017

ii. RADARS System GTNet Program: 1st quarter 2012 – 2nd quarter 2017

iii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program: 2nd quarter 2017, 4th quarter 2017

d. United States:

i. RADARS System Treatment Center Programs Combined: 3rd quarter 2017 – 4th quarter 2017

ii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program: 3rd quarter 2016, 1st quarter 2017, 3rd quarter 2017

iii. RADARS System Web Monitoring Program: 3rd quarter 2017 – 4th quarter 2017

iv. AAPCC's NPDS: 1st quarter 2013 – 4th quarter 2017

- **Population**

The surveillance population will include the entire population enrolled by each data source, as described below.

EUROPAD Program

The surveillance population consists of individuals seeking treatment for substance use disorders (other than alcohol) at sites that offer treatment for opioid use disorders in France, Germany, and Italy.

Treatment Center Programs Combined

The surveillance population consists of patients entering treatment for opioid dependence in the United States.

GTNet Program

The surveillance population consists of exposure cases recorded by participating poison centres in France, Germany, and Italy.

National Poison Data System

The surveillance population consists of exposure cases recorded by 55 regional poison control centers in all 50 states covering 100% of the total United States population.

Survey of Non-Medical Use of Prescription Drugs Program

The surveillance population consists of the adult general population via an online survey panel company. The sample is stratified by United States Census region and gender, mirroring the distribution of the population in both percentage and gender representation (approximately 50% female, 50% male within each region). The samples from France, Germany and Italy are stratified by *gender and Nomenclature des unités territoriales statistiques* (NUTS) 1 level regions.

Web Monitoring Program

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

- **Variables**

  Rates or prevalence estimates of four outcomes (non-medical use, misuse, abuse, and intentional exposures) will be calculated separately for pregabalin and each comparator. Indication for all prescription and over-the-counter (OTC) drugs (pregabalin and comparators) cannot be obtained within the RADARS System programs or NPDS data; therefore, outcomes may include off-label use or prescription drugs obtained through diversion. Medical records are not being accessed in this study. Outcome definitions are as follows:

  Non-Medical Use

  Non-medical use will only be described in the RADARS System Survey of Non-Medical Use of Prescription Drugs Program. In the RADARS System Survey of Non-Medical Use of Prescription Drugs Program, a non-medical use case is defined as a respondent who endorses "use without a doctor's prescription or for any reason other than what was recommended by their doctor".

  Misuse

  In the AAPCC's NPDS data, misuse is defined as those cases with a reason for exposure of intentional misuse. The definition for intentional misuse is "an exposure resulting from the intentional improper or incorrect use of a substance."

  In the RADARS System Survey of Non-Medical Use of Prescription Drugs Program, misuse is defined as those non-medical use cases with a reason of: "to self-treat my pain" or "to treat a medical condition, other than pain".

  In the RADARS System Web Monitoring Program, misuse is defined as "a mention that indicates the improper or incorrect use of a drug for reasons other than the pursuit of a psychotropic effect."

  Abuse

In the AAPCC's NPDS data, abuse is defined as those cases with a reason for exposure of intentional abuse. The definition for intentional abuse is "an exposure resulting from the intentional improper or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect."

In the RADARS System EUROPAD Program, an abuse case is defined as a survey response endorsing use "to get high" in the past 90 days.

In the RADARS System Treatment Center Programs Combined, an abuse case is defined as a survey response endorsing use "to get high" in the past month.

In the RADARS System Survey of Non-Medical Use of Prescription Drugs Program, an abuse case is defined as a survey response endorsing non-medical use of a product with a reason of "for enjoyment/to get high."

In the RADARS System Web Monitoring Program, abuse is defined as "a mention that indicates the use of a drug to gain a high, euphoric effect or some other psychotropic effect."

Intentional exposures (misuse/abuse/diversion)

Intentional exposures will only be described in the RADARS System GTNet Program. In the RADARS System GTNet Program, intentional exposures are defined as any exposure resulting from the intentional improper or incorrect use of a substance.

- **Data sources**

  American Association of Poison Control Centers' National Poison Data System will be used as well as five component data sources of the RADARS System: EUROPAD Program, GTNet Program, Survey of Non-Medical Use of Prescription Drugs Program, Treatment Center Programs Combined, and Web Monitoring Program. Drug utilization data (estimates for dosage units dispensed and standard units) will be obtained from a vendor, IQVIA™ (Danbury, CT) that provides information, services and technology for the healthcare industry, and used to generate rates adjusted for drug utilization. In addition, population data from the United States Census and EUROSTAT will be used to generate population-based rates.

- **Study size**

  This evaluation is not intended to test a pre-specified statistical hypothesis; therefore a pre-determined sample size is not calculated.

- **Data analysis**

  Objective 1: Summarize misuse and abuse data for pregabalin and each comparator

  The approach for the first objective will be to calculate rates of misuse and abuse for pregabalin and each comparator within each country. Evaluation of data from the Web Monitoring Program will not include the calculation of rates.

  Objective 2: Perform a statistical analysis of trends over time for pregabalin and each comparator

Trend analysis will be performed for pregabalin and each comparator when continuous coverage for at least five year-quarters of data is available. Five continuous year-quarters of data allows for a more accurate trend line to be fit; less than five continuous year-quarters of data are not as stable and have the potential for more variability. Trends will be modeled using the rates of misuse and abuse.

- **Milestones**

  Final study reports (one for each country of interest) will be completed by 31 August 2018.

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned date
Registration in EU PAS Register	30 May 2018
Start of data collection[a]	15 June 2018
End of data collection[b]	30 June 2018
Final study reports completed	31 August 2018

PAS: post authorization study.
[a]For studies with secondary data collection, the start of data collection is defined as the planned date for starting data extraction for the purposes of the primary analysis.
[b] For studies with secondary data collection, the end of data collection is defined as the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data to perform the statistical analysis for the primary objective.

6. RATIONALE AND BACKGROUND

Alpha-2-delta (α(2)δ) Ligands (e.g. pregabalin and gabapentin) are widely used in neurology, psychiatry, and primary healthcare but are increasingly being reported globally as possessing a potential for misuse and abuse. These drugs are primarily prescribed as anticonvulsants for the treatment of neuropathic pain as well as for the treatment of generalized anxiety disorders (Martinotti et al., 2012). Numerous international guidelines recommend pregabalin and gabapentin as first-line treatments for neuropathic pain (Attal et al., 2010; Bril et al., 2011; Dworkin et al., 2010; Finnerup et al., 2015; Moulin et al., 2014; National Institute for Health and Clinical Excellence, 2010). There has been a large increase in prescriptions of these drugs over the last decade (Johansen, 2018; NHS Digital). In the United States, pregabalin is listed as one of the 30 most prescribed medications as of 2011 (Grosshans et al, 2013).

