REDACTED PROTOCOL

(Survey Instrument was removed to allow unbiased data collection)

NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

Post-Authorisation Safety Study (PASS) Information

Title	Survey of pharmacists to evaluate the effectiveness of the Viagra Connect national additional Risk Minimisation Measure (aRMM) in the United Kingdom (UK)
Protocol number	A1481334
Protocol version identifier	1.2
Date of last version of protocol	13 June 2018
EU Post Authorisation Study (PAS) register number	Study not yet registered. Registration will be performed upon Medicines and Health Products Regulatory Agency (MHRA) approval of protocol
Active substance	Sildenafil citrate
Medicinal product	Viagra Connect Anatomical therapeutic chemical (ATC) Code: G04B E03
Product reference	Viagra Connect 50 mg Film Coated Tablets PL 00165/0392
Procedure number	UK/H/6416/01/DC
Marketing Authorisation Holder (MAH)	Pfizer Consumer Healthcare Ltd
Joint PASS	No

Research question and objectives	To evaluate the effectiveness of the Viagra Connect national aRMM by assessing: • The pharmacists' knowledge of the key risk messages contained in the Viagra Connect training materials; • The pharmacists' participation in the Viagra Connect pharmacist training; • The pharmacists' utilisation of the optional Viagra Connect Pharmacy Checklist at the point of dispensing.
Country(-ies) of study	UK
Author	Joanna (Asia) Lem, MPH Director Pfizer, Inc. 235 East 42nd Street 219/09/01 New York, NY 10017 Dr Janine Collins Senior Director United Biosource Corporation (UBC) Chemin des Coquelicots 16 1214 Vernier Switzerland

Marketing Authorisation Holder(s)

MAH	Pfizer Consumer Healthcare Ltd Ramsgate Road, Sandwich, Kent CT130NJ UK
MAH contact person	Mrs Michelle Riddalls Director, Regulatory Affairs Northern European Cluster Lead Pfizer Consumer Healthcare Ltd Walton Oaks Dorking Road Tadworth Surrey KT20 7NS

This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorised purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
aDCT	Annotated data collection tool
AE	Adverse event
AEM	Adverse event monitoring
aRMM	Additional Risk Minimisation Measure
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CRO	Contract research organisation
CV	Cardiovascular
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4
DCP	Decentralised procedure
EC	Ethics Committee
ED	Erectile dysfunction
EDC	Electronic data capture
EHR	Electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GPP	Good pharmacoepidemiology practices
GVP	Good pharmacovigilance practices
HCP	Healthcare provider
HIV	Human immunodeficiency virus
IEA	International Epidemiological Association
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IT	Information technology
KRM	Key Risk Message
MAH	Marketing Authorisation Holder
MHRA	Medicines and Health Products Regulatory Agency
NAION	Non-arteritic anterior ischemic optic neuropathy
NIS	Non-interventional study
PAS	Post Authorisation Study
PASS	Post-authorisation safety study
PDE-5i	Phosphodiesterase type 5 inhibitor
PGD	Pharmacy group direction
PPIs	Proton pump inhibitors

Abbreviation	Definition
RMS	Reference member state
RPS	Royal Pharmaceutical Society
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SDLC	System development life cycle
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
UAT	User acceptance testing
UBC	United Biosource Corporation
UK	United Kingdom
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Joanna (Asia) Lem, MPH	Director	Epidemiology Worldwide Safety and Regulatory Pfizer Inc.	235 East 42nd Street 219/09/01 New York, NY 10017
Dr. Janine Collins	Senior Director	Safety, Epidemiology, Registries and Risk Management UBC	Chemin des Coquelicots 16 1214 Vernier Switzerland
Dr. Klaus W. Freivogel	Principal Statistician	Biostatistics UBC	UBC (Germany) GmbH
Paul Crossley	Associate Project Director	Clinical Operations UBC	26-28 Hammersmith Grove London, W6 7HA UK
Milena Toncheva	Senior Project Manager	Clinical Operations UBC	26-28 Hammersmith Grove London, W6 7HA UK

Country Coordinating Investigators

Not Applicable. The study is a survey without country coordinating investigators.

3. ABSTRACT

Title:

Survey of pharmacists to evaluate the effectiveness of the Viagra Connect national additional Risk Minimisation Measures (aRMM) in the UK. Version: 1.2, 13 June 2018.

Authors:

Joanna (Asia) Lem, MPH
Director
Epidemiology
Worldwide Safety and Regulatory
Pfizer Inc.
235 East 42nd Street
219/09/01
New York, NY 10017

Dr Janine Collins MBBS, LLM
Senior Director
Safety Epidemiology Registries and Risk Management
UBC
Chemin des Coquelicots 16
1214 Vernier
Switzerland

Rationale and Background

Sildenafil citrate (Viagra®), supplied via prescription, was approved in the United States (US) in 1998, and in the European Union (EU) in 1999 for treatment of erectile dysfunction (ED). A decentralised procedure (DCP) application for non-prescription (ie, behind the counter) 50 mg sildenafil (to be marketed as Viagra Connect 50 mg film-coated tablets) was approved in November 2017.

