NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**SURVEY TO EVALUATE THE EFFECTIVENESS OF RISK MINIMISATION MEASURES FOR ATEZOLIZUMAB USE IN THE EUROPEAN UNION**
PROTOCOL NUMBER:	WO40486
VERSION NUMBER:	Draft 1.4
EU PAS REGISTER NUMBER:	EUPAS21920
ACTIVE SUBSTANCE:	Atezolizumab
STUDIED MEDICINAL PRODUCT:	Tecentriq
PRODUCT REFERENCE NUMBER:	MPDL3280A
PROCEDURE NUMBER:	EMEA/H/C/004143/MEA/010
JOINT PASS:	No
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

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RESEARCH QUESTION AND OBJECTIVES:	The <u>primary objective</u> of this study is to assess for the target physician population: - The receipt of the atezolizumab HCP Guide and PAC and the level of knowledge of key messages related to IrADRs outlined in the atezolizumab HCP Guide and PAC. <u>Secondary objectives are to assess:</u> - The understanding of the atezolizumab HCP Guide. - The use of the atezolizumab HCP Guide and PAC.

	- The behaviour consistent with key messages related to IrADRs outlined in the atezolizumab HCP Guide and PAC. - Knowledge according to receipt and use of the atezolizumab additional risk minimisation measures (aRMMs). - Behaviour consistent with key message, according to receipt and use of the atezolizumab aRMMs.
COUNTRIES OF STUDY POPULATION:	UK, Italy, Spain, Germany, Sweden, and Denmark
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	Dr. [redacted] MD [redacted] Genentech, a member of the Roche Group 1 DNA Way MS [redacted] South San Francisco, CA 94080, USA

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
aRMM	Additional Risk Minimisation Measure
ASOCS	Association of Opinion and Behaviour in health field research companies
AST	Aspartate aminotransferase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Electronic Case Report Form
DMP	Data Management Plan
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	Register of non-interventional post-authorisation studies
FSR	Final Study Report
GPP	Good Pharmacoepidemiological Practice
GVP	EU Guideline on Good Pharmacovigilance Practices
HCP	Healthcare professional
IEC	Independent Ethics Committee
IrADR	Immune-related Adverse Drug Reactions
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
MAH	Marketing Authorisation Holder
NCI	National Cancer Institute
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
PAC	Patient Alert Card
PASS	Post-Authorization Safety Study
PD-L1	Programmed Death Ligand 1
PRAC	Pharmacovigilance Risk Assessment Committee

Abbreviation	Definition
QPPV	Qualified Person for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SDV	Source Data Verification
SOP	Standard Operating Procedures
STROBE	Strengthening the reporting of observational studies in epidemiology
UC	Urothelial carcinoma

2. RESPONSIBLE PARTIES

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Roche Registration GmbH is the Marketing Authorisation Holder (MAH)

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3. SYNOPSIS

TITLE:	**SURVEY TO EVALUATE THE EFFECTIVENESS OF RISK MINIMISATION MEASURES FOR ATEZOLIZUMAB IN THE EUROPEAN UNION**
PROTOCOL NUMBER:	WO40486
VERSION NUMBER:	Draft 1.4
DATE OF SYNOPSIS:	3 December 2018
EU PAS REGISTER NUMBER:	EUPAS21920
STUDIED MEDICINAL PRODUCT:	Tecentriq
SCIENTIFIC RESPONSIBLE	Dr. [redacted]
MAIN AUTHOR:	[redacted], [redacted]
PHASE:	IV, non-interventional study
INDICATION:	Treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%. Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer either after prior chemotherapy among patients that are EGFR wildtype or ALK negative or after targeted therapy among patients with an EGFR mutation or ALK rearrangement.

MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

Rationale and Background

TECENTRIQ® (atezolizumab) is an Fc-engineered, humanized, monoclonal antibody targeting human programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells and tumor cells. TECENTRIQ® received marketing authorisation from the European Commission in September 2017 for the treatment of locally advanced or metastatic urothelial carcinoma (UC) and locally advanced or metastatic non-small cell lung cancer (NSCLC) patients.

The following important immune-related reactions (IrADRs) associated with the use of atezolizumab were identified to require additional risk minimisation measures (aRMMs): immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, and infusion related reactions (IRRs). The aim of the atezolizumab aRMMs (healthcare professional [HCP] Guide and patient alert card [PAC]) is to minimise the consequences of these adverse reactions by increasing the physicians' awareness of IrADRs to facilitate early detection and prompt treatment.

The MAH also proposed a physician survey to the EMA to assess receipt of, understanding and use, knowledge and behavior outlined in the aRMMs among physicians and to assess whether the aRMMs are effective in informing physicians to recognize and manage IrADRs.

Research Question and Objectives

- Have the atezolizumab HCP Guide and PAC reached the target physician population?
- Are the atezolizumab HCP Guide and PAC understood and used (including reading the HCP Guide) as intended by the target physician population?
- What is the level of knowledge for key messages related to IrADRs in the atezolizumab HCP Guide and PAC by the target physician population?
- What is the level of behaviour consistent with key messages related to IrADRs in the atezolizumab HCP Guide and PAC?
- Is the atezolizumab HCP Guide effective in informing the physician target population of the early recognition and management of IrADRs?

The primary objective of this study is to assess the receipt of the atezolizumab HCP Guide and PAC for the target physician population and to assess the level of knowledge of key messages related to IrADRs outlined in the atezolizumab HCP Guide and PAC.

This study will help assess the effectiveness of the atezolizumab aRMMs, with success declared if ≥ 70% of participating HCPs in the survey confirm receipt and demonstrate knowledge consistent with the key safety messages. These results, and threshold, will be interpreted in wider context of the secondary objectives and results of individual questions, response rates, recruitment and individual country results and needs.

Additional information from the conduct of the study and externally may be used to help understand the experience with the aRMMs, and to determine what actions, if any, should be taken.

The secondary objectives of this study are to assess:

- The understanding of key messages related to IrADRs outlined in the atezolizumab HCP Guide.
- The use of the atezolizumab HCP Guide and PAC.
- The behaviour consistent with key messages related to IrADRs outlined in the atezolizumab HCP Guide and PAC.o
- Knowledge according to receipt and use of the atezolizumab aRMMs.
- Behaviour consistent with key message, according to receipt and use of the atezolizumab aRMMs.

Study Design

This is a multi-country, one-wave, cross-sectional physician survey conducted in a selection of European countries (UK, Italy, Spain, Germany, Denmark and Sweden), where atezolizumab has been launched. This initial country selection was based on approval dates and predicted uptake of atezolizumab. Other countries may be added to meet the study timeline or if recruitment proves challenging. Data collection in each country is planned to start within the 9 to 18 months period from each country-specific launch to allow time for uptake of atezolizumab and familiarity and use of the materials by the physicians, but to also assure the start of data collection does not vary greatly between countries.

Description of Study

The survey will be hosted online. The survey questionnaire will comprise multiple-choice and true/false questions, with no free text fields. The survey questionnaire will be developed in English and translated into the language of the participating countries using ´forward and back translation´. The local versions of the questionnaire will be tested and culturally adapted in a sample of 18 physicians (3 per country).

Population

A sample of 300 physicians (