Although pregabalin and gabapentin are prescribed for several therapeutic indications, there may be alternative motives for taking these drugs. There are reports of abuse of pregabalin and gabapentin from the European Union (Chiappini 2016), from the US and globally (Evoy et al., 2017). Abuse occurs at supratherapeutic doses and is more prevalent among those with a current or past opioid use disorder (Evoy et al., 2017). At dosages exceeding the therapeutic dosages, both drugs have anecdotally been reported by users to produce both sedative and dissociative/psychedelic effects (Schifano et al., 2011). Reported pregabalin abuse among an addiction services population in Ireland suggests that pregabalin is an attractive drug to opioid dependent drug users (McNamara et al., 2015). Further, concomitant opioid and gabapentin exposure has been found to be associated with a 49% higher risk of opioid-related death. (Gomes et al., 2017) Both pregabalin and gabapentin may also be used off label to treat substance use disorders (Evoy et al., 2017).

This protocol outlines an evaluation of the misuse and abuse of pregabalin and comparators in the United States and the European Union (France, Germany, and Italy). This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

Objective 1: Summarize misuse and abuse data for pregabalin and each comparator

Summarize misuse and abuse data for pregabalin and each comparator within each country using the following data sources:

a. France, Germany, Italy:

   i. Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System European Opioid Treatment Patient Survey (EUROPAD) Program

   ii. RADARS System Global Toxicosurveillance Network (GTNet) Program

   iii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program

b. United States:

i. RADARS System Treatment Center Programs Combined
ii. RADARS System Survey of Non-Medical Use of Prescription Drugs Program
iii. RADARS System Web Monitoring Program
iv. American Association of Poison Control Centers' (AAPCC's) National Poison Data System (NPDS)

Objective 2: Perform a statistical analysis of trends over time for pregabalin and each comparator

Perform a statistical analysis of trends over time for pregabalin and each comparator to assess changes in misuse and abuse within each country and data source.

8. RESEARCH METHODS

This evaluation using RADARS System programs in the United States, France, Germany, and Italy and using AAPCC's NPDS in the United States will assess the rates of misuse and abuse of pregabalin and comparators. France, Germany, and Italy were selected for this evaluation because more RADARS System programs are operational in these three European countries than any other European country except for the United Kingdom and because RADARS System programs in these countries have reported pregabalin and gabapentin cases. The United Kingdom was excluded because pregabalin data from the RADARS System Survey of Non-Medical Use of Prescription Drugs Program in the United Kingdom were already analyzed in 2016. The United States was selected for this evaluation to provide context from a country with elevated rates of misuse and abuse (National Institute on Drug Abuse, 2015).

These data sources perform active surveillance, which allows near-real time evaluation of non-rare adverse drug-related events (U.S. Food and Drug Administration, 2010). 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 (AEs), and enhance the understanding of safety concerns emerging in the post-market period by supplementing other sources of safety information, such as spontaneous AE reporting (Stang et al., 2010).

Misuse and abuse of prescription and/or illicit drugs 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 prescription and/or illicit drug misuse and abuse are revealed include acute health events, encounters with the criminal justice system, entry into a drug treatment facility, 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).

Since 2006 RADARS System 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-specific 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). In total, RADARS System has produced over 75 peer-reviewed publications.

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 source adequately captures this breadth of experience with drug abuse. Taken as a group, however, data from multiple perspectives creates a mosaic image of drug abuse (Dart, et al. 2015).

This evaluation will utilize five RADARS System data sources and data from the AAPCC's NPDS, each of which records information during different types of encounters in which prescription and/or illicit drug misuse and abuse 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).

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). Similarly, this evaluation will employ data triangulation to assess misuse and abuse of pregabalin and comparators.

In summary, by triangulating these RADARS System and AAPCC's NPDS data sources, this evaluation will provide a timely, sensitive, and reliable assessment of trends in misuse and abuse over time.

8.1. Study design

Objective 1: Summarize misuse and abuse data for pregabalin and each comparator

The approach for the first objective will be to calculate rates of misuse and abuse for pregabalin and each comparator within each country. Evaluation of data from the Web Monitoring Program will not include the calculation of rates.

Objective 2: Perform a statistical analysis of trends over time for pregabalin and each comparator

Trend analysis will be performed for each drug and comparator when continuous coverage for at least five year-quarters of data is available. Five continuous year-quarters of data

allows for a more accurate trend line to be fit; less than five continuous year-quarters of data are not as stable and have the potential for more variability. Trends will be modeled using the rates of misuse and abuse.

The study design is unique to each outcome measure and data source. Table 1 outlines the outcome measures studied within each data source.

Table 1. Outcome Measures by Data Source

	EUROPAD Program	Treatment Center Programs Combined	GTNet Program	AAPCC's NPDS	Survey of Non-Medical Use of Prescription Drugs Program	Web Monitoring Program
Non-Medical Use					X	
Misuse				X	X	X
Abuse	X	X		X	X	X
Intentional exposures (misuse/ abuse/ diversion)			X			

Outcome measures are defined in Annex 3

8.1.1. Comparison Groups

This evaluation will compare pregabalin at the active pharmaceutical ingredient level (API; all branded and generic products combined) to the following comparison groups in each country (Tables 2 and 3). The comparator drugs represent other central nervous system compounds that are known to be misused and abused, limited to the data available in each program in each country which accounts for the differences in comparators across countries and data sources. No formal hypothesis tests will be conducted between pregabalin and comparators.

Table 2. Comparator Groups for France, Germany, and Italy

EUROPAD Program		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Branded and generic products with gabapentin as an API, including unknown formulations	Similar indication
Benzodiazepines	Total drug class level (drug substances rollup; data on individual APIs are not collected)	Drug with potential for abuse
Opioid analgesics	Branded and generic products with one of the following opioids as an API, , including unknown formulations, combined into a single comparator group • Buprenorphine	Pain relievers with potential for abuse