Pfizer has developed a training programme in the UK for pharmacists, consisting of a training guide with essential information regarding the safe supply of Viagra Connect to the ED patient and an optional checklist which pharmacists can choose to use when a patient requests to purchase Viagra Connect behind the counter. The training guide and the checklist are considered UK national aRMM which, with agreement of the MHRA, will be put in place to minimise the risk of Viagra Connect being sold to patients who may be unsuitable to take the product without prior consultation with their doctor. This training began roll out in February 2018 prior to launch of Viagra Connect in April 2018.

This study will evaluate the effectiveness of these national aRMM activities.

Research Question and Objectives

The overall objective of the study will be to evaluate the effectiveness of the Viagra Connect national aRMM by assessing:

- The pharmacists' knowledge of key risk messages contained in the Viagra Connect Training materials;
- The pharmacists' participation in Viagra Connect pharmacist training;
- The pharmacists' utilisation of the optional Viagra Connect Pharmacy Checklist at the point of dispensing.

Study Design

The study is a cross-sectional, non-interventional web-based survey that will be conducted in the UK. All survey aspects will be conducted anonymously among pharmacists who have received at least one patient request to supply Viagra Connect within the six months preceding the survey administration. The survey will be conducted approximately six months after the drug becomes available behind the counter in UK pharmacies.

Prior to finalisation of the survey, user-testing will be performed with samples of pharmacists. Survey user-testing will assess the clarity of the survey questions as presented to pharmacists, the interest and acceptance of the surveys among all prospective respondents, as well as the flow and ease of completing the surveys. Findings and recommendations from survey pre-testing will be incorporated into the surveys.

Population - "Population" includes the setting and study population

The survey will take place approximately six months after the availability of Viagra Connect in the UK market to allow sufficient time for the following.

Pharmacists must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Willing/consent to participate in this self-administered survey (Answered "Yes" to a survey question asking "Do you agree to proceed with this survey");
- A practicing pharmacist in the UK;
- Received at least one patient face-to-face request to supply Viagra Connect in the past six months.

Variables – include exposures, outcomes, and key co-variates

The questionnaire includes questions/statements that will assess how effectively the pharmacist training has been implemented including, but not limited, to whether or not training has been completed, use of the checklist and knowledge of the key risk messages.

Data Sources

A structured self-administered questionnaire comprised of closed ended questions or statements with multiple response choices (ie, questions or statements asking the pharmacists to choose from a defined list of responses) will be used to collect the survey data.

Study Size

The goal for this survey is a sample size of 200 completed surveys from pharmacists who have received at least one patient request for the supply of Viagra Connect.

Data Analysis

Data collected from the survey will be reported as descriptive statistics. No statistical inferences will be made. Frequency distributions with 95% confidence intervals (CIs) will be calculated for pharmacist's responses to all questions that address the survey objectives. Survey data will be stratified by participating in the training and by other key pharmacist's characteristics if sample sizes are large enough (ie, no less than 25 in the minority group).

Milestones

The study will be initiated following MHRA protocol approval, approximately six months after the launch of Viagra Connect, in April 2018. The training roll out commenced in February 2018. The final study report is anticipated to be completed in July 2019.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned Date
Viagra Connect Approval in UK	November 2017
User Testing of Survey Instrument	December 2017 – February 2018
Roll out of pharmacist training	February 2018
Viagra Connect availability in UK pharmacies	April 2018
Anticipated date of protocol approval	July 2018
Start of data collection for the pilot survey*	July 2018
End of data collection for the pilot survey*	August 2018
Pilot results report and updated survey protocol (if warranted) Submitted to the Agency	October 2018
Feedback from the MHRA (anticipated)	December 2018
Registration in the EU PAS register	December 2018
Start of data collection for full survey (estimated)*	January 2019
End of data collection for full survey (estimated)*	March 2019
Final study report	July 2019

* Contingent upon using the current amended version of the survey questionnaire. The Electronic Data Capture (EDC) development must start 1 April 2018 in order for pilot data collection to start in July 2018.

* Contingent upon the MHRA feedback/approval of final survey protocol. The Anticipated dates for feedback/approval are indicated.

6. RATIONALE AND BACKGROUND

Sildenafil citrate (Viagra®), supplied via prescription, was approved in the US in 1998, and in the EU in 1999 for treatment of ED. A DCP application for non-prescription (ie, behind the counter) 50 mg sildenafil (to be marketed as Viagra Connect 50 mg film-coated tablets) was approved in November 2017 and will be available in pharmacies in April 2018. The UK is the Reference Member State (RMS).

