REDACTED PROTOCOL

(Survey Instrument was removed to allow unbiased data collection; additionally the risk minimization materials were removed due to document size restriction)

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the European Union (EU)
Protocol number	A1501102
Protocol version identifier	1.0
Date of last version of protocol	08 July 2015
EU Post Authorisation Study (PAS) register number	Study not registered
Active substance	Voriconazole (a broad spectrum triazole antifungal agent) ATC code: J02A C03
Medicinal product	Voriconazole (Vfend®)
Product reference	EU/1/02/212/001 —— 027
Procedure number	EMEA/H/C/000387
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint Post-Authorisation Safety Study	No

(**PASS)**	
Research question and objectives	The objective of the study is to evaluate the effectiveness of the additional risk minimisation measures (aRMMs) being implemented across the EU to mitigate the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients using voriconazole.
Country(-ies) of study	France, Germany, United Kingdom (UK), Italy, Netherlands, Hungary, Austria, Denmark, Ireland, Spain
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Marketing Authorisation Holder(s)

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APPENDICES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CIs	Confidence Intervals
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HCPs	Healthcare Professionals
HSCT	Hematopoietic stem cell transplant
IA	Invasive Aspergillosis
IEA	International Epidemiological Association
IEC	Independent Ethics Committees
ID	Identifier
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
LFTs	Liver Function Tests
NIS	Non-interventional Study
PASS	Post-Authorisation Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
Q&A	Question &Answer
RM	Risk Management

Abbreviation	Definition
RMP	Risk Minimisation Plan
aRMMs	Additional Risk Minimisation Measures
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCC	Squamous Cell Carcinoma
SDLC	System Development Life Cycle
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SPF	Sun Protection Factor
UBC	United BioSource Corporation
URL	Uniform Resource Locator

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Protocol # A1501102 Version 1.0, 08 July 2015, An Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the European Union (EU).

Joanna (Asia) Lem, MPH, Senior Manager, Epidemiology, Pfizer Inc.

Rationale and Background

Pfizer Inc. will conduct a survey of healthcare professionals (HCPs) to evaluate the effectiveness of the additional risk minimisation measures (aRMMs) being implemented across Europe to mitigate the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients prescribed voriconazole (Vfend®), a broad spectrum triazole antifungal agent used to treat or prevent a range of serious fungal infections in both in-patient and out-patient settings.

To ensure that the risks are adequately managed, aRMMs in the EU are being implemented beginning in April 2014. These include an updated voriconazole Summary of Product Characteristics (SmPC)[1] (routine) and a new comprehensive education programme at the point of patient care that will educate/remind HCPs about the risks of phototoxicity, SCC of the skin and hepatic toxicity and how to manage them. The details of the Risk Minimisation (RM) tools for the educational programme and how these tools will be implemented across the EU are described in the Risk Management Plan (RMP). The RM tools are the HCP Checklist, HCP Question & Answer (Q&A) Brochure and Patient Alert Card.

Research Question and Objective

The overall objective is to evaluate the effectiveness of the aRMMs to mitigate the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients using voriconazole. The evaluation is being conducted in 10 of the 33 countries in the EU where RM tools are being implemented. Specifically, the goals of the study are to:

1. Assess HCPs' awareness of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge receiving the tools.

2. Assess HCPs' utilization of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge reading and utilizing the tools.

3. Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole by estimating the proportion of targeted HCPs with correct responses to risk knowledge questions.

4. Assess whether HCPs' self-reported behaviour/practices with respect to minimizing the risks of phototoxicity, SCC of the skin and hepatic toxicity are in accordance with the voriconazole SmPC.[1] This will be evaluated by estimating the proportion of targeted HCPs whose responses to the practice related questions are consistent with the SmPC's[1] prescribing information.

Study Design

The study objectives will be accomplished by means of a cross-sectional survey of all targeted HCPs who received the aRMMs and self-report as prescribers of voriconazole in the following 10 countries: France, Germany, UK, Italy, Netherlands, Hungary, Austria, Denmark, Ireland, and Spain. These countries represent the highest volume of voriconazole users across the EU and thereby are expected to provide representativeness across the EU in understanding the effectiveness of the aRMMs. The data from the HCPs will be collected using a structured, self-administered questionnaire. The HCPs will be invited to take the survey online using a secure uniform resource locator (URL) that requires a unique identifier to access the survey.

Population

Voriconazole is mainly prescribed by select specialty care physicians (ie, infectious disease physicians, oncologists, haematologists, solid organ transplant physicians- however the speciality that actually prescribes voriconazole can vary by country). These speciality care physicians in, Austria, Hungary, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain and the UK, will constitute the study population for the survey.