	• Codeine (prescription and OTC) • Fentanyl • Hydromorphone • Morphine • Oxycodone • Sufentanil • Tramadol	
Buprenorphine	Branded and generic products with buprenorphine as an API, including unknown formulations	Used for treatment of opioid use disorder
Methadone	Branded and generic products with methadone as an API, including unknown formulations	Used for treatment of opioid use disorder and pain
Tramadol	Branded and generic products with tramadol as an API, including unknown formulations	Pain reliever with potential for abuse
Heroin	All heroin mentions, regardless of form	A high risk illicit abused opioid
GTNet Program		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Branded and generic products with gabapentin as an API, including unknown formulations	Similar indication
Benzodiazepines	Branded and generic products with one of the following benzodiazepines as an API, , including unknown formulations, combined into a single comparator group • Alprazolam • Diazepam • Flunitrazepam • Flurazepam • Lorazepam • Lormetazepam • Nitrazepam • Oxazepam • Temazepam (France and Germany only)	Drug with potential for abuse
Opioid analgesics	Branded and generic products with one of the following opioids as an API, , including unknown formulations, combined into a single comparator group • Buprenorphine • Codeine (prescription and OTC) • Fentanyl • Hydromorphone (France only) • Morphine • Oxycodone • Pethidine (meperidine) • Tramadol (France and Germany only)	Pain relievers with potential for abuse

Buprenorphine	Branded and generic products with buprenorphine as an API, including unknown formulations	Used for treatment of opioid use disorder
Methadone	Branded and generic products with methadone as an API, including unknown formulations	Used for treatment of opioid use disorder and pain
Tramadol (France and Germany only)	Branded and generic products with tramadol as an API, including unknown formulations	Pain reliever with potential for abuse
Survey of Non-Medical Use of Prescription Drugs Program		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Branded and generic products with gabapentin as an API, including unknown formulations	Similar indication
Baclofen	Branded and generic products with baclofen as an API, including unknown formulations	Similar indication
Benzodiazepines	Total drug class level (drug substances rollup; data on individual APIs are not collected)	Drug with potential for abuse
Opioid analgesics	Branded and generic products with one of the following opioids as an API, including unknown formulations, combined into a single comparator group • Buprenorphine • Codeine (prescription and OTC) • Dihydrocodeine • Fentanyl • Hydromorphone • Morphine • Oxycodone • Sufentanil • Tramadol	Pain relievers with potential for abuse
Buprenorphine	Branded and generic products with buprenorphine as an API, including unknown formulations	Used for treatment of opioid use disorder
Methadone	Branded and generic products with methadone as an API, including unknown formulations	Used for treatment of opioid use disorder and pain
Tramadol	Branded and generic products with tramadol as an API, including unknown formulations	Pain reliever with potential for abuse
Heroin	All heroin mentions, regardless of form	A high risk illicit abused opioid

Table 3. Comparator Groups for United States

Treatment Center Programs Combined		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Branded and generic products with gabapentin as an API, including unknown formulations	Similar indication
Opioid analgesics	Branded and generic products with one of the following opioids as an API, including unknown formulations, combined into a single	Pain relievers with potential for abuse

	comparator group • Buprenorphine • Fentanyl • Hydrocodone • Hydromorphone • Morphine • Oxycodone • Oxymorphone • Sufentanil • Tapentadol • Tramadol	
Buprenorphine	Branded and generic products with buprenorphine as an API, including unknown formulations	Used for treatment of opioid use disorder
Methadone	Branded and generic products with methadone as an API, including unknown formulations	Used for treatment of opioid use disorder and pain
Tramadol	Branded and generic products with tramadol as an API, including unknown formulations	Pain reliever with potential for abuse
Heroin	All heroin mentions, regardless of form	A high risk illicit abused opioid
AAPCC's NPDS		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Cases coded to the Micromedex® Poisindex® generic code for gabapentin	Similar indication
Baclofen	Cases coded to the Micromedex Poisindex generic code for baclofen	Similar indication
Benzodiazepines	Cases coded to the Micromedex Poisindex generic code for benzodiazepines (individual APIs are not assigned separate Micromedex Poisindex generic codes)	Drug with potential for abuse
Opioid analgesics	Cases coded to the Micromedex Poisindex generic code for the following opioids, combined into a single comparator group • Buprenorphine • Fentanyl • Hydrocodone alone or in combination • Hydromorphone • Morphine • Oxycodone alone or in combination • Oxymorphone • Sufentanil • Tapentadol • Tramadol	Pain relievers with potential for abuse
Tramadol	Cases coded to the Micromedex Poisindex generic code for tramadol	Pain reliever with potential for abuse
Heroin	Cases coded to the Micromedex Poisindex	A high risk illicit abused opioid

	generic code for heroin	
Survey of Non-Medical Use of Prescription Drugs Program		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Branded and generic products with gabapentin as an API, including unknown formulations	Similar indication
Baclofen	Branded and generic products with baclofen as an API, including unknown formulations	Similar indication
Benzodiazepines	Total drug class level (drug substances rollup; data on individual APIs are not collected)	Drug with potential for abuse
Opioid analgesics	Branded and generic products with one of the following opioids as an API, including unknown formulations, combined into a single comparator group • Buprenorphine • Fentanyl • Hydrocodone • Hydromorphone • Morphine • Oxycodone • Oxymorphone • Sufentanil • Tapentadol • Tramadol	Pain relievers with potential for abuse
Buprenorphine	Branded and generic products with buprenorphine as an API, including unknown formulations	Used for treatment of opioid use disorder
Methadone	Branded and generic products with methadone as an API, including unknown formulations	Used for treatment of opioid use disorder and pain
Tramadol	Branded and generic products with tramadol as an API, including unknown formulations	Pain reliever with potential for abuse
Heroin	All heroin mentions, regardless of form	A high risk illicit abused opioid
Web Monitoring Program		
Comparison Group	**Definition**	**Rationale**
Gabapentin	Branded and generic products with gabapentin as an API, including unknown formulations	Similar indication
Opioid analgesics	Branded and generic products with one of the following opioids as an API, including unknown formulations, combined into a single comparator group • Fentanyl • Hydrocodone • Oxycodone • Oxymorphone • Morphine	Pain relievers with potential for abuse

8.1.2. Surveillance Periods

Surveillance periods for the evaluation will include each RADARS System data source for the period when pregabalin data collection began in that program and will include the last five years for NPDS as described in Table 4:

Table 4. Surveillance Periods by Data Source and Country

	France	Germany	Italy	United States
RADARS System EUROPAD Program	1st quarter 2015 – 4th quarter 2017	4th quarter 2014 – 4th quarter 2017	4th quarter 2014 – 4th quarter 2017	
RADARS System GTNet Program	1st quarter 2012 – 4th quarter 2016	1st quarter 2012 – 2nd quarter 2017	1st quarter 2012 – 2nd quarter 2017	
RADARS System Survey of Non-Medical Use of Prescription Drugs Program	2nd quarter 2017, 4th quarter 2017	4th quarter 2017	2nd quarter 2017, 4th quarter 2017	3rd quarter 2016, 1st quarter 2017, 3rd quarter 2017
RADARS System Treatment Center Programs Combined				3rd quarter 2017 – 4th quarter 2017
RADARS System Web Monitoring Program				3rd quarter 2017 – 4th quarter 2017
AAPCC's NPDS				1st quarter 2013 – 4th quarter 2017

8.2. Setting

The surveillance (study) population will include the entire population enrolled by each data source, as described below.

