Non-interventional Post-authorization Safety Study (PASS)

Protocol

Johnson & Johnson Consumer Inc.,
McNeil Consumer Healthcare Division

Non-interventional Post-authorization Safety Study - Protocol

Misuse and Abuse of Loperamide in the United States

Protocol MA-161205104527-DHEP

Imodium (Loperamide)

EU PAS Register Number: EUPAS16778

Protocol version: 2.0 **Version date:** 10 July 2019

Prepared by: Denver Health and Hospital Authority, Rocky Mountain Poison and Drug Center on behalf of Johnson & Johnson Consumer Inc., McNeil Consumer Healthcare Division

Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

1. PASS INFORMATION

Title:	**Misuse and Abuse of Loperamide in the United States**
Protocol version:	2.0
Date of last version of the protocol:	19 December 2016
EU PAS Register No:	EUPAS16778
Active substance (INN common name):	Loperamide
Pharmacotherapeutic group (ATC Code):	ATC code: A07DA03
Medicinal product(s):	Loperamide
Product reference:	ATC code: A07DA03
Procedure number:	Not applicable
Name of Marketing Authorization Holder(s)	Johnson & Johnson Inc., McNeil Consumer Healthcare Division
Joint PASS	No
Research question and objectives	The objective of this study is to characterize misuse and abuse of loperamide using United States poison center exposure data as well as an online survey of non-medical use of medications in the general adult population.
Country(-ies) of study	United States
Author	Richard C. Dart, MD, PhD Denver Health and Hospital Authority Rocky Mountain Poison & Drug Center 777 Bannock Street, MC 0180 Denver, Colorado 80204 Richard.Dart@rmpdc.org +1 303 389 1240

2. MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Johnson & Johnson Consumer Inc., McNeil Consumer Healthcare Division
Address:	7050 Camp Hill Rd, Fort Washington, PA 19034
Contact Details:	Study Director: Alison Hughes + 44 162 862 7088 ahughe29@its.jnj.com Study Manager: Hedvig Bennet Mobile: +46 (0)73 828 80 66 hbenne11@its.jnj.com Henny Eideberg mobile: +46 70 388 82 81 mobile heideber@its.jnj.com
Qualified Person Pharmacovigilance:	
Name:	Maria Spyt mspyt@its.jnj.com

3. RESPONSIBLE PARTIES

Principal Investigator:	Richard C. Dart, MD, PhD
Coordinating Investigator:	Katherine M. Reynolds, MPH
Contact person for this protocol:	Katherine M. Reynolds, MPH
E-mail address or telephone number of contact person:	Kate.Reynold@rmpdc.org +1 303 389 1753

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ADDITIONAL INFORMATION PROVIDED IN ANNEX 1

AMENDMENTS AND UPDATES
Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and will follow the review and approval process in accordance with local regulations.

There are no amendments for this protocol.

4. Amendments and Updates

The purpose of this amendment is to update the Principal Investigator, Coordinating Investigator, contact person for the protocol, marketing authorization holder study managers, and sponsor's responsible medical officer. A study report for the original protocol dated 30 June 2017 was previously submitted. The original study report included exposures reported to NPDS from 01 January 2012 to 31 December 2015. In addition to the aforementioned changes, this amendment is also to extend the NPDS study period to include exposures reported from 01 January 2016 to 31 December 2017 (total NPDS study period: 01 January 2012 to 31 December 2017). The study period has been updated in order to include the most recent NPDS data available.

5. ABSTRACT

Protocol Title: Misuse and Abuse of Loperamide in the United States (2.0, 10 July 2019)

Sponsor's Responsible Medical Officer: Alison Hughes

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

There have been reports of massive overdose of loperamide resulting in serious cardiovascular events. Reports from the United States regarding the use of loperamide to self-treat opioid withdrawal or to induce euphoria have been the subject of recent medical literature. This type of aberrant behavior is difficult to study and is not often detected in randomized controlled trials. Existing data sources provide valuable ways of better understanding abuse and misuse of medications. Two such sources include the National Poison Data System (NPDS) and the Non-Medical Use of Prescription Drugs (NMU-Rx) Program. These two existing secondary data sources will be studied to further characterize the patients and characteristics of loperamide abuse and misuse.