Variables

The variables for analyses will be derived from the survey data to address the objectives outlined as follows:

1. Awareness of each of the RM tools among HCPs,

2. Utilization of the RM tools,

3. Assessment of HCPs' knowledge/understanding of the risks of phototoxicity, SCC of the skin and hepatic toxicity, and

4. HCPs' self-reported practices with regard to strategies to mitigate the risks.

Data Sources

A structured self-administered questionnaire (Appendix 1.1) comprised of closed-ended questions or statements with multiple response choices (ie, questions or statements asking the HCPs to choose from a defined list of responses) will be used to collect the survey data. The questionnaire will collect data on HCP characteristics in addition to their responses pertaining to the effectiveness of the aRMMs.

Study Size

A sample size of approximately 750 completed surveys is being targeted across the 10 countries, which is based on both statistical and practical considerations. With a sample size of 750, the statistical precision around the estimate will be ±3.6%; the precision will increase with increasing the sample size beyond 750 surveys. It is to be noted that the final survey sample size will depend on HCPs' willingness to participate in the survey. The final study size will be determined by the number of responses received during a 60 day period in which the survey will remain open for data collection. The survey will not be closed at the 750 completed survey mark but rather the 60 day data collection milestone. All completed surveys will be included in the final study report.

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. Frequency distributions with 95% confidence intervals (CIs) will be calculated for HCPs' responses to all questions that address the survey objectives. Depending on the sample size, survey data will be stratified by country and medical specialty. In the final analysis of all specialists there will be weighted analysis completed based on HCP speciality.

Milestones

In accordance with the Guideline on Good Pharmacovigilance Practices Module XVI (Risk minimisation measure: selection of tools and effectiveness indicators - April 2014)[2] data collection will begin 12 months following the initial mailing of the approved RM tools in each of the 10 study countries. This time period will allow for the time required for utilization of the tools within each countries health care system. The planned timeline is contingent upon the date of the finalization and distribution of the RM tools within each country and the protocol endorsement by the European Medicines Agency (EMA).

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Timeline*
Start of data collection	Approximately 12 months after RM tools are mailed to HCPs in the 10 study countries. This will be accomplished on a rolling basis- the survey will open in each country at approximately the 12 month mark based on the date of approval that would be unique to the study country.
End of data collection	60 days after the start of data collection across the study countries.
Registration in the EU PASS register	Prior to start of data collection
Final study report	3 months after the final data collection for the last study country that received the RM tools.

*The study will be initiated after the distribution of the RM tools across the 10 study countries and protocol endorsement by EMA. Therefore, the planned timeline is contingent upon the date of the approval of the RM tools by the local Health Authorities and protocol endorsement by EMA.

7. RATIONALE AND BACKGROUND

Voriconazole (Vfend®) is a broad spectrum triazole antifungal agent used in the treatment of a range of serious fungal infections in both in-patient and out-patient settings. The clinical benefit of voriconazole has been demonstrated for the treatment of invasive aspergillosis (IA), candidemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*), serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. for which voriconazole is authorised for use in the European Union (EU). Voriconazole is also indicated in the EU for the prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

Phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity have been designated as important 'identified' risks with administration of voriconazole in the Risk Management Plan (RMP) and are currently described in the Summary of Product Characteristics (SmPC).[1] To ensure that these risks are adequately managed, additional risk minimisation measures (aRMMs) across the EU are being implemented beginning April 2014. These included updating the voriconazole SmPC[1] with revisions to information on hepatotoxicity, phototoxicity, SCC of the skin (routine risk minimisation activity), and developing a comprehensive educational programme at the point of patient care that will educate/remind HCPs about the risks and how to manage them. These aRMMs target specialty care physicians who prescribe voriconazole, ie, infectious disease physicians, haematologists, oncologists, and solid organ transplant physicians (hereafter referred to as "HCPs"). The details of the Risk Minimisation (RM) tools for the education programme and how these tools are being implemented in the EU are described in the RMP. The three components of the RM tools are the HCP Checklist, HCP Question & Answer (Q&A) Brochure and Patient Alert Card. A brief description of each follows:

- **HCP Checklist for the risks of phototoxicity, SCC of the skin and hepatic toxicity:** This is the core RM tool (Appendix 1.4) that reminds HCPs about: i) the risks of phototoxicity, SCC of the skin and hepatic toxicity with the use of voriconazole, ii) the appropriate use of voriconazole, and management of patients with underlying hepatic impairment and those developing hepatic injury during voriconazole therapy as described in the SmPC,[1] iii) the dermatological examination and liver function monitoring required per the SmPC,[1] iv) discussing the importance of monitoring these risks with patients, and, v) providing the Patient Alert Card (described below) to each patient prescribed voriconazole. The HCPs have been instructed to complete the HCP Checklist for all new patients receiving voriconazole and retain it in the patient's medical record.