EUROPAD Program

The surveillance population consists of individuals seeking treatment for substance use disorders (other than alcohol) at sites that offer treatment for opioid use disorders in France, Germany, and Italy.

Treatment Center Programs Combined

The surveillance population consists of patients entering treatment for opioid dependence in the United States.

GTNet Program

The surveillance population consists of exposure cases recorded by participating poison centres in France, Germany, and Italy.

National Poison Data System

The surveillance population consists of exposure cases recorded by 55 regional poison control centers in all 50 states covering 100% of the total United States population.

Survey of Non-Medical Use of Prescription Drugs Program

The surveillance population consists of the adult general population via an online survey panel company. The sample is stratified by United States Census region and gender, mirroring the distribution of the population in both percentage and gender representation (approximately 50% female, 50% male within each region). The samples from France, Germany and Italy are stratified by *gender and Nomenclature des unités territoriales statistiques* (NUTS) 1 level regions.

Web Monitoring Program

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

8.2.1. Inclusion criteria

EUROPAD Program

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

1. Completed the survey.
2. Age 18 years or older.

Treatment Center Programs Combined

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

1. Completed the survey.
2. Age 18 years or older.
3. Provided a valid three digit ZIP code.

GTNet Program

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

1. Report of human exposure to pregabalin or comparators.

National Poison Data System

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

1. Report of human exposure to pregabalin or comparators

Survey of Non-Medical Use of Prescription Drugs 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.

Web Monitoring Program

1. Online posts originating in the United States which mention pregabalin or comparators.

8.2.2. Exclusion criteria

There are no exclusion criteria (other than subjects who do not meet the inclusion criteria (e.g. pediatric subjects for the *EUROPAD Program*)) for subjects in the EUROPAD Program, Treatment Center Programs Combined, GTNet Program, or NPDS.

Subjects are excluded from the Survey of Non-Medical Use of Prescription Drugs Program if they 1) complete the survey too quickly (<2/5 of the median survey time) or 2) report last week use of all illicit drugs and last seven day non-medical use of all opioid products, all benzodiazepines, or all stimulant products.

In the Web Monitoring Program, posts that meet the following exclusion criteria are not included in the analysis: posts in a language other than English, posts containing names of drugs used in a context unrelated to the drugs of interest, posts determined to be outside of the geographical region of interest (United States), and posts that are from a media source other than "social media" or "blogs/forums". Additionally, posts with themes determined to be N/A, unable to determine, spam, online pharmacy only, news only, or pop culture reference only are excluded.

8.3. Variables

The variables to be used in this evaluation are identified in Table 5 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 outcomes, by data source, are provided in Annex 3.

Table 5. Variables in the Pregabalin Evaluation

Variable	Role	Data source(s)[§]
Non-Medical Use	Outcome	NMURxP
Abuse	Outcome	NPDS, EUROPAD, TCPC, NMURxP, WMP*
Misuse	Outcome	NPDS, NMURxP, WMP*
Intentional exposures	Outcome	GTNet
Covered population	Denominator	Census
Dosage units dispensed	Denominator	IQVIA
Standard units	Denominator	IQVIA

[§]TCPC = Treatment Center Programs Combined; NMURxP = Survey of Non-Medical Use of Prescription Drugs Program; WMP = Web Monitoring Program

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

Note: Operational definitions for all variables will be included in the SAP. Detailed descriptions of the outcomes are provided in Annex 3.

8.4. Data sources

8.4.1. Drug utilization data

Utilization of pregabalin and comparators will be obtained from a vendor, IQVIA™ (Danbury, CT), that provides information, services and technology for the healthcare industry. Drug utilization estimates obtained for the United States represent drug dispensed from physical pharmacies and are denoted Dosage Units Dispensed. Drug utilization estimates obtained for European countries represent the amount of products sold from manufacturers to pharmacies in each country and are denoted Standard Units. Drug utilization rates for the heroin comparator will not be calculated as drug utilization estimates from IQVIA are only available for prescription drugs.

8.4.2. Population data

8.4.2.1. United States population data

Population data are based on information made available from the United States Census. Each population rate is calculated by dividing the sum of the cases by the sum of the population across three-digit ZIP codes covered by the Treatment Center Programs Combined. In the Survey of Non-Medical Use of Prescription Drugs Program, annual estimates of regional populations from the US Census are used to provide regional population values. This value is scaled per 100,000 population (or other appropriate scaling). Extrapolation using the 2000 and 2010 population is utilized to adjust for population growth.

8.4.2.2. France, Germany and Italy population data

Annual estimates of regional populations are captured from the EUROSTAT website for the most current data available at the time of the survey launch, and data represented within this report were for adults ages 18 and older found at the website below:

http://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/database

8.4.3. RADARS System EUROPAD Program data

The EUROPAD Program is a multi-centre observational study comprised of medication-assisted maintenance treatment programs. The Associazione per l'Utilizzo delle Conoscenze Neuroscientifiche a fini Sociali (AU-CNS), in partnership with physician members of the European Opiate Addiction Treatment Association (EUROPAD) and research personnel at the Rocky Mountain Poison & Drug Center (RMPDC), work collaboratively to recruit and manage investigative sites in Europe. The population is composed of individuals seeking treatment for substance use disorders (other than alcohol) at sites that offer treatment for opioid use disorders. Interested patients are asked to complete a self-administered paper-based questionnaire upon entrance to the treatment program.

8.4.4. RADARS System Treatment Center Programs Combined data

The Treatment Center Programs Combined provides data from two distinct RADARS System programs: Opioid Treatment Program and Survey of Key Informants' Patients Program. These two programs use the same core data collection form, enabling data to be combined, and complement each other by providing information from patients entering both

private and public opioid addiction treatment programs. Patients enrolling in the study voluntarily complete a self-administered anonymous questionnaire within the first week of admission. These programs will estimate one-month prevalence and route-specific rates of prescription and illicit drugs among patients admitted to treatment. These rates are adjusted for population as well as drug utilization.

8.4.4.1. Opioid Treatment Program

In 2016, the Opioid Treatment Program involved 65 treatment programs in both urban and rural areas across 31 states. These primarily public medication-assisted maintenance treatment programs are geographically diverse with representation from urban and rural centers.

8.4.4.2. Survey of Key Informants' Patients Program

In 2016, the Survey of Key Informants' Patients Program involved 129 substance abuse treatment programs covering 45 states. These primarily private treatment centers are geographically diverse with representation from urban, suburban, and rural centers.