Pfizer believes that the launch of Viagra Connect in the UK, and its availability as a pharmacy medicine, will make it easier for men to seek help at an earlier stage of their ED. Not only will this allow pharmacists to help men to deal with both the physical and emotional impact of ED, but it also creates a good opportunity to engage with men around the wider potential health concerns associated with ED. Most of these men are unaware of the link between ED and cardiovascular disease (CVD).[1]

The pharmacy and trained pharmacist can therefore play a key role in ensuring any CVD issues are identified earlier and that the man is directed to see his doctor for a check-up as soon as possible within 6 months of his initial enquiry, helping to improve his overall health prognosis. The doctor can then help determine the best course of action for the man and his future health management.

Pharmacist role and training

Pharmacists have been identified as having an important role in facilitating and counselling patients to determine suitability for use, and in directing to their doctors those for whom the over the counter sildenafil is unsuitable. Accordingly, Pfizer has developed a training programme in the UK for pharmacists, consisting of a training guide with essential information regarding the safe supply of Viagra Connect to the ED patient and an optional checklist which pharmacists can choose to use when a patient requests to purchase Viagra Connect behind the counter. The training guide and the checklist are considered UK national aRMM which, with agreement of the MHRA, will be put in place to minimise the risk of Viagra Connect being sold to patients who may be unsuitable to take the product without prior consultation with their doctor.

The pharmacy training will be offered in a variety of modalities to ensure the widest opportunity for learning. This will include online resources, regional meetings, printed materials and in-store face-to-face training. The pharmacy training started at the end of February 2018 prior to launch of Viagra Connect in April 2018.

Key Risk Messages for Pharmacists

The training guide and the checklist include risk messages for pharmacists to consider when 1) determining the suitability of a patient for Viagra Connect and 2) other important messages for pharmacists to consider during consultation. The key risk messages (KRMs) extracted from these aRMM tools are presented in two distinct parts below:

Part I: Key risk messages for pharmacists to consider when determining the suitability of a patient for Viagra Connect

1. ***Supply criteria.***

   Viagra Connect is only intended for men 18 years and older who are experiencing ED (ie, difficulty in getting and/or maintaining an erection satisfactory for sexual performance). This product must not be supplied to men who do not have ED.

   Men currently prescribed 50 mg of sildenafil per day can be supplied this product if they meet the criteria for pharmacy supply, provided they do not take more than 50 mg daily. If a man is using a different dose of sildenafil or another ED treatment, he should be referred to his doctor.

2. ***Patients' cardiovascular (CV) health should be considered by a pharmacist when dispensing Viagra Connect.***

   Viagra Connect should not be supplied to patients who answered affirmatively to any question about the potential underlying presence of certain CVDs, including:

   - Have you had a myocardial infarction (heart attack) or stroke within the last 6 months.

- Have you experienced any of the following:
    a. **Uncontrolled** hypertension or hypotension;
    b. **Unstable** angina (chest pain) or arrhythmias;
    c. Valvular heart disease;
    d. Cardiomyopathies;
    e. Blood flow issues (eg, left ventricular outflow obstruction, aortic narrowing or severe cardiac failure).
- Men already advised by a doctor that they are not fit enough for any physical/sexual activity.
- Men who are identified as not fit for sex from the Viagra Connect Checklist, ie, they feel very breathless or experience chest pain with light-to-moderate physical activity, such as walking briskly for 20 minutes or climbing two flights of stairs.

3. Patients' concomitant medication use should be assessed by a pharmacist when dispensing Viagra Connect.

Viagra Connect should not be supplied to a patient who answered affirmatively to any questions pertaining to concomitant medication use which include:

- Nitrates for chest pain;
- Recreational drugs called "poppers" (eg, amyl nitrite);
- Riociguat or other guanylate cyclase stimulators for lung problems;
- Ritonavir for human immunodeficiency virus (HIV) infection;
- Patients not therapeutically stabilised while taking cytochrome P450 3A4 (CYP3A4) inhibitors or alpha-blockers.

4. Pharmacists should ask patients about concomitant conditions.

Viagra Connect should not be supplied to a patient who answered affirmatively to any questions pertaining to patient's concomitant conditions including:

- Previously diagnosed hepatic disease or severe renal impairment;
- Peyronie's disease or other deformation of the penis;
- Loss of vision because of a damage to the optic nerve (such as non-arteritic anterior ischemic optic neuropathy (NAION)) or have an inherited eye disease (such as retinitis pigmentosa);

- Galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption;
- Sickle cell anaemia, multiple myeloma or leukaemia;
- Bleeding disorders or active stomach ulcers.

Part II: Other important key messages for pharmacists to consider during consultation

5. ***Pharmacists should consider possible causes of ED.***

   Pharmacists should consider possible causes of ED such as undiagnosed depression, anxiety, diabetes, atherosclerosis, excessive alcohol use and taking certain medicines. Examples of classes of medicines that have the potential to precipitate or cause ED include diuretics, anti-hypertensives, corticosteroids, anticonvulsants and recreational drugs. Whilst it may be appropriate to supply the product, pharmacists should provide lifestyle advice and/or recommend to follow-up with a doctor.