- **HCP Q&A Brochure for the risks of phototoxicity, SCC of the skin and hepatic toxicity:** This brochure in Q&A format (Appendix 1.3) provides detailed information to HCPs about: i) the risks of phototoxicity, ii) counselling patients regarding the risks of hepatotoxicity and SCC of the skin, iii) alerting patients/caregivers to the signs and symptoms that warrant contacting the doctor immediately, iv) regular dermatological examination and liver function monitoring as described in the SmPC,[1] v) discontinuing voriconazole if premalignant lesions or SCC are identified; and, vi) providing the Patient Alert Card to patients prescribed voriconazole. This brochure also provides information

about the HCP Checklist and Patient Alert Card and instructs HCPs how to use these tools when managing patients receiving voriconazole.

- **Patient Alert Card for the risks of phototoxicity and SCC of the skin:** The purpose of this wallet-sized folded card (Appendix 1.5) is to help remind patients about the need for dermatological evaluations on a regular basis (if phototoxic reactions occur). It also prompts the patient to report phototoxic symptoms that increase the risk of SCC of the skin. Further, patients are reminded to avoid exposure to sunlight, to use protective clothing and sunscreen with high sun protective factor (SPF) and to inform their physicians if they develop sunburn or severe skin reactions or skin abnormalities. The HCPs were instructed to fill in their contact details on the card and give a card to each patient undergoing treatment with voriconazole.

The content and layout of the RM tools are non-promotional in nature. User testing of the RM tools was conducted in October 2013 with a sample of HCPs in the UK and France prior to the finalization of RM tools and subsequent distribution in April 2014. Specifically, prototypes of each tool (ie, HCP Checklist, HCP Q&A Brochure, and Patient Alert Card) were reviewed in a one-on-one, moderator-guided interview for clarity and comprehension of the content and purpose of each piece. Findings from this user testing allowed for the improvement of the tools' content and format to enhance comprehension of the product's risks and how to manage them.

The initial RM tools were distributed in the UK and France in April 2014 and continue to be distributed across 31 EU countries (33 total countries). The other 31 countries are as follows: Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, and Sweden.

Once local Health Authority approval is obtained the RM tools are mailed to the country within 4 weeks. The RM tools are in various stages of review/approval by the local National Health Authorities in the remaining 8 study countries - Austria, Ireland, Denmark, Germany, Spain, Italy, Netherlands, and Hungary (Table 1). During the period between July and December 2014, the RM tools were disseminated to the target HCPs in each of those countries depending on the approval timelines from the local National Health Authority. Finally in some of the countries, depending on local rules and regulations, the RM tools have been posted to various webpages, including local Pfizer country offices and local National Health Authority.

Table 1. Study Country Timelines

Study Country	Date RM Tools Submitted to Local Health Authority	Date RM Tools Mailed to HCP's	Approximate Survey Open Date
UK	January 2014	April 2014	July 2015
France	January 2014	April 2014	July 2015
Austria	June 2014	August 2014	August 2015
Ireland	June 2014	August 2014	August 2015
Denmark	June 2014	December 2014	December 2015
Germany	June 2014	November 2014	November 2015
Spain	June 2014	December 2014	December 2015
Italy	June 2014	October 2014	October 2015
Netherlands	June 2014	November 2014	November 2015
Hungary	June 2014	September 2014	September 2015

"In the same way that public health interventions aim to minimise risks associated with a pharmaceutical product, it is imperative to systematically evaluate the effectiveness of the intervention in order to determine whether the intended effect/outcome has been achieved or an alternative activity needs to be identified and implemented" (Prieto et al, 2012).[3] Accordingly, a comprehensive plan is being proposed to periodically assess the effectiveness of the additional RMMs as described above, ranging from awareness of the RM tools among the HCPs, utilization of the tools, HCPs' knowledge of the risks, to HCPs' behaviour/practices with respect to mitigating the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients receiving voriconazole therapy in accordance with the SmPC.[1]

The objective of this protocol is to describe in detail the methods that will be employed to evaluate the effectiveness of the aRMMs across Europe as well as outline the estimated timeline for the major study milestones (Section 6 Milestone). This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA. For the purposes of conducting the effectiveness evaluation survey, ten countries with high use of voriconazole use (see Table 1 above) were selected for practical purposes while preserving the generalisability of the data collected.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective is to evaluate the effectiveness of the additional RMMs being implemented across Europe to mitigate the risks of phototoxicity, SCC of the skin and hepatic toxicity with the use of voriconazole.

Specifically, the objectives of this research are to:

1. Assess HCPs' awareness of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge receiving the tools.

2. Assess HCPs' utilization of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge reading and utilizing the tools.

3. Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole by estimating the proportion of targeted HCPs with correct responses to risk knowledge questions.

4. Assess whether HCPs' self-reported practices with respect to minimising the risks of phototoxicity, SCC of the skin and hepatic toxicity are in accordance with voriconazole SmPC.[1] This will be evaluated by estimating the proportion of targeted HCPs whose responses to the practice-related questions are consistent with the SmPC[1] prescribing information.