8.4.5. RADARS System GTNet Program data

The GTNet Program conducts ongoing surveillance of human exposures to prescription drugs of interest as reported to participating poison centres and describes the historical and current trends of prescription drug abuse, misuse, and diversion worldwide. GTNet was established in 2011 to serve as a collaborative, worldwide network of participating poison centres with the ability to provide information about drug substances involved in acute health events. The GTNet aims to cultivate research partnerships in order to foster collaborative efforts, harmonize data collection and definitions, and solidify an infrastructure that allows for the global monitoring of any substance of interest. Membership is open to any poison centre worldwide that is able to provide sufficient exposure data or information regarding drug substances of interest.

8.4.6. American Association of Poison Control Centers' National Poison Data System data

The NPDS is the data repository for the regional poison centers of the American Association of Poison Control Centers. American Association of Poison Control Centers member centers offer coverage for the entire United States, providing free medical management services to both healthcare professionals and the general public. Data from regional poison centers is uploaded in real-time to the NPDS. The NPDS will be searched to identify human exposures to heroin. Exposures confirmed to be non-exposures and non-human exposures will be excluded. An exposure is defined as an actual or suspected contact with any substance, which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation. These rates are adjusted for population.

8.4.7. RADARS System Survey of Non-Medical Use of Prescription Drugs Program data

The Survey of Non-Medical Use of Prescription Drugs Program employs an online survey of the general adult population to understand non-medical use of prescription drugs. Volunteers from the general population are queried about non-medical use of prescription medications

defined as *use without a doctor's prescription or for any reason other than what was recommended by their doctor.* Respondents who endorse non-medical use of prescription medications are queried about the reasons for non-medical use of prescription medications, which include misuse (defined as *to self-treat my pain* or *to treat a medical condition, other than pain*) or abuse (defined as *use for enjoyment/to get high*). This program collects demographic information and whether the respondent is a student, healthcare professional, or current/former member of the armed forces. The survey also solicits information on lifetime, last 12 months, last 90 day, last 30 day, and last 7 day non-medical use of prescription and OTC drugs, including reason for non-medical use, frequency of non-medical use, route of administration, and source of drug acquisition. Questions regarding illicit drug use, chronic and acute pain, substance abuse treatment, and history of mental health disorders are also included. The Modified Drug Abuse Screening Test (DAST-10) is incorporated into the survey to evaluate the degree of consequences related to drug abuse (McCabe et al., 2007). Quota sampling is used to provide a distribution of survey respondents that is proportional to census populations across geographic regions and equal proportions of males/females in each region. Surveys are conducted biannually (approximate respondents by country: United States – 30,000; France and Italy – 10,000; Germany – 15,000). Respondents are excluded from analysis if they 1) complete the survey too quickly (<2/5 of the median survey time) or 2) report last week use of all illicit drugs and last seven day non-medical use of all opioid products, all benzodiazepines, or all stimulant products. Survey results are weighted to provide a national prevalence estimate of non-medical use of specific medications among the general population of adults. Prevalence estimates, population rates, and drug utilization based rates are also calculated.

8.4.8. RADARS System Web Monitoring Program data

The Web Monitoring Program is a real-time surveillance system that analyzes data regarding posts about prescription drugs on social media websites, blogs, and forums. A commercially available web monitoring platform is utilized to search and organize posts. This software collects posts from over 150 million websites worldwide (e.g., forums, blogs). For this study, data will be subset to those determined to be within the US, using the top level domain of the website, IP address of the website, and the home location of the user for social media websites (if available). Specific search-string criteria (including branded products, misspellings, and slang words) and time period are entered into the web monitoring platform, and all posts matching these criteria are returned. Posts are reviewed by a team of trained coders to characterize salient themes and to identify posts relating to abuse and misuse. When the number of posts is too large to code every post, a sampling plan is applied to randomly select a representative subset of posts. These supplemental data are primarily qualitative and add context to the rates generated from the complimentary programs.

8.5. Study size

This evaluation is not intended to test a pre-specified statistical hypothesis; therefore a pre-determined sample size is not calculated.

8.6. Data management

Access to the data is restricted to qualified individuals who must complete training through standard operating procedures implemented by a quality system. The network where the data

are stored is secure, accessed only via username/password, and fully encrypted. All staff members are required to openly show and wear identification while on the premises.

8.6.1. Drug utilization data management

Drug utilization data by drug product and geographic region are obtained from IQVIA quarterly and are uploaded via a file transfer protocol (FTP) site. A RADARS System team member transfers the data file into a secure internal network location. Upon delivery, data are checked to ensure completeness of fields and are compared to prior data for any new drugs not reported in previous quarters. This later step is undertaken to ensure that new drugs are appropriately categorized by drug class, active pharmaceutical ingredient, and drug product.

8.6.2. Population data management

8.6.2.1. United States census data management

Population data at the three-digit ZIP code level are available from the United States Census website for the 2000 and 2010 censuses. Extrapolation by linear regression is performed at the three-digit ZIP code level to estimate the population each quarter through the study period.

8.6.2.2. France, Germany and Italy population data management

Regionally-estimated population-based rates are calculated, stratified at the second level of the Nomenclature of Territorial Units (NUTS) and the corresponding population.

8.6.3. RADARS System EUROPAD Program data management

Paper-based questionnaires are designed for self-administration. However, at some participating sites, questionnaires are administered with the assistance of an addiction specialist or counselor. The survey enquires about basic demographic information (e.g. gender, age, history of substance abuse treatment), residential postal code, primary drug of abuse, primary route of abuse, opioid drugs used in the past 90 days “to get high” by specific drug or drug product, routes of administration for each drug abused, and source of drug acquisition. Completed questionnaires from all sites are submitted to the coordinating centre (AU-CNS) for review and data management.

The questionnaire is periodically revised in order to add newly-marketed drug products of interest and further refine the instrument based on local investigator recommendations and emerging topics in substance abuse trends.

Each completed questionnaire is reviewed to assess completeness and consistency. Queries regarding missing or conflicting data are returned to the original site for reconciliation. Predefined data rules are applied to recurring issues (e.g. more than one response for an item that allows only one response). A database quality audit is performed by RMPDC at the completion of data entry to ensure accuracy of data entered to the web-based portal as compared to the source document (patient questionnaires). In addition, all statistical programs used to summarize and compare data are validated per current standard operating procedures.