6. ***Pharmacists should advise Patients to STOP TAKING Viagra Connect and seek medical attention immediately if they experience any serious side effects.***

   Men should be advised to STOP TAKING Viagra Connect and seek medical attention immediately if they experience any of the following symptoms: chest pains, a persistent and sometimes painful erection that lasts longer than 4 hours, a sudden decrease or loss of vision, an allergic reaction, serious skin reactions, seizures or fits.

7. ***Pharmacist should advise all men who seek to purchase Viagra Connect to consult their doctor within 6 months of their first behind the counter purchase.***

   Erectile Dysfunction can be associated with a number of contributing conditions (eg, hypertension, diabetes mellitus, hypercholesterolemia or CVD. As a result, all men with ED should be advised to consult their doctor as soon as possible within 6 months for a clinical review of potential underlying conditions and risk factors associated with ED. Pharmacists should provide the patient with the completed tear off slip contained in the checklist for the patient to give to his doctor.

8. ***Pharmacists should advise men who have not been supplied the product to consult their doctor.***

   Most men who are not suitable to be given Viagra Connect should be advised to go to their doctor for a review, as their ED might be caused by another condition such as high blood pressure or heart disease. Pharmacists should provide such patients who have not been supplied Viagra Connect with the completed tear off slip contained in the checklist for the patient to give to his doctor.

Please see Annex 3 for the full Viagra Connect Pharmacy training materials.

Evaluation of Effectiveness

This evaluation of effectiveness of the Viagra Connect aRMM is a cross-sectional survey of pharmacists in the UK who have received at least one patient request to supply Viagra Connect. As such this survey will assess process indicators for the evaluation of the effectiveness of the aRMM.

In deciding the best methodology for assessing aRMM effectiveness, Pfizer had considered both process and outcome indicators. However, assessment by means of outcome indicators was not considered feasible in this setting for the following reasons:

- The typical approach to assess outcome indicators in the prescription setting would be to use electronic health records (EHR) or claims databases to evaluate, in an unbiased manner, that the appropriate patients are receiving a product and/or to assess other measures of compliance and safety. However, in the behind the counter setting, no such patient database exists that could link behind the counter purchases with health data and therefore this data must be obtained by direct questioning of the patient;

- Self-report of outcome indicators (ie, "Did the patient report being sold Viagra Connect in a pharmacy despite being found unsuitable?") may not allow the assessment of outcome indicators with adequate precision and in an unbiased manner and may be a substantial barrier to scientific interpretability. However, the feasibility of conducting a patient survey for exploratory purposes will be assessed.

This non-interventional study (NIS) is designated as a PASS and is a commitment to the MHRA.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of the study will be to evaluate the effectiveness of the Viagra Connect national aRMM by assessing:

- The pharmacists' knowledge of key risk messages contained in the Viagra Connect Training materials;

- The pharmacists' participation in Viagra Connect pharmacist training;

- The pharmacists' utilisation of the optional Viagra Connect Pharmacy Checklist at the point of dispensing.

8. RESEARCH METHODS

8.1. Study Design

The study is a cross-sectional, non-interventional web-based survey that will be conducted in the UK. All survey aspects will be conducted anonymously among pharmacists who have received at least one patient request to supply Viagra Connect within the six months preceding the survey administration. The survey will be conducted approximately six

months after the drug becomes available behind the counter in UK pharmacies. This will allow sufficient time for the pharmacists to participate in the training and gain experience with dispensing the drug and counselling patients.

Prior to finalisation of the survey, user-testing will be performed with samples of pharmacists. Survey user-testing will assess the clarity of the survey questions as presented to pharmacists, the interest and acceptance of the surveys among all prospective respondents, as well as the flow and ease of completing the surveys. Findings and recommendations from survey pre-testing will be incorporated into the surveys.

The pharmacist survey will be hosted on-line and, pending the results of a pilot study, is expected to take approximately 20-30 minutes to complete. The pilot study will monitor the time taken to complete the survey. The survey questions can be found in Annex 3.

8.2. Setting

The protocol is expected to be approved in July 2018, around the same time as Viagra Connect will be available in pharmacies across the UK. The pharmacist training started at the end of February 2018.

The survey will take place approximately six months after the availability of Viagra Connect in the UK market to allow sufficient time for the following:

- Pharmacists to complete the training, gain experience with dispensing the product over the counter and counselling patients;

- A pilot survey to be conducted and for the findings to be incorporated into the final version of the survey protocol.

8.2.1. Recruitment

Since one of the objectives of the survey is to evaluate to what extent the pharmacist training has been implemented, the survey recruitment plan will follow the roll-out of the pharmacist training to the extent feasible.

For the purpose of issuing survey invitations, a random sample of pharmacists will be selected by Precision Marketing a vendor acting on behalf of Pfizer Consumer Healthcare Ltd, from one of the following sources:

- 1. If feasible, the complete contact lists of all pharmacies (the majority of which would include the names and contact information for pharmacy owners or managers) for the purpose of training implementation will be obtained by UBC from the training supply vendor who has been tasked to implement the pharmacist training.