9. RESEARCH METHODS

This section presents methods that will be employed to evaluate the effectiveness of the additional RMMs across 10 countries in the EU: UK, France, Austria, Ireland, Denmark, Germany, Spain, Italy, Netherlands, and Hungary.

9.1. Study Design

The study objectives will be accomplished by means of a cross-sectional survey of all targeted HCPs that received the RM tools in the following countries: UK, France, Austria, Ireland, Denmark, Germany, Spain, Italy, Netherlands, and Hungary. These countries represent the highest volume of voriconazole users across the EU and thereby are expected to provide representativeness across the EU in understanding the effectiveness of the aRMMs. Any additional changes to the countries for evaluation or sample size will be included in the final study report. The data from the HCPs will be collected using a structured self-administered questionnaire.

Potential prescribers of voriconazole throughout the EU will be sent the approved RM materials (ie, infectious disease physicians, oncologists, haematologists, solid organ transplant physicians- however the speciality that actually prescribes voriconazole can vary by country and will be described in further detail within the final study report). For the purposes of conducting the effectiveness evaluation survey, ten countries (see Table 1 above) were selected for practical purposes while preserving the generalisability of the data collected. The ten countries comprise the largest market for adequate sample and are also deemed to be a heterogeneous sample including various types of prescribers and practice patterns likely to be representative of all EU countries.

9.2. Setting

Voriconazole is mainly prescribed by select specialty care physicians (ie, infectious disease physicians, haematologists, oncologists and solid organ transplant physicians). These speciality care physicians across the study countries will constitute the study population for the survey.

9.2.1. Method of HCP Recruitment for Participation

This survey aims to recruit approximately 750 voriconazole prescribers across the 10 study countries.

All HCPs in the study countries that received the RM tools will be invited to participate in the evaluation survey (n~35,000). Those HCPs who self-report writing at least one prescription for voriconazole within 12 months of receiving the additional RM tools will be eligible to complete the survey. The survey response rate will be monitored every 3 days by the vendor and a report will be sent to the MAH to ensure the target sample size is met (see 9.5 Study Size). If the survey response rate is too low based on milestones established by Pfizer Inc., additional reminder notices will be sent to physicians who were mailed the RM tools. Depending on the sample size, survey data will be stratified by country and medical specialty.

The respondent's understanding of the appropriate use and risks of voriconazole will be evaluated using an online survey. Each invitation will include information on how to access the survey online, and will include a unique code for each prescriber to ensure that the invitation is used only once. Pfizer, Inc. will reimburse HCPs for their time spent completing the survey as governed by local laws and country regulations.

To ensure comprehension of the invitation and survey, all of the HCP outreach will be conducted in the local country language. The survey and invitation as well as any reminder letters will be translated by a certified translation vendor.

9.2.2. Inclusion Criteria

The HCPs must meet all of the following criteria to be eligible for inclusion in the survey:

- Willing/consent to participate in this self-administered survey.
- Prescribed voriconazole within the past 12 months.

9.2.3. Exclusion Criteria

The HCPs meeting any of the following criteria will not be included in the survey:

- Participated in the User Testing of the RM tools (described in Section 7 Rationale and background) and/or User Testing of the draft questions for the survey (described in Section 9.4 Data sources).
- Employed in full time research or hospital administration (ie, non-practising physicians).
- Employment by Pfizer, Inc or any research organization/vendor contracted by Pfizer to administer the survey.

9.3. Variables

The variables for analyses will be derived from the survey data to address the objectives outlined in 'Section 8 Research Questions and Objectives', as follows:

- Awareness of each of the RM tools among HCPs,
- Utilization of the RM tools,
- Assessment of HCPs' knowledge/understanding of the risks of phototoxicity, SCC of the skin and hepatic toxicity, and
- HCPs' self-reported practices with regard to strategies to mitigate the risks.

9.4. Data Sources

A structured self-administered questionnaire (Appendix 1.1) comprised of closed-ended questions or statements with multiple response choices (ie, questions or statements asking the HCPs to choose from a defined list of responses) will be used to collect the survey data. The questionnaire will collect data on HCP characteristics and their responses to the risk knowledge questions. The data collected from the surveys will be used to inform the evaluation of the effectiveness of the additional RMMs.

The questionnaire will begin with a screening module with questions to confirm eligibility. Depending on the answers to the screening questions, survey participation could 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 is allowed to continue survey participation.

Screening questions for the HCPs:

- Consent to participate.
- Whether the HCP managed patient(s) treated with voriconazole during the last 12 monthsperiod preceding the survey.
- Employment by Pfizer or any research organization/vendor contracted by Pfizer to administer the survey.
- Participation in User Testing of RM materials or survey questionnaire.

Data on HCP demographic characteristics:

- Location (city/country/suburb/urban).
- HCP medical specialty type (eg, infectious disease physician, haematologist, oncologist solid organ transplant physician).