Research Question and Objectives

This study aims to characterize the abuse and misuse of loperamide in the United States (US) through the evaluation of two independent surveillance data systems.

The objectives of this study are:

1) to describe abuse and misuse of loperamide as reported to the National Poison Data System (NPDS)

2) to describe non-medical use of loperamide as reported via an online survey of Non-Medical Use of Prescription Drugs (NMU-Rx) by a general adult population sample.

Study Design

This is a retrospective non-interventional study of secondary data sources to document the misuse and abuse of loperamide in the US.

Setting and Patient Population

NPDS data represent loperamide exposures reported to US poison centers from 2012 through 2015. These include patients of all ages and may be contacts made by the public or healthcare professionals.

NMU-Rx data represent information captured via an ongoing online survey of the general adult population who have registered to participate in online surveys in exchange for modest compensation. The NMU-Rx survey was conducted in July/August 2016.

Variables

Variables collected by NPDS included in this protocol for evaluation include the following list.

- Demographic data including age and gender
- Exposure characteristics including product and other substances involved and site of exposure
- Outcome variables including management site (healthcare facility or not), level of healthcare facility (if healthcare facility care is received) and medical outcome

Variables collected by NMU-Rx included in this protocol for evaluation include the following list:

- Demographics including age, gender, ethnicity/race
- Population characteristic including history of pain, substance abuse treatment, assessment of risk of abuse severity (Drug Abuse Screening Test [DAST-10]) and number of drugs/drug classes used non-medically
- Lifetime use, non-medical use of loperamide
- Frequency of recent non-medical use of loperamide (number of days in past 7, 30, 90 days)
- History of illicit drug use

Data Sources

NPDS and NMU-Rx are two independent data sources and will be used to study abuse and misuse of loperamide in the US. Both of these data sources are considered secondary data sources as the information was initially collected for a purpose other than the stated objectives of this protocol. US Census data and product sales data from IRI will also be used to calculate population-based rates and drug utilization-based rates, respectively.

Study Size

NPDS is a secondary data source which relies on spontaneous reporting, hence the convenience sample (all reported exposures) will be used in the analyses.

Over 30,000 survey participants completed the NMU-Rx survey during the 2016 launch. The full sample will be used to compare patients who did and did not report loperamide misuse.

Data Analysis

Descriptive analyses will be used to characterize the key measures in each of the secondary data sources. No formal statistical analyses are planned.

6. MILESTONES

The initial planned dates for key milestones in this study are outlined below.

Milestone:	Planned Date:
Start of data collection	After protocol finalization
End of data collection	When IRI data is available for analysis (estimated: April-May 2019)
Registration in the EU PAS register	After protocol finalization
Final report of study results	June-July 2019

Abbreviations

EU PAS Register	The European Union electronic Register of Post-Authorisation Studies
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NMU	Non-medical Use
NMU-Rx	Non-Medical Use of Prescription Drugs
NPDS	National Poison Data System
US	United States

Definition of Term(s)

Retrospective non-interventional study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.
Post Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
National Poison Data System (NPDS) Abuse	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.
National Poison Data System (NPDS) Misuse	An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.
Non-Medical Use of Prescription Drugs (NMU-Rx) Non-Medical Use	Positive response to “used without a doctor's prescription or for any reason other than what was recommended by your doctor”
Non-Medical Use of Prescription Drugs (NMU-Rx) Abuse	Positive response to “used without a doctor's prescription or for any reason other than what was recommended by your doctor” for the specific reason “for enjoyment/to get high”
Non-Medical Use of Prescription Drugs (NMU-Rx) Misuse	Positive response to “used without a doctor's prescription or for any reason other than what was recommended by your doctor” for the specific reason “to self-treat my pain” or “to treat a medical condition, other than pain”

7. BACKGROUND AND RATIONALE

Loperamide is a μ-opioid agonist that is used as a medicine for symptomatic treatment of diarrhea. It is available in oral dosage forms both as prescription-only and over-the-counter medicines. In the past few years there has been an increase in the number of reports concerning the intentional misuse of massive doses of loperamide to self-treat opioid withdrawal or to induce euphoria [1–8]. The use of loperamide in this way can cause serious heart problems including sudden death [1, 9]. The increase in the abuse/misuse of loperamide in the US is concerning and requires additional investigation to further investigate this potential public health risk.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question

This study aims to characterize the abuse and misuse of loperamide in the US through the evaluation of two independent surveillance data systems.