- If (1.) above is found to be insufficiently feasible, an alternative recruitment methodology will be explored:

- 2. Lists of pharmacists from panels used for market research will be obtained.

Prior to obtaining the pharmacy lists or contacting any pharmacists from any of the above sources, it will be verified that all applicable data protection requirements have been complied with. The random sample of pharmacists will be eligible to be invited in the survey regardless of whether they had already completed the training or not. Invitations will be sent by postal mail by Precision Marketing. The invitation will describe the purpose of the survey, how the data will be reported and to whom and the measures that will be taken to preserve their confidentiality. A link to the electronic survey will be provided in the invitation.

Precision marketing, once the initial invite letter has been sent, will follow up initially via email, and if there is still no response, then will follow up via phone. If the target sample size has not been reached after the survey has reached end of enrolment, additional random sample may be selected (if available) from the sources described above and invited to participate. The size of that additional sample will be driven by the sample size achieved already.

8.2.2. Inclusion Criteria

Pharmacists must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Willing/consent to participate in this self-administered survey (Answered "Yes" to a survey question asking "Do you agree to proceed with this survey");
- A practicing pharmacist in the UK;
- Received at least one patient face-to-face request to supply Viagra Connect in the past six months.

8.2.3. Exclusion Criteria

Pharmacists meeting the following criteria will not be included in the study:

- Pharmacists who answer affirmatively to a question asking if they or their immediate family members currently work for Pfizer, another pharmaceutical company, or the survey vendor (UBC), the European Medicines Agency (EMA) or the MHRA;
- Pharmacists who work only as on-line pharmacists and who do not participate in face-to-face consultations.

8.3. Variables

The questionnaire includes questions/statements that will assess how effectively the pharmacist training has been implemented including but not limited to whether or not training has been completed, use of the checklist and knowledge of the key risk messages. Specifically, the variables to be collected include:

a. Screening questions;

b. *Pharmacist characteristics;*

c. *Pharmacist's experience with Viagra Connect;*

d. *Pharmacist's knowledge of key risk messages;*

e. *Source of knowledge of the key risk messages pertaining to Viagra Connect;*

f. *Pharmacists' participation in Viagra Connect pharmacist training;*

g. *Utilisation of pharmacist checklist at the point of dispensing;*

h. *Utilisation of patient record tear off slip;*

i. *Attitude towards Viagra Connect pharmacist training material and patient counselling.*

8.4. Data Sources

A structured self-administered questionnaire (Annex 3) comprised of closed-ended questions or statements with multiple response choices (ie, questions or statements asking the pharmacists to choose from a defined list of responses) will be used to collect the survey data.

The survey is designed to be completed voluntarily and is programmed to encrypt all identifiable information and respondent identifiers, which are stored separately within the database. The collection of any personal identifying information from respondents will be stored separately and only used for the processing of the respondents honorarium where applicable. Each participant will be given a unique code to access the survey. Each code is deactivated upon its use to prevent the code from being used to complete the survey multiple times. Once the participant has started the survey, it must be completed and there is no opportunity to return to the survey at a later time. The participant will be permanently logged out of the survey following 30 minutes of inactivity. Each code is randomly assigned. Once the survey is completed, it will not be possible to link the survey to an individual. The participants do not have to actively 'decline to complete the survey'. Therefore, there is no ability to track which participants are actively deciding to not complete the survey. This survey design encourages participation and answering honestly by ensuring that the responses are completely anonymous.

Following a question to obtain the pharmacist's consent to participate, the survey will next include a screening module with questions to confirm eligibility. Depending on the answers to the screening questions, survey participation will either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent will continue with survey participation.

8.5. Study Size

The goal for this survey is a sample size of 200 completed surveys from pharmacists who have received at least one patient request for the supply of Viagra Connect. A sample size of 200 has been selected taking into account statistical and practical considerations of participation in such a survey.

The following table shows the precision of the estimated level of understanding key risk messages with 95% CIs for a fixed sample size of 200 completed surveys. Two-sided CIs are used to indicate that for an estimated comprehension level, the true population level of comprehension is at least as high as the lower limit of the 95% CI, and may be as high as the upper limit of the 95% CI.

Table 1. Precision of Estimated Comprehension Rate with a Sample Size of 200 (2-sided 95% CI) (Clopper Pearson Exact Method)

	Estimated CI		
Estimated Rate of Understanding	**Low**	**High**	**Precision**
50%	42.9%	57.1%	-7.1%; +7.1%
55%	47.8%	62.0%	-7.2%; +7.0%
60%	52.9%	66.8%	-7.1%; +6.8%
65%	58.0%	71.6%	-7.0%; +6.6%
70%	63.1%	76.3%	-6.9%; +6.3%
75%	68.4%	80.8%	-6.6%; +5.8%
80%	73.8%	85.3%	-6.2%; +5.3%
85%	79.3%	89.6%	-5.7%; +4.6%
90%	85.0%	93.8%	-5.0%; +3.8%
95%	91.0%	97.6%	-4.0%; +2.6%

CI = Confidence interval.