- Number of years practicing medicine.
- Number of self-reported voriconazole-treated patients the HCP managed in the last 12 month period preceding the survey.

Data pertaining to evaluation of the effectiveness of the additional RMMs:

The questionnaire includes questions/statements that will assess the risk knowledge of the HCPs. The knowledge level analysed using descriptive statistics and confidence intervals, will be used to determine the effectiveness of the aRMMs:

- Awareness of each of the RM tools among the HCPs.
- Receipt of each of the RM tools.
- Utilization of the tools in clinical practice.
- Knowledge/ comprehension of the risks of phototoxicity, SCC of the skin and hepatic toxicity.
- Self-reported practices with respect to mitigating the risks, as described in the SmPC.[1]

The key messages informing HCPs about the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole, and instructions on how to manage these risks when treating patients with voriconazole have been identified from the most current version of the SmPC[1] and will be used for evaluation of the HCP's knowledge.

User Testing of the survey questions

The proposed questions for the survey were User Tested in the UK for clarity and comprehension prior to survey launch in the study countries. The User testing of the survey was completed on 12 December, 2014. The testing included structured interviews with 12 HCPs in the UK. Findings from the testing along with HCPs' recommendations were used to improve clarity and comprehension of the survey questions. The final questionnaire with user testing findings incorporated can be found in Appendix 1.1. A description of the results from the user testing including any changes to the survey questions will be included in the final study report.

9.4.1. Data Collection Process

Eligible HCPs (those HCPs to whom the RM tools were mailed) will receive a letter in the postal mail inviting them to participate in the survey. The invitation letter (Appendix 1.2) will include: an overview of the rationale for the survey, reminder about the educational materials, the secure URL to be copied and pasted into their browser, and a unique user identifier (ID). The survey data collection will be open for a maximum of 60 days. The survey start date begins 12 months after the date of distribution of the RM tools in the

individual countries listed for evaluation within this protocol. This date will vary by country based on the date of approval by the local Health Authority.

Data will be collected using an electronic data capture (EDC) system developed following a full validation process. A rigorous System Development Life Cycle (SDLC) is used for validation that complies with 23 internal IT Standard Operating Procedures (SOPs) of United BioSource Corporation (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 management-related applications. The internet-based repository will be used to store survey data and other relevant programme information. The system is Annex 11 and 21 Code of Federal Regulations (CFR) Part 11 compliant. Healthcare professional identifying information is stored separately from survey data.

Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomized to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

Follow-up reminder process

The HCP database will be routinely updated with responders and, after each mailing, the database will be cross-checked with any correspondence that had an invalid address, bounced back or had incorrect contact details. The target sample for this survey reminder process is HCPs who received the invitation (ie, no reason for not receiving, such as invalid address) but did not respond by 30 days from initial mailing.

Using the updated database, thirty days following the initial invitation mailing, a total of one reminder will be sent to the sample defined above. However, the number of reminders will be based on the response rate at predefined recruitment milestones identified by Pfizer Inc. The interval between the reminders will be approximately 15 days. Previous experience has shown that thirty days allows enough time for postal mailing to arrive, be routed through hospital or re-routed to another clinic location if necessary. The time allowed between initial mailing and the reminder mailing also minimise the potential for reaching out to the physician too soon (without allotting sufficient time for review of the materials). In previous similar survey programmes, the majority of respondents took the initiative to log onto the survey within 72 hours of receiving the invitation. If the mailings are taking place during holiday seasons, further consideration will be given to timing of reminder intervals.

9.5. Study Size

This section presents sample size and precision of estimate calculations for various survey sample sizes. The precision of the estimate calculations are based on the following assumptions:

- The confidence intervals (CIs) around the estimate are 2-sided.

- The probability of type-I error (alpha) is 5%.

- 50% of the HCPs will correctly answer key questions about the risks of phototoxicity, hepatic toxicity and SCC of the skin with voriconazole (or 50% of HCPs' practices with regard to mitigating the risks of photoxicity, SCC of the skin and hepatic toxicity are in accordance with the SmPC[1] prescribing information). Basing the sample size estimate on this assumption of 50% accurate risks comprehension (or 50% of HCPs practices in accordance with the SmPC[1]) is the most conservative approach, since either a higher or lower percentage than 50% will lead to higher statistical precision.

The table below provides precision of the estimate (width of 95% CI around the estimate) for a range of sample sizes.