8.6.4. RADARS System Treatment Center Programs Combined data management

The American Association for the Treatment of Opioid Dependence collects data from patients admitted to opioid treatment programs nationally. A survey is administered to Opioid Treatment Program patients at the time they are admitted into treatment with the goal of determining prevalence of past month prescription or illicit drug abuse in that population. On a weekly basis, the opioid treatment programs submit completed surveys to the project coordinator.

Database quality assurance includes data entry and verification as well as data edit checking (e.g., letters appearing in ZIP code or duplicate cases in the data). Data are audited each quarter. The RADARS System Data Manager generates a random sample from unique identifiers for a given quarter. Data for the random sample are sent to an auditor who checks for errors against the source documents and generates an error percentage.

The Survey of Key Informants' Patients Program is conducted at Washington University at St. Louis (WUSTL). The project manager or designee at WUSTL mails hard copies of questionnaires to the Key Informants who have opted to enlist their patients to complete the Patient Questionnaires. Upon receipt of completed questionnaires, each questionnaire is logged in the Key Informants' binder, indicating date received. All data are then entered into a SQL database using a proprietary website. All data entry is double-checked and verified for accuracy. Data undergo an audit each quarter.

8.6.5. RADARS System GTNet Program data management

Participating poison centres in the GTNet Program collect data on human exposure cases using standardized data fields and data collection methods. These data are collected as part of the centre's daily routine activities as they provide medical management assistance to healthcare providers and the public (depending on the centre). Standardized data fields for each case include case number, postal code, date of exposure, patient age, gender, exposure reason, exposure route, drug class, product name, and medical outcome.

The specific data fields, definitions, and collection processes vary between poison centres so harmonization of the data is required. The GTNet Program members use a standardized data template to organize their data for submission to RMPDC. Uniform categorical data fields with written definitions were agreed upon for each participating poison centre. The fields are assigned numeric codes in order to easily translate multiple languages into a standard code. All data are de-identified prior to submitting to RMPDC to protect the privacy of the patients.

Each participating poison centre employs their own quality assurance measures and controls in terms of accurate and complete recording of the reported exposures. Each centre then extracts exposure data into a standardized electronic format, which is electronically transferred to the coordinating centre at RMPDC. RMPDC then reviews the data for conformance to the standardized structure. In the process, invalid or outlying values are identified and queried with the originating centre. Corrected data are then electronically re-transferred to RMPDC where data are stored in a secure, centralized location as per institution requirements.

8.6.6. American Association of Poison Control Centers' National Poison Data System data management

Information on exposures reported to poison centers in the NPDS are obtained from the American Association of Poison Control Centers. Data are uploaded via an FTP site. A RADARS System team member transfers the data file into a secure internal network location. Data are checked to ensure that no inconsistencies (e.g. differences from previous requests, incomplete or missing fields) are present.

8.6.7. RADARS System Survey of Non-Medical Use of Prescription Drugs Program data management

The Survey of Non-Medical Use of Prescription Drugs Program is a self-administered, confidential, online survey. Respondents are recruited through the use of a survey panel company in which respondents voluntarily register to complete surveys for modest compensation. Non-probability quota sampling is used to provide a distribution of survey respondents across geographic regions within each country and an equal distribution of gender within each region.

For each launch, the data are transported from a secure hosting site once all sampling quotas have been obtained. These data are then stored in their raw format on an internal, secure server. Exclusion criteria are applied after data collection to remove respondents with implausible responses. Respondents are excluded from the sample if they: 1) complete the survey too quickly (<2/5 of the median survey time) or 2) report last week use of all illicit drugs and last seven day non-medical use of all opioid products, all benzodiazepines, or all stimulant products.

8.6.8. RADARS System Web Monitoring Program data management

Radian6™, a secure, commercially available web monitoring platform, is utilized to search and organize posts on the internet. Specific search-string criteria, time period, language, and region are entered into the web monitoring platform, and all posts matching these criteria are returned, downloaded, and stored on an internal secure server in CSV format.

Precoding is applied to the raw data in order to automatically exclude posts that do not meet inclusion criteria using SAS; posts from news outlets, spam, and other non-substantive posts. When the volume of posts is large, a sampling plan is applied to generate a random selection of posts for manual review and coding. Duplicate posts are identified and one post from each duplicate group is coded utilizing REDCap™, a secure web application designed to support data capture for research studies. These coded values are then applied to all posts within their respective duplicate group. Unique posts are coded in the same manner as duplicate posts within the REDCap interface. Data for multiple drug products and timeframes are stacked by quarter into a single file. The number of raw posts in the source files is compared to the output of the final stacked file to verify that no posts were lost or duplicated during the stacking process. Next, predetermined exclusionary criteria are applied to the dataset to remove non-substantive content. A random sample of 500 posts from the resulting excluded dataset is validated manually in order to verify there were no errors made during this step. Finally, themes are automatically applied to posts containing certain predetermined keywords, and these posts are split into a separate file. The number of posts with automatically assigned themes is checked against the number of posts in the newly created

file to verify they are equal. Fully-coded data are exported from REDCap to SAS, and SAS analysis datasets are created.

8.7. Data analysis

The primary objective will be to estimate rates or prevalence estimates for each of the outcomes (non-medical use, misuse, abuse, intentional exposures) by program for pregabalin and comparators within each country using descriptive statistics. No rates will be calculated in the evaluation of data from the Web Monitoring Program.

For the secondary objective, trends over time will be performed for pregabalin and each comparator for each of the outcomes by program within each country. Trends will be fitted by product or group when there are at least five year-quarters of consecutive data collection on a given drug and outcome. Five continuous year-quarters of data allows for a more accurate trend line to be fit; less than five continuous year-quarters of data are not as stable and have the potential for more variability. Both population and drug utilization will be used as denominators for the fitting of the trend models.

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 outcome definitions or their analyses would be reflected in a protocol amendment.

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 and NPDS 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. Limitations of the research methods

IQVIA data are used as an indicator of quarterly drug utilization based upon a sample of data and a proprietary projection algorithm. Each of the RADARS System programs and NPDS is based on self-reported information which presents a potential bias of ambiguous answers or incomplete data. NPDS and GTNet Program data represent a spontaneous reporting system while the Treatment Centers Combined, EUROPAD Program, and Survey of Non-Medical Use of Prescription Drugs Program data represent a non-probability sampling strategy.

Indication for all prescription and OTC drugs (pregabalin and comparators) cannot be obtained within the RADARS System programs or NPDS data; therefore, outcomes may include off-label use or prescription drugs obtained through diversion. This is a limitation common to all surveys. Medical records are not being accessed in this study.