8.6. Data Management

UBC's proprietary EDC System will be used for this programme and will be designed to collect survey data for evaluation and analysis. This system will be validated and EudraLex Annex 11 compliant.

All data collected during the survey will be held confidentially by UBC. The EDC system used for data collection encrypts all respondent-identifying information, and respondent identifiers are stored separately from the survey responses. The survey is programmed to ensure respondents cannot skip ahead and cannot go back to modify answers and will only allow for missing data when caused by skip patterns. In instances where there are missing data not due to skip patterns (that is, respondent did not complete the survey), the respondent will not be considered in the analysis. A completed survey is defined as a survey in which all questions are answered and none are skipped other than due to skip logic.

Skip logic as well as the ability to select only one response or multiple responses are part of the programming for the survey administration and minimise the occurrence of data entry errors. There will be no queries to respondents for this project.

8.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term DCT should be understood to refer to an electronic data record, or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included participant. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The study vendor, United BioSourceLLC. shall ensure that the DCTs are securely stored at the vendor site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The study vendor (ie, United Biosource Corporation) has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that the DCTs are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs must be affirmed by the study vendor or by an authorized staff member to attest that the data contained on the DCTs are true. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. Due to the nature of this survey there are no source documents which require revision. However, UBC, will ensure that every survey completed through the electronic DCT complies with ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

In some cases, the DCT may also serve as the source document. In these cases, a document should be available at the vendor site and at Pfizer that clearly identifies those data that will be recorded on the DCT, and for which the DCT will stand as the source document.

8.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the study vendor (ie, United BioSource Corporation) agrees to keep records, including the identity of all participating pharmacists (sufficient information to link records, eg, DCTs and hospital records), all original signed informed consent documents (if applicable), copies of all DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the vendor according to local regulations or as specified in the vendor contract, whichever is longer. The vendor must ensure that the records continue to be stored securely for so long as they are retained.

If the study vendor becomes unable, for any reason, to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study vendor records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The study vendor must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Data Analysis

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

Data collected from the survey will be reported as descriptive statistics. No statistical inferences will be made. Frequency distributions with 95% CIs will be calculated for pharmacist's responses to all questions that address the survey objectives. Survey data will be stratified by participating in the training and by other key pharmacist's characteristics if sample sizes are large enough (ie, no less than 25 in the minority group).

The following will be reported as part of the analysis:

- Survey administration statistics:
    - Number of pharmacists to whom at least one invitation has been sent;
    - Total number of invitations sent;
    - Contact rate: number of invitations sent as a proportion of total pharmacist pool;
    - Number of pharmacists screened for participation (pharmacists who respond to the survey invitation and provide the unique code);
    - Response rate: number of pharmacists screened for participation as a proportion of number of pharmacists who received at least one invitation;
    - Number of pharmacists eligible for participation following screening;
    - Number of pharmacists ineligible for participation and reason for being ineligible;
    - Eligibility rate: number of pharmacists eligible for participation as a proportion of those screened;

- Number of pharmacists completing the survey;
- Cooperation rate: number of pharmacists completing the survey as a proportion of those eligible following screening;
- Refusal rate: number of pharmacists invited less the number of pharmacists screened for participation.

- Demographic and other pharmacist characteristics of the survey completers:
  - Gender;
  - Age;
  - Time practicing as pharmacist;
  - Location of pharmacy (urban or rural);
  - Type of pharmacy (pharmacy chain or independent);
  - Experience with requests for Viagra Connect in the preceding six months.
- Responses to the questions pertaining to the knowledge about the key risk messages associated with Viagra Connect.
- Distribution of the number of correct responses by key risk message and by key risk message group, ie, the number of respondents who answered 0, 1, 2, etc. questions correctly). 95% CI will be calculated for the percentages of respondents who answered the targeted 70% of the questions correctly in each KRM group individually and who reached the target in both KRM groups.
- Response to questions on the source of knowledge of the key risk messages.
- Responses to questions pertaining to participation in the Viagra Connect pharmacist training.
- Responses to questions pertaining to the use of the Viagra Connect pharmacist's checklist.
- Responses to questions pertaining to the use of the Viagra Connect patient record tear off slip.
- Responses to questions pertaining to attitude towards patient counselling.
- Responses to questions pertaining to attitude towards Viagra Connect pharmacist's training.

The table below shows the number of questions pertaining to each of the Key Risk Message Questions.