Objectives

The objectives of this study are:

1) to describe abuse and misuse of loperamide as reported to the National Poison Data System (NPDS)

2) to describe non-medical use of loperamide as reported via an ongoing online survey of Non-Medical Use of Prescription Drugs (NMU-Rx) by a general adult population sample.

Primary Objectives

The primary objectives of this study are to quantify abuse, misuse, and non-medical use rates of loperamide in the US as reported to two independent data sources. The rates will be adjusted for population as well as product sales (surrogate for drug utilization) during the study period.

From the NPDS data source, the following primary objectives will be studied:

- Population-based rate of loperamide abuse as reported to NPDS
- Sales-based rate of loperamide abuse as reported to NPDS
- Population-based rate of loperamide misuse as reported to NPDS
- Sales-based rate of loperamide misuse as reported to NPDS

From the NMU-Rx data source, the following primary objectives will be studied:

- Population-based rate of loperamide non-medical use as reported to NMU-Rx
- Sales-based rate of loperamide non-medical use as reported to NMU-Rx

Secondary Objectives

The secondary objectives are to further characterize the patient population reporting abuse, misuse, or non-medical use of loperamide and identify potential risk factors in this population.

- Describe the populations at-risk for the misuse and abuse of loperamide and associated outcomes as reported to NPDS.

- Describe the populations at-risk for non-medical use of loperamide and potential risk factors as reported to NMU-Rx.

9. RESEARCH METHODS

9.1. Study Design

This is an evaluation of existing data sources to study the real-world abuse, misuse, and non-medical use of loperamide. Aberrant behaviors such as abuse and misuse are difficult to study and are not reliably detected during prospective randomized clinical trials. Hence the use of medical records recorded during medical management of loperamide exposures reported to US poison centers via NPDS as well as an online confidential survey of non-medical use of prescription and other drugs via NMU-Rx is a more valid approach than using randomized control trials for this purpose. These data adjusted for population and product sales (surrogate of drug utilization) provide information on both the overall public health burden as well as the overall risk associated specifically with loperamide-containing products. Further characterization of the at-risk population from both data sources will be included as well as potential risk factors identified by comparing to a negative control group from the NMU-Rx data source.

9.1.1. Overview of Study Design

This is a retrospective, non-interventional study to document abuse, misuse, and non-medical use of loperamide in the US as reported to two independent surveillance systems (secondary data sources).

Regional poison centers throughout the US provide medical management of exposures to pharmaceutical and non-pharmaceutical substances. Data are collected using a standardized coding system into local databases at each regional poison center. Data are then uploaded in near real-time to the NPDS, which serves as a national repository of all US exposures. Only data collected per standard work will be utilized in this study.

For this study, NPDS will be queried for all exposures to loperamide-containing products from 2012 to 2017. This retrospective data set will be characterized by demographics, exposures characteristics, products/substances involved, and associated medical outcomes. These data will be further stratified by those reporting loperamide abuse and loperamide misuse.

National sales data for loperamide products will be obtained from IRI (Chicago, IL). Sales data will be used as a surrogate of drug utilization and allow for adjustment to changes in product availability during the study period. Rates of exposure per dose unit sold will be calculated. These rates will be used to evaluate the magnitude of the risk associated with misuse and abuse of loperamide.

9.1.2. Rationale for Study Design Elements

This retrospective observational study provides characteristics and associated outcomes of actual exposures to loperamide reported across the US as well as from self-report of non-medical use via an online survey of the general population. These sources collect information not available through other sources, including behavior that is aberrant and unlikely to be reported during randomized controlled trials.

As there is no measure of actual doses administered for nonprescription products like loperamide, sales data serve as a surrogate for availability and approximate measure of the number of potential exposures to a given product.

9.2. Setting and Patient Population

For the NPDS data, these are exposures to loperamide that occurred in the US that resulted in contact with a poison center for the purpose of medical management assistance between 2012 and 2017. Contact may be initiated by the public or healthcare professionals. These include patients of all ages. This secondary data source is then accessed retrospectively to characterize loperamide exposures.