8.10. Strengths of the research methods

The RADARS System and NPDS data are usually available within three months of data capture. An additional strength is the large catchment area covered; programs cover large areas of each country, and NPDS covers the entire United States. Cases arise from both

large metropolitan areas as well as rural populations, thus providing results that are more broadly applicable than those from a smaller geographic region. The joint use of multiple RADARS System programs and NPDS is a mosaic approach, allowing for the assessment of trends in various populations and in different settings to enhance the generalizability of the data and convergent validity. Comprehensive results from independent programs and data sources evaluate the totality of the evidence and provide better understanding of the trends of interest.

8.11. Other aspects

Not applicable.

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 RADARS System data are being collected under existing RADARS System protocols. The NPDS data was determined to be non-human subjects research. For these reasons, 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 RADARS System data sources. Those protocols have already been reviewed and approved by IRBs as described below. The approvals allow for unlimited analysis of data. In addition, the NPDS data was determined to be non-human subjects research. Further, the work in this protocol involves no interaction with human subjects. A separate IRB review of this protocol is therefore not necessary.

9.3.1 RADARS SYSTEM TREATMENT CENTER PROGRAMS COMBINED

The protocol for the Opioid Treatment Program was originally approved on 11 May 2004 by the Institutional Review Board at the National Development and Research Institutes, Inc. with the most recent authorization provided on 12 February 2018 by the Colorado Multiple Institutional Review Board (COMIRB).

The protocol for the Survey of Key Informants' Patients Program was originally approved on 28 September 2006 by the WUSTL Human Research Protection Office and became a RADARS System program on 01 January 2008, with the most recent authorization provided on 29 March 2017.

9.3.2 RADARS SYSTEM EUROPAD PROGRAM

The protocol for the EUROPAD Program was originally approved on 15 October 2013 by COMIRB, with the most recent authorization provided on 16 November 2017. In addition, the study protocol was reviewed by local Ethics Committees and resulted in approvals/determinations for each participating site.

9.3.3 RADARS SYSTEM GTNET PROGRAM

The GTNet Program was determined to be not human subject research from COMIRB on 03 November 2011, and no continuing review is required. Each participating poison centre follows its own local ethics board's requirements and regulations in order to participate in the program.

9.3.4 RADARS SYSTEM SURVEY OF NON-MEDICAL USE OF PRESCRIPTION DRUGS PROGRAM

The Survey of Non-Medical Use of Prescription Drugs Program study protocol was reviewed and approved by COMIRB prior to the first launch of the survey of program in the United States. COMIRB granted a certificate of exemption on 05 July 2016.

9.3.5 RADARS SYSTEM WEB MONITORING PROGRAM

The Web Monitoring Program study protocol was reviewed and approved by COMIRB prior to the initiation of the Web Monitoring Program. COMIRB granted the project approval in the United States on 18 September 2013. Since the posts obtained through the Web Monitoring Program are both anonymous and publicly available, COMIRB determined this project to be non-human subject research and exempt from further review.

9.3.6 AMERICAN ASSOCIATION OF POISON CONTROL CENTERS' NATIONAL POISON DATA SYSTEM

In alignment with COMIRB's Policies and Procedures for the Protection of Human Subjects, the Principal Investigator determined that analysis of NPDS data involves non-human subjects research per 45 CFR 46.102(f)(2).

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* issued by the International Society for Pharmacoepidemiology, Good Epidemiological Practice guidelines issued by the International Epidemiological Association, International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, European Medicines Agency European Network of Centres for Pharmacoepidemiology and Pharmacovigilance 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

RADARS System EUROPAD Program, GTNet Program, Treatment Center Programs Combined, Survey of Non-Medical Use of Prescription Drugs Program, and NPDS

These programs includes unstructured data (e.g., 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 AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

Web Monitoring Program

The RADARS System Web Monitoring Program consists of a structured database of posts retrieved from various blogs, forums, and social media sites that have been systematically coded with respect to various characteristics (e.g., product referenced). On behalf of subscribers to their services, RADARS System queries this structured database to provide aggregate-level information about posts related to subscriber products and comparator groups. In this structured database, 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 AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and AE are not reportable as individual AE reports.

In addition, in the event that RADARS System performs human review of individual posts within the Web Monitoring Program per Pfizer's request, AE reporting requirements are not applicable because this database does not retain identifying information regarding the individual responsible for a post (ie, the reporter). Therefore, reporters are not contactable and AE reporting criteria cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The various final country study reports will be submitted to Pfizer by the RADARS System. The study protocol and abstract(s) of results will be posted on the EU PAS register. A study abstract(s) may be submitted to a scientific conference(s) and a manuscript summarizing the study results may also be submitted to a peer-reviewed journal for publication.

12. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., 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 NI study protocol that the investigator becomes aware of.

13. REFERENCES

1) Martinotti G. Pregabalin in clinical psychiatry and addiction: pros and cons. Expert Opin Investig Drugs 2012; 21: 1243–1245

2) Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1468-1331.

3) Bril V, England J, Backonja M, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758-1765.

4) Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010;85:S3-14.

5) Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults:a systematic review and meta-analysis. Lancet Neurol 2015;14:162-173.

6) Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19:328-335.

7) National Institute for Health and Clinical Excellence. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non- specialist settings. March 2010; Published online at: http://www.nice.org.uk/guidance/CG96. Accessed 07 March 2018.

8) Johansen ME. Gabapentinoid use in the United States: 2002 through 2015. JAMA Intern Med 2018; 178: 292-294.

9) NHS Digital. Central nervous system national charts. Available online at: https://digital.nhs.uk/home. Accessed 07 December 2017.

10) Grosshans M, Lemenager T, Vollmert C, Kaemmerer N, Schreiner R, Mutschler J, Wagner X, Kiefer F, Hermann D. Pregabalin abuse among opiate addicted patients. Eur J Clin Pharmacol 2013; 69: 2021-2025.

11) Chiappini S, Schifano F. A decade of gabapentinoid misuse: an analysis of the European Medicines Agency's "Suspected Adverse Drug Reactions" database. CNS Drugs 2016; 30: 647-54.

12) Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, Di Melchiorre G, Di Furia L, Farre´ M, Flesland L, Mannonen M, Majava A, Pagani S, Peltoniemi T, Siemann H, Skutle A, Torrens M, Pezzolesi C, van der Kreeft P, Scherbaum N. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom 2011; 80: 118–22

13) McNamara S, Stokes S, Kilduff R, Shine A. Pregabalin abuse amongst opioid substitution treatment patients. IMJ 2015; 108: 309-310.

14) Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLoS Med 2017; 14: https://doi.org/10.1371/journal.pmed.1002396.

15) Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. Drugs 2017; 77: 403-426.

16) National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. National Survey on Drug Use and Health Nationwide Trends. June 2015. Published online at: https://www.drugabuse.gov/publications/drugfacts/nationwide-trends. Accessed: 29 May 2018.