Table 2. Precision of the Estimate for a Range of Sample Sizes

Sample Size	Statistical Precision (%)
100	±9.8
150	±8.0
200	±6.9
250	±6.2
300	±5.7
350	±5.2
400	±4.9
450	±4.6
500	±4.4
550	±4.2
600	±4.0
650	±3.8
700	±3.7
750	±3.6
800	±3.5
850	±3.4
900	±3.3
950	±3.2
1000	±3.1

A sample size of approximately 750 completed surveys aggregated across 10 countries is being targeted, which is based on both statistical and practical considerations. The below table provides the number of HCPs that were mailed the additional risk minimisation materials in each of the countries for evaluation. With a sample size of 750, the statistical precision around the estimate will be ±3.6%; the precision will increase with larger sample sizes. It is to be noted that the final survey sample size will depend on HCPs' willingness to participate in the survey. While the target is 750 respondents, all completed responses received by the cutoff will be included in the analysis. Based on the vendor's recent prior

experience of conducting similar surveys in Europe, a response rate of maximally 5-7% is expected but may be as low as 3% in some countries.

Table 3. Number of Physicians mailed aRMM Documents in the Study Countries

Study Country	Total Number of Physicians mailed aRMMs *
UK	4852
France	6253
Austria	377
Ireland	317
Denmark	886
Germany	3154
Spain	4857
Italy	10545
Netherlands	3624
Hungary	889
Total	~35, 754 (this number will be adjusted in the final study report to account for returned mailings, etc).

*Cegedim 2014 HCP database

9.6. Data Management

All data collected during the survey will be held confidentially by the vendor. The EDC system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses. The data from the surveys collected in all 10 countries will be combined for the data analysis in the final study report.

Skip logic for certain questions as well as the ability to mark only one response or multiple responses are part of the programming for the survey administration, which minimises the occurrence of data entry errors. There will be no queries to respondents for this project.

9.7. 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. Frequency distributions with 95% CIs will be calculated for HCPs' responses to all questions that address the survey objectives. Depending on the sample size, survey data will be stratified by country and medical specialty. In the final analysis of all specialists there will be weighted analysis completed based on HCP speciality.

The evaluation of the data from this education programme offers the MAH and the Pharmacovigilance Risk Assessment Committee (PRAC) an opportunity to gain insights into the HCPs level of understanding of the educational materials and to make any modifications, if needed, to optimise it. As described in the Guideline on Good Pharmacovigilance Practices (GVP) Module XVI- Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators (EMA),[1] the percentage of participants responding correctly to the knowledge questions will be analysed and discussed. The minimum acceptable threshold of understanding will be defined at 80% correct response rate per risk questions.

The distribution of the responses to questions assessing all study objectives will be presented in the study report. It is to be noted that the selection of this threshold for success is subjective (7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2) and not based on a priori knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualized within the context of other available information.

The following will be reported as part of the analysis:

- Survey administration
    - The number of HCPs by select medical specialty (ie, infectious disease physicians, oncologists, haematologists, solid organ transplant physicians) in the 10 study countries.
    - The number of survey invitations issued by strata (ie, by country and speciality).
    - The number of survey invitations returned due to incorrect mailing address of HCPs invited to participate in the survey.
    - The number of HCPs screened for participation in the survey.
    - The number of HCPs eligible for participation in the survey.
        - Reasons for ineligibility.
    - The number of eligible HCPs who completed the survey.
- Demographic characteristics of participants
    - Distribution of participants by country.
    - Distribution by medical specialty.
    - Distribution of participants by years in medical practice.

- Distribution of participants by number of patients treated with voriconazole in the past 12 months.

- HCP responses to questions pertaining to the survey objectives:

  - Awareness of the RM tools.

  - The number and percentage of HCPs who acknowledged receiving each of the tools.

1. Utilization of the RM tools

   - The number and percentage of HCPs indicating which tools they utilized when treating patients with voriconazole:

     - Utilized HCP Checklist

     - Read HCP Q&A Brochure

     - Utilized Patient Alert Card

2. HCP's knowledge/understanding of the risks

   - The number and percentage of HCPs who correctly responded to each question/item about the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole.

3. Assessment whether HCPs' self-reported practices with regards to mitigating the risks of phototoxicity, SCC of skin and hepatic toxicity are consistent with voriconazole SmPC.[1]

   - The number and proportion of HCPs whose responses to each behavior/practice related questions are consistent with the SmPC[1] prescribing information.

9.8. Quality Control

The survey data will be collected using a secure online EDC survey system. The proposed data entry system has been validated and is secure for receiving and storing survey data. A web-based data repository will be used to warehouse survey data and other relevant programme information. This EDC system is an EU Annex 11 compliant platform for the entry, storage, manipulation, analysis and transmission of electronic information. This platform ensures compliance with all relevant regulatory guidelines.

The EDC application is a core technology for capturing, managing and reporting data. Data may be exported in a variety of formats including Statistical Analysis Software (SAS) Transport®, Excel and delimited ASCII files. Based on Microsoft's NET technologies, the EDC platform is integrated with reporting services, to enable real-time access to data collected via the web. All data entered will be single data entered by the respondent. Data

will be checked in real time against the programmed edit specifications as they are entered to ensure that data are being entered according to acceptable parameters and requirements.