Table 2. Number of Questions Pertaining to Each of the Key Risk Message Questions

Key Risk Message	Question Number	Number of Questions/Response Options within the Main Question
Part I: Key risk messages for pharmacists to consider when determining the suitability of a patient for Viagra Connect		
Supply Criteria	13	4
Patients Cardiovascular health should be considered	14	3
	15	9
Patients' concomitant medication use should be assessed	16	8
Pharmacists should ask patients about concomitant conditions	17	4
Total number of questions pertaining to KRM Part I	**5**	**28**
Part II: Other important key messages for pharmacists to consider during consultation		
Causes of ED	18	8
Undiagnosed depression, anxiety or alcohol abuse	19	2
Advise patients to consult doctor	20	4
Advise patients when to stop taking Viagra Connect	21	9
Total number of questions pertaining to KRM Part II	**4**	**23**

8.8. Quality Control

Data will be collected using a secure online EDC system that has been developed and fully validated. A rigorous System Development Life Cycle (SDLC) is used for validation that complies with 23 internal information technology (IT) Standard Operating Procedures (SOPs) of UBC. Unit testing and formal validation occur on all appropriate systems and components during the build stage. The SDLC is fortified with SOPs addressing validation for all clinical and risk minimisation-related applications. The Internet-based repository will be used to store survey data and other relevant programme information. The system is EudraLex Annex 11 (and 21 CFR Part 11 in the US) compliant for the entry, storage, manipulation, analysis and transmission of electronic information. This platform ensures compliance with all relevant regulatory guidelines. Respondent-identifying information is stored separately from survey data.

The system will be reviewed by Quality Control and simulated users [User Acceptance Testing (UAT)] prior to implementation.

At the completion of data collection, data will be extracted from the EDC and mapped to SAS (Statistical Analysis Software)® datasets (SAS V9.1.3 or higher). The mapping of the EDC data to SAS datasets ('original' datasets) as defined in the Annotated Data Collection Tool (aDCTs), as well as the programming of the analysis datasets and summary tables, will be validated by double programming and Quality Control per SOP.

UBC has an IT Quality Assurance Group that is responsible for managing and overseeing system/application development and validation, as well as related compliance functions.

8.9. Limitations of the Research Methods

The survey methodology has some inherent limitations, including the following:

8.9.1. Absence of Baseline

The Sponsor's ability to measure the extent to which pharmacist knowledge or behaviours can be attributed to the pharmacist training will be limited, given that the training will be put in place at the time of initial marketing authorisation, and therefore no baseline measures of knowledge or behaviour among pharmacists in the absence of the training will be available. However, knowledge and behaviour of responding pharmacists reporting having taken the pharmacist training can be compared to those responding pharmacist who reported not participating in the training, provided that the numbers of respondents across both strata are sufficient.

8.9.2. Product Familiarity

There is a possibility that there is a difference between those pharmacists who choose to take the voluntary training and those who do not. Pharmacists who are already familiar with the product and already have some knowledge of the key risk messages may be less likely to undertake the training than those who have little knowledge of the product.

8.9.3. Recollection

The pharmacists will be asked if they recall having received the training and to recall key information from the training. Although it is generally accepted that surveys should be performed within a 6 to 12 month period after educational material distribution and this survey will be conducted approximately six months after product availability, some pharmacists may not recall having taken the training or the training's content. Similarly, they will be asked to recall their encounters with patients requesting Viagra Connect and there is the possibility of inaccurate recall.

8.9.4. Selection Bias

The potential for selection bias of pharmacists participating in a survey is an inherent bias/limitation to any study based on volunteer participation. Those pharmacists who participate may differ in an important way from those who choose not to participate. No data will be available to compare characteristics of those who do and do not participate. A further selection bias could occur if only pharmacists who have supplied Viagra Connect were able to participate. This bias has been minimised by allowing all pharmacists who have received at least one patient request for Viagra Connect to participate.

8.9.5. Social Desirability

As in all surveys, this survey may promote social desirability bias which refers to the tendency of pharmacists to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, eg, pharmacists may report

counselling consumers appropriately or refusing them Viagra Connect if found unsuitable when in reality they are not adherent to the recommendations in the training material. It will not be possible to assess this behaviour in the survey.

8.10. Other Aspects

None.

9. PROTECTION OF PERSONAL DATA

This survey is a non-interventional PASS that has been prepared in order to comply with Article 21a.(b) of Directive 2001/83/EC and the request of the MHRA to evaluate the effectiveness of the Viagra Connect national aRMM. The survey protocol will be reviewed and approved by the MHRA prior to study commencement.

All data collected during the survey will be held confidentially by UBC, the CRO contracted by Pfizer, and used only for the purposes stated in the survey instructions.

UBC's proprietary system, EDC, will be used to collect survey data for evaluation and analysis. All personal data relating to the participants will remain in the UK and not transmitted outside of the UK. The EDC system used for data collection encrypts all identifiable information and respondent identifiers, which are stored separately from the survey responses. Respondent names and addresses are collected only for the purposes of mailing a thank you letter and payment of a voluntary compensation consistent with fair market value, if applicable, after the survey is completed.

The inclusion and exclusion criteria mentioned in Sections 8.2.2 and Section 8.2.3 above will be checked through the pharmacist response to a specific question addressing this criterion at hand, before he/she can start responding the rest of the survey questions.