The data collection period for the 2016 NMU-Rx Program was July-August 2016. This survey is an ongoing survey conducted independently of this study. Non-probability quota sampling was used to provide a proportional distribution of survey respondents across regions of the US and an approximately equal distribution of males and females within each region. Survey respondents were recruited through an online survey panel company which sends email invitations to complete surveys in exchange for modest compensation.

9.2.1. Selection Criteria

Each potential patient must satisfy the following criteria to be eligible for data collection in this study:

NPDS query criteria include:

1. Exposure to at least one loperamide-containing product.

2. Exposure occurred between 01 January 2012 and 31 December 2017.

NMU-Rx query criteria include:

1. Completion of the 2016 NMU-Rx survey.

2. Residing in the US at the time of survey completion.

9.3. Variables

Variables collected by NPDS included in this protocol for evaluation include the following list.

- Demographic data including age and gender
- Exposure characteristics including product and other substances involved and site of exposure
- Route of exposure
- Outcome variables including management site (healthcare facility or not), level of healthcare facility (if healthcare facility care is received), clinical effects, and medical outcome

Variables collected by NMU-Rx included in this protocol for evaluation include the following list:

- Demographics including age, gender, ethnicity/race
- Population characteristic including history of pain, substance abuse treatment, assessment of risk of abuse severity (DAST-10) and number of drugs/drug classes used non-medically
- Lifetime use, non-medical use of loperamide
- Frequency of recent non-medical use of loperamide (number of days in past 7, 30, 90 days)
- Reason for non-medical use
- Route of administration
- History of illicit drug use

9.4. Data Sources

9.4.1. National Poison Data System (NPDS)

The NPDS dataset of loperamide exposures reported from 2012 through 2017 will be utilized as a secondary data source. Exposures are defined as any 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. Data for each exposure is collected at regional poison centers into medical record systems and continuously uploaded to NPDS. These medical record systems are designed with standardized fields and field definitions, so the type of data collected is consistent across poison centers. Data edit checks are implemented at the time of data upload to NPDS to ensure the compliance of data. All poison center personnel who manage exposures and document the records receive specific training on how to obtain the most precise information from callers, which include both non-medical professionals (e.g., patients and caregivers) and healthcare providers. Every substance reportedly involved in an exposure is assigned a code from Poisindex® which is a database of over 350,000 commercial products, chemicals, drugs, toxic plants, and animals. In addition to these tools, all poison centers employ local quality assurance processes that ensure the consistency, accuracy, and completeness of the data.

9.4.2. Non-Medical Use of Prescription Drugs (NMU-Rx) Program

The NMU-Rx Program is a large-scale, repeated, cross-sectional, self-administered online survey. The NMU-Rx Program was designed to study non-medical use (NMU) of medications among the general population and to characterize associated behaviors and outcomes. This detailed questionnaire is used to gather information about respondent demographics, lifetime use and NMU of prescription and over-the-counter drugs, frequency of NMU, reasons for NMU, route of administration for NMU, source of drug acquisition for NMU, and price paid through illicit channels. Lifetime NMU on the questionnaire is defined as ever using the product for any reason other than what was recommended by your doctor/dentist/pharmacist/the package insert. The questionnaire also gathers information about tobacco, alcohol, and illicit drug use, substance abuse treatment, history of chronic and acute pain, mental health, and doctor shopping. Illicit drug use includes any of the following: cannabis, cocaine powder, crack cocaine, ecstasy (e.g. MDMA), gamma-Hydroxybutyrate (GHB)/gamma-Butyrolactone (GBL), non-pharmaceutical amphetamine (e.g., speed), non-pharmaceutical fentanyl (e.g., China white, Apache, China girl, etc.), heroin, ketamine, and mephedrone.

Survey respondents also complete the DAST-10 if they report lifetime NMU of any prescription or over-the-counter medication, or any lifetime use of an illicit drug [10]. This scoring system measures the degree of problems related to drug abuse. DAST-10 scores were categorized according to the degree of problems related to drug abuse: None (0), Low (1-2), Moderate (3-5), Substantial (6-8), and Severe (9-10).

9.4.3. United States (US) Census

The US Census 2010 data will be used to calculate population based rates.

9.4.4. IRI

IRI is a commercially available data source providing point of sales data for loperamide products. IRI (Chicago, IL) provides nationwide estimates of volume and unit sales for over-the-counter products. National sales data for loperamide products will be obtained, used as a surrogate of drug utilization and allow for adjustment to changes in product availability during the study period. Rates of exposure per dose unit sold will be calculated.