17) U.S. Food and Drug Administration. The Sentinel Initiative – An update of FDA's progress in building a national electronic system for monitoring the postmarket safety of FDA-approved drugs and other medical products. July 2010; p. 4. Published online at: http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf. Accessed: 24 August 2017.

18) Stang PE, Ryan PB, Racoosin JA, Overhage JM, Hartzema AG, Reich C, Welebob E, Scarnecchia T, Woodcock J. Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership. Ann Int Med 2010;153:600-6.

19) Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, Green JL. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015 15;372(3):241-8.

20) Cicero TJ, Dart RC, Inciardi JA, Woody GE, Schnoll S, Munoz S. The development of a comprehensive risk-management program for prescription opioid analgesics: Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®). Pain Med 2007a;8:157-70.

21) Cicero TJ, Inciardi JA, Surratt H. Trends in the use and abuse of branded and generic extended release Oxycodone and fentanyl products in the United States. Drug Alcohol Depend 2007b;91:115-20.

22) Inciardi JA, Surratt HL, Stivers Y, Cicero TJ. FDA approvals of generic drugs: impact on the diversion of opioid analgesics with a potential for abuse. J Opioid Manag 2009;5:81-7.

23) Schneider MF, Bailey JE, Cicero TJ, Dart RC, Inciardi JA, Parrino M, Munoz A. Integrating nine prescription opioid analgesics and/or four signal detection systems to summarize statewide prescription drug abuse in the United States in 2007. Pharmacoepidemiol Drug Saf 2009;18;778-90.

24) Spiller H, Lorenz DJ, Bailey EJ, Dart RC. Epidemiological trends in abuse and misuse of prescription opioids. J Addict Dis 2009;28;130-6.

25) Thurmond VA. The point of triangulation. J Nursing Scholarship 2001;33:253-8.

26) Hales D. An introduction to triangulation. Published online at: http://www.unaids.org/en/media/unaids/contentassets/documents/document/2010/10_4-Intro-to-triangulation-MEF.pdf. Accessed: 24 August 2017.

27) McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. Addict Behav 2007;32(3):562-75.

28) Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, et al. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. Clin Toxicol (Phila). 2017 Dec;55(10):1072-1252. PubMed PMID: 29185815.

14. LIST OF TABLES

15. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
An Evaluation of the Misuse and Abuse of Pregabalin using RADARS® System Programs in the United States and the European Union

Study reference number: A0081363

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Study progress and interim progress reports will not be provisioned.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

This evaluation will not use hypothesis testing to evaluate the outcomes.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.1
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

This evaluation is not testing for association; rather, this evaluation is a report of occurrences only.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	7
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	8.1.2
	4.2.2 Age and sex?	☐	☐	☒	
	4.2.3 Country of origin?	☒	☐	☐	7
	4.2.4 Disease/indication?	☐	☐	☒	
	4.2.5 Duration of follow-up?	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Study population will not be defined in terms of age, sex, disease/indication, and duration of follow up; this evaluation is a report of occurrences only.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

The exposure in the evaluation is based on drug utilization in the geographic region and is not linked to an individual.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3 and Annex 3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3 and Annex 3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

The outcomes reported in this evaluation are spontaneously reported events, and non-reports of these outcomes are not assessed.

This evaluation does not have any endpoints relevant for Health Technology Assessment.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.6

Comments:

The outcomes reported in this evaluation are spontaneously reported events, and non-reports of these outcomes are not assessed and reports themselves cannot be validated.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

The outcomes reported in this evaluation are spontaneously reported events, and non-reports of these outcomes are not assessed and reports themselves cannot be validated.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

No coding system will be used. This evaluation will analyze de-identified data; therefore, the evaluation will not be able to link patients between data sources.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7
10.2 Are descriptive analyses included?	☒	☐	☐	8.7
10.3 Are stratified analyses included?	☒	☐	☐	8.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.1, 8.4
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	8.5

Comments:

The outcomes reported in this evaluation are spontaneously reported events, and non-reports of these outcomes are not assessed and reports themselves cannot be validated.

This evaluation is not intended to test a pre-specified statistical hypothesis; therefore a pre-determined sample size is not calculated.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6, 8.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

No system is in place for independent review of study results since this evaluation will analyze de-identified data only.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Study feasibility is not addressed because this evaluation is not attempting to achieve a desired sample.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.3
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.3
13.3 Have data protection requirements been described?	☒	☐	☐	9.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	

Comments:

Name of the main author of the protocol: Kofi Asomaning, PhD

Date: dd/Month/year 04/June/2018

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

OUTCOME DEFINITIONS

Indication for all prescription and OTC drugs (pregabalin and comparators) cannot be obtained within the RADARS System programs or NPDS data; therefore, outcomes may include off-label use or prescription drugs obtained through diversion. Medical records are not being accessed in this study.

Non-Medical Use

In the RADARS System Survey of Non-Medical Use of Prescription Drugs Program, a non-medical use case is defined as a respondent who endorses *use without a doctor's prescription or for any reason other than what was recommended by their doctor.*

Misuse

In the AAPCC's NPDS data, misuse is defined as those cases with a reason for exposure of intentional misuse. The definition for intentional misuse is "an exposure resulting from the intentional improper or incorrect use of a substance." (Gummin et al., 2017)

In the RADARS System Survey of Non-Medical Use of Prescription Drugs Program, misuse is defined as a non-medical use case with a reason of: "to self-treat my pain" or "to treat a medical condition, other than pain".

In the RADARS System Web Monitoring Program, misuse is defined as "a mention that indicates the improper or incorrect use of a drug for reasons other than the pursuit of a psychotropic effect."

Abuse

In the AAPCC's NPDS data, abuse is defined as those cases with a reason for exposure of intentional abuse. The definition for intentional abuse is "an exposure resulting from the intentional improper or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect." (Gummin et al., 2017)

In the RADARS System EUROPAD Program, an abuse case is defined as a survey response endorsing use "to get high" in the past 90 days.

In the RADARS System Treatment Center Programs Combined, an abuse case is defined as a survey response endorsing use "to get high" in the past month.

In the RADARS System Survey of Non-Medical Use of Prescription Drugs Program, an abuse case is defined as a non-medical use case with a reason of "for enjoyment/to get high."

In the RADARS System Web Monitoring Program, abuse is defined as "a mention that indicates the use of a drug to gain a high, euphoric effect or some other psychotropic effect."

Intentional exposures (misuse/abuse/diversion)

In the RADARS System GTNet Program, intentional exposures are defined as any exposure resulting from the intentional improper or incorrect use of a substance.