Pfizer will not have access to any participants' personal identifiable data.

Each participant will be given a unique code to access the survey randomly. Once the survey is completed, it will not be possible to link the survey to an individual.

The agreement with the agency will be in compliance with the UK data protection regulations.

9.1. Participant Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored by Precision Marketing, a vendor assisting the MAH with pharmacist recruitment, in encrypted electronic form and will be password protected ensure that only authorized study staff have access. The study database owner (ie, the study vendor, United BioSource Corporation) will implement appropriate technical and organizational

measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study vendor shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, participant names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, participant-specific code. In the case that the study vendor (Precision Marketing) maintains a confidential list of pharmacist's who participated in the study, linking each participant's numerical code to his or her actual identity, this list will not be passed from Precision Marketing Group to UBC and/or Pfizer. However, in case of unanticipated data transfer, Pfizer will maintain high standards of confidentiality and protection of pharmacist personal data consistent with the vendor agreement and applicable privacy laws.

9.2. Participant Consent

The informed consent language and any participant recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent language as incorporated within the survey tool and any participant recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC), as locally required, before use, and available for inspection.

The study vendor must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The study vendor further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

9.3. Pharmacist Withdrawal

Respondents can decline to participate or stop taking the survey at any time. Only complete surveys will be included in the analysis.

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

It is the responsibility of the vendor (UBC) to have prospective approval of the study protocol and survey questions and any protocol amendments, if applicable, from the Ethics Committee (EC). All correspondence with the EC should be retained in the Study File. Copies of EC approvals should be forwarded to Pfizer.

9.5. 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 Pharmacovigilance Practices (GVP) Module XVI-Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators issued by the EMA, Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organisations of Medical Sciences (CIOMS), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

This study does not involve data collection on clinical endpoints on individual patients. There is no mechanism by which information on safety events for an individual patient will be captured by a study participant during the course of data collection; thus reporting of adverse events (AEs) is not feasible in the data collection process. However, any information on a safety event inadvertently volunteered by a study participant during the course of this research must be reported as described below.

The survey for this study will be completed online via a secure website. The survey does not include questions that could potentially identify a safety event, nor does it provide a free text field where study participants could specify information that may constitute a safety event. Further, routine communication with study participants via email or phone with the Programme staff or study vendor is not expected during the conduct of the study. However, it is possible that a study participant may provide information that could constitute a safety event (eg, serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to Programme staff or the study vendor while in conversation about the survey for any other reason (eg, seeking information about the purpose of the study). In the event that a study participant in this study reports a safety event associated with the use of the Pfizer product, the Programme staff or the study vendor will complete a NIS adverse event monitoring (AEM) Report Form and submit it to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information as the reporter, as well as the contact information for the applicable primary healthcare provider (HCP); complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form will be assessed and processed according to Pfizer's SOPs, including requests for follow-up regarding the safety event to the study participant, or as appropriate, the individual patient's primary HCP.

All Programme staff or study vendor will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by the Programme staff or study vendor prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable electronic format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current "Your Reporting Responsibilities training materials.*"*

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the survey objectives, detailed methods, results, discussion, and conclusions will be developed at the end of the survey for submission to MHRA within the timeframe specified in 'Section 5, Milestones.' In addition, the study results will be posted on the EU PAS register.

COMMUNICATION OF ISSUES

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

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

12. REFERENCES

1. Miner, M, Kim ED. Cardiovascular disease and male sexual dysfunction. *Asian J Androl*. 2015;17(1):3-4.

13. LIST OF TABLES

14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Survey of pharmacists to evaluate the effectiveness of the Viagra Connect national additional Risk minimisation Measure in the UK

Study reference number: A1481334

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

Comments:

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? (eg, 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? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

[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.

Section 3: Study Design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, 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?	☐	☐	☒	
3.3	Does the protocol specify measures of occurrence? (eg, incidence rate, absolute risk)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (eg, 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? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and Study Populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	8
	4.2.2 Age and sex?	☐	☐	☒	
	4.2.3 Country of origin?	☐	☐	☒	
	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? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8

Comments:

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? (eg, 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? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (eg, 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:

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?	☒	☐	☐	7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7
6.3 Does the protocol address the validity of outcome measurement? (eg, 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? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (eg, healthy user bias)	☒	☐	☐	8.9
7.2.2. Information biases (eg, misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

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

Comments:

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? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8
	9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8
	9.1.3 Covariates?	☐	☐	☒	
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
	9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
	9.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (eg, 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? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

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? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

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:

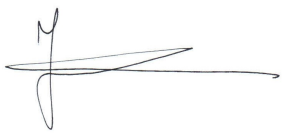
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☒	

Comments:

Name of the main author of the protocol: Joanna (Asia) Lem

Date: 21/11/2017

Signature:



ANNEX 3. ADDITIONAL INFORMATION

Removed to allow unbiased data collection.