A Data Monitoring Committee is not required as this study only uses secondary data sources.

9.5. Study Size

NPDS is a secondary data source which relies on spontaneous reporting, hence the convenience sample (all reported exposures) will be used in the analyses. Approximately 1200 loperamide exposures are reported to NPDS each year. Up to 7800 exposures for the 2012 to 2017 study period are expected to be included.

Over 30,000 survey participants completed the NMU-Rx survey during the 2016 launch. The full sample will be used to compare patients who did and did not report non-medical use of loperamide.

No formal hypotheses are to be tested hence power calculations are not applicable.

9.6. Data Management

All data used in this study are considered secondary data sources. Data management specific to this protocol is limited to the receipt and validation of provisioned data.

The NPDS data are provided by the American Association of Poison Control Centers in Excel worksheets. An analysis dataset is then created in SAS and validated using internal standard operating procedures. All analyses are performed in SAS or R software and validated using internal standard operating procedures.

The locked NMU-Rx analysis dataset is accessed directly via SAS.

9.7. Data Analysis

All calculations and analyses will be conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

9.7.1. Patient Stratification

For the NPDS analyses, patients will be stratified by those who report intentional abuse or misuse and those who report another reason for exposure.

For the NMU-Rx analyses, respondents will be stratified by NMU of any survey medication, NMU of loperamide, and NMU of loperamide plus other survey medication.

9.7.2. Main Summary Measures

Demographic characteristics for both NPDS and NMU-Rx will be summarized using descriptive analysis. Mean and standard deviation or median and interquartile range (IQR) will be calculated for continuous variables. Frequencies and proportions will be calculated for categorical variables.

For NPDS, the main summary measures will be patient demographics, exposure characteristics, level of healthcare facility, and medical outcome.

For NMU-Rx, the main summary measures will be respondent demographics, respondent characteristics, lifetime use and non-medical use of loperamide, frequency of recent non-medical use of loperamide, as well as reason and route of non-medical use.

9.7.3. Main Statistical Methods

Descriptive statistics only are utilized in this study; no formal statistical analyses are planned.

9.7.4. Missing Values

Not applicable.

9.8. Quality Control

Quality control measures are in place for the initial collection of NPDS data at each of the regional US poison centers. The data received from both NPDS and NMU-Rx as secondary data sources are validated using standard operating procedures.

9.9. Limitations of the Research Methods

Not all exposures are reported to US poison centers thus abuse and misuse of loperamide presented are reported rates, not actual rates. Both cumulative rates as well as rate trends during the study period are evaluated. NPDS data are self-reported exposures. Regional poison centers train personnel to obtain the most precise information from callers, which include both non-medical professionals (e.g., patients and caregivers) and healthcare providers. The medical record systems used by regional poison centers are designed with standardized fields and field definitions, so the type of data collected is consistent across poison centers. Data edit checks are implemented at the time of data upload to NPDS to ensure the accuracy of data.

NMU-Rx relies on self-report. This may include recall bias in relation to lifetime use, lifetime non-medical use, and frequency of non-medical use reported. While the survey is confidential, it is unknown if that completely mitigates reporting bias associated with aberrant behaviors. NMU-Rx relies on a sample from an online survey company. The representativeness of the survey panel of the general adult population is in the process of being evaluated.

There is no measure of the number of people exposed to over-the-counter products like loperamide, but IRI data provide national estimates of product sales which will be used as a surrogate in the analysis plan.

10. PROTECTION OF HUMAN SUBJECTS

Designation of this protocol as non-human subjects research was received by the Colorado Multiple Institutional Review Board on 09 December 2016. This protocol meets the criteria for non-human subjects research because no human subject contact is required to complete this study nor are any patient identifying data being obtained. All data used in this study are considered secondary data sources.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable for NPDS and NMU-Rx. These are data extracted electronically from secondary data sources and will not be reviewed as individual cases. If accessed, abstracts of fatality reports associated with loperamide will be submitted to the Company's Consumer Care Center within 24 hours via secure exchange, MBox https://mboxnaprd.jnj.com/#/MCCUS_CCA_CCC_Rocky_Mountain_Loperamide/ .