The vendor has an independent Information Technology (IT) Quality Assurance Group that is responsible for managing and overseeing system/application development and validation, as well as related compliance functions.

9.9. Limitations of the Research Methods

The participating HCPs will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of voriconazole prescribers for participation.

A secondary limitation inherent in survey research is the reliance on the respondent's recall for whether or not the additional RM tools were received, in order to evaluate the scope of aRMMs. If the respondent says she/he did not receive a particular tool, the risk minimisation programme is evaluated as not optimally disseminating material. It is possible, however, that prescribers may simply not recall receiving the tools that were sent and received. It is also possible that they have acceptable understanding of the risks and appropriate behaviors despite not receiving or recalling receipt of the tools. All data from the survey are self-reported and therefore susceptible to possible reporting bias. This is also applicable to the prescribers' self-reporting of their practice behaviors to minimise the risks. There may be discrepancies between what HCPs would report about their practices and their *actual* behaviors. Therefore, it will be difficult to validate whether HCPs responses to practice related questions are consistent with their actual behaviors in this self-reported survey.

All questions must be answered in order to complete the survey. In each survey, response options presented in a list will be presented in random order (where appropriate) to minimise positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

Selection and non-response bias will be assessed by comparing select characterictics between survey non-responders and responders using descriptive statistics, and will be included in the final study report.

Due to variable country regulations and requirements for conducting such a survey, in some countries it may not be possible to invite all HCPs who received the RM tools.

Finally the MAH acknowledges that an a priori threshold of 80% correct per risk questions will be used to define the success of the program. However as acknowledged by EMA, the selection of this threshold for success is subjective (7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2) and not based on a prior knowledge, experience, or established scientific criteria in the education or risk communication literature. The MAH expects that the knowledge may differ by key risk message, clinical practice, HCP specialties, and countries. This evaluation of the education programme offers the MAH and the PRAC an opportunity to gain insights into the level of

understanding and to make modifications to the educational materials (if needed) to achieve an optimal understanding of the risk minimisation materials.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Healthcare Provider Information and Consent

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

Due to the nature of the study, informed consent is not required. Participants need to go to the survey website in order to complete the survey. Consent is implied by these actions. Additionally, at the beginning of the survey, the respondent is asked if he/she agrees to take part in the survey. If yes, the respondent continues with the survey questions. If no, the survey is terminated.

10.2. Patient Withdrawal

Not applicable.

10.3. Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments and other relevant documents, (eg, recruitment advertisements), if applicable, from the individual country's Ethics Committee (EC). All correspondence with the EC should be retained in the Investigator File. Copies of EC approvals should be forwarded to Pfizer.

Approval of this protocol by the respective local ECs (if required) will be sought prior to initiating the survey in each country.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Guideline on Good Pharmacoviglilance Practives (GVP) Module XVI- Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators (EMA), *Good Pharmacoepidemiology Practices* (GPP)[4] issued by the International Society for Pharmacoepidemiology (ISPE), *Good Epidemiological Practice* (GEP) guidelines[5] issued by the International Epidemiological Association (IEA), *Good Outcomes Research Practices*[6] issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organizations of Medical Sciences (CIOMS),[7] European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and

Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*[8] and FDA Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.*[9]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve data collection on clinical endpoints on individual patients. However, safety information may be identified during the course of data collection (ie, through a free text field). Any safety information for an individual patient that is volunteered by a study participant (eg, health care professional) during the course of this research must be reported as described below.

The following safety events must be reported on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form: serious and non-serious adverse events (AEs) when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

All Programme staff at UBC 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 will be provided to the UBC Programme staff prior to commencement of the study. 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 format. The study vendor will also provide copies of all signed training certificates to Pfizer.

Study participants will complete the survey online via a secure website. The survey does not include questions that could potentially identify a safety event, and does provide an opportunity (eg, free text field) where study participants could provide information that may constitute a safety event. Further, routine communication with participants via email or phone with the UBC Programme staff may not be expected during the conduct of the survey. 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 the UBC Programme staff while in conversation about the survey for any reason (eg, seeking information about the purpose of the survey). UBC Programme staff will be trained to identify safety event information. In the event that a study participant reports a safety event associated with a Pfizer product, the UBC Programme staff will complete the NIS AEM Report Form and submit 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; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form can be assessed and processed

according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

12. 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 EMA within the timeframe specified in 'Section 6 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 NI study protocol that the investigator becomes aware of.

13. REFERENCES

1. Vfend Combined Annexes SmPC/Labelling and Package Leaflet (HA approved), Combined Annexes (123.0), 23 June 2014.

2. Guideline on Good Pharmacovigilance Practives Module XVI (Risk minimisation measure: selection of tools and effectiveness indicators- April 2014).

3. Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimisation measures. Pharmacoepidemiol Drug Saf. 2012 Aug;21(8):896-9. Doi: 10.1002/pds.3305. Epub 2012 Jun 22.

4. Guidelines for Good Pharmacoepidemiology Practices (GPP). International Society for Pharmacoepidmiology (ISPE). Pharmacoepidemiology and Drug Safety 2008; 17:200-208.

5. Guidelines for Good Epidemiological Practice (GEP). International Epidemiological Association (IEA); April 2010.

6. Good Outcomes Research Practices. International Society for Pharmacoeconomic and Outcomes Research (ISPOR). http://www.ispor.org/research_initiatives/hs_initiatives.asp

7. International Ethical Guidelines for Epidemiological Studies, issued by the Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO) Press, Geneva Switzerland. April 2009.

8. Guide on Methodological Standard in Pharmacoepidemiology. European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology (ENCePP); June 2013. (http://www.encepp.eu/standards_and_guidances).

9. Food and Drug Administration. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment US Dept of Health and Human Services. Food and Drug Administration. Rockville, Maryland. March 2005.

14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable

16. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Combined Annexes (123.0)	23 June 2014	Vfend Combined Annexes SmPC/Labelling and Package Leaflet (HA approved)[1]

Appendix 1.1. HCP Survey Questionnaire

Removed to allow unbiased data collection.

Appendix 1.2. Draft Survey Invitation Letter for Healthcare Professionals (HCPs)

[Date]

[Addressee's name] [Title]
[Street address]
[City, State, zip code]
[Country]

Re: Invitation to Participate in VFEND® Survey
Dear Dr. [insert HCP LAST NAME],

On behalf of Pfizer Inc, we would like to invite you to participate in a voluntary research survey about VFEND (voriconazole). The survey is part of a post-marketing agreement between Pfizer and the European Medicines Agency (EMA), and should take no more than 20 minutes to complete. If you complete the survey, you will be receiving compensation based on your local rules and regulations to thank you for your time.

You may be eligible to participate if you have prescribed VFEND in the past 12 months and have received a set of risk minimization materials for VFEND. The survey can be completed on or before [END DATE], and for your convenience can be completed online at **[www.surveyURL.com]** at any time.

You will need the following ID code when completing the survey: **[CODE_ID]**.

Participating in this survey is entirely voluntary. All information which is collected during the course of the survey will be kept strictly confidential. Results will be reported in aggregate form only. Your participation in the survey and your answers to the survey questions will not affect your ability to prescribe VFEND. You will not be contacted for marketing purposes. Neither Pfizer, nor its contractors, will sell, transfer, or rent your information. This letter and this survey have been approved by the EMA and your responsible Ethics Committee (EC), if required.

Thank you in advance for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customized accordingly}

Appendix 1.3. Health Care Professional Q&A Brochure for Phototoxicity, Squamous Cell Carcinoma of the Skin and Hepatic Toxicity

Removed due to document size restriction.

Appendix 1.4. Health Care Professional Checklist for Phototoxicity, Squamous Cell Carcinoma of the Skin and Hepatic Toxicity

Removed due to document size restriction.

Appendix 1.5. Patient Alert Card for Phototoxicity and Squamous Cell Carcinoma of the Skin

Removed due to document size restriction.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the European Union (EU)

Study reference number:

Protocol # A1501102

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	11

[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 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	8, 14
2.1.2 The objective(s) of the study?	☒	☐	☐	8, 14
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9, 15
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (eg, cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9, 15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.3 Does the protocol describe the measure(s) of effect? (eg, 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)	☐	☒	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15-16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	14
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	15
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

The study population is healthcare professionals only; no patients.

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? (eg, operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (eg, 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? (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?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This protocol is a HCP survey to evaluate the effectiveness of risk minimisation measures without patient paticipation with no medical intervention.

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?	☐	☒	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (eg, collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (eg, collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	20-
8.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (eg, International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (eg, Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	18

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19-20

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	21
10.4 Are stratified analyses included?	☒	☐	☐	21
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect				

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
modification?	☐	☐	☒	

Comments:

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.

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	18-19
11.3 Are methods of quality assurance described?	☒	☐	☐	23
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	23

Comments:

For point 11.1, the design of the EDC system is such that respondents must complete each answer before advancing so there should not be missing data.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	24
12.1.2 Information biases? (e.g. 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, sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	24
12.3 Does the protocol address other limitations?	☒	☐	☐	23-24

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	25
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	24

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

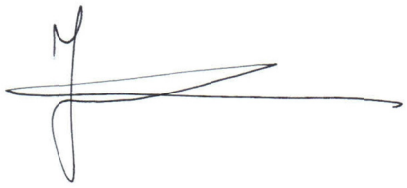
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	26
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	26

Comments:

Name of the main author of the protocol: __Joanna (Asia) Lem, MPH_____

Date: 08/07/2015

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Not applicable