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a study report generated by the sponsor, which will contain data collected from all data sources identified in the study protocol. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator) shall be the property of the sponsor as author and owner of copyright in such work.

13. REFERENCES

1. FDA. Loperamide (Imodium): Drug Safety Communication - Serious heart problems with high doses from abuse and misuse. 2016. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm505303.htm
2. Daniulaityte R et al. "I just wanted to tell you that loperamide WILL WORK": a web-based study of extra-medical use of loperamide. *Drug Alcohol Depend*. 2013;130(1-3):241-4. http://dx.doi.org/10.1016/j.drugalcdep.2012.11.003
3. Marraffa JM et al. Cardiac conduction disturbance after loperamide abuse. *Clin Tox*. 2014;52(9):952–7. http://dx.doi.org/10.3109/15563650.2014.969371
4. MacDonald R et al. Loperamide dependence and abuse. *BMJ Case Rep*. 2015. http://dx.doi.org/10.1136/bcr-2015-209705
5. Spinner HL et al. Ventricular tachycardia associated with high-dose chronic loperamide use. *Pharmacotherapy*. 2015;35(2):234-8. http://dx.doi.org/10.1002/phar.1540
6. Lasoff DR et al. Ventricular dysrhythmias from loperamide misuse. *J Emerg Med*. 2016;50(3):508-9. http://dx.doi.org/10.1016/j.jemermed.2015.11.017
7. Hughes et al. A retrospective review of a US Poison Center's experience with loperamide-induced cardiotoxicity. *J Med Toxicol*. 2016;12(3):29 http://dx.doi.org/10.1007/s13181-016-0538-8 see also: http://www.acmt.net/_Library/2016_ASM_Posters/Abstract_78.pdf
8. Wightman RS et al. Not your regular high: cardiac dysrhythmias caused by loperamide. *Clin Tox*. 2016;54(5):454–8. http://dx.doi.org/10.3109/15563650.2016.1159310
9. Kang J et al. Proarrhythmic mechanisms of the common anti-diarrheal medication loperamide: revelations from the opioid abuse epidemic. *Naunyn Schmiedebergs Arch Pharmacol*. 2016. http://dx.doi.org/10.1007/s00210-016-1286-7
10. Skinner, H. A. (1982). The Drug Abuse Screening Test. *Addictive Behavior*, 7(4),363–371.

ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Standalone Documents

None

Annex 1.2: Regulatory Documentation

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, where applicable. A study may not be initiated until any applicable local regulatory requirements are met.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☒	☐	☐	9
1.1.2 The objectives of the study?	☒	☐	☐	9
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	11
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	11-13
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	11-13
2.2.2 Age and sex?	☒	☐	☐	11-13
2.2.3 Country of origin?	☒	☐	☐	11
2.2.4 Disease/indication?	☐	☐	☒	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	13

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9
3.2 Is the study design described? (e.g., cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	10
3.3 Does the protocol describe the measure(s) of effect? (e.g., relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	14
3.4 Is sample size considered?	☒	☐	☐	13
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	12
4.1.2 Endpoints? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	9
4.1.3 Covariates?	☒	☐	☐	12
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	12
4.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9
4.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	12
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g., International Classification of Diseases [ICD]-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	9
4.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	12
4.4 Is the linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g., operational details for defining and categorising exposure)	☒	☐	☐	10
5.2 Does the protocol discuss the validity of exposure measurement? (e.g., precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☒	☐	☐	10
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	9
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	15

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address: 7.1.1 Selection biases?	☒	☐	☐	15
7.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
7.2 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	15
7.3 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	15

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	14
8.2 Is the choice of statistical techniques described?	☐	☐	☒	
8.3 Are descriptive analyses included?	☒	☐	☐	14
8.4 Are stratified analyses included?	☒	☐	☐	14
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility, and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	15
9.2 Are methods of quality assurance described?	☒	☐	☐	15
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☒	
9.4 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	7
9.5.2 Any progress report?	☐	☐	☒	
9.5.3 End of data collection?	☐	☐	☒	
9.5.4 Reporting? (i.e., interim reports, final study report)	☒	☐	☐	7
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	5
9.7 Are communication methods to disseminate results described?	☒	☐	☐	16
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	15
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

LAST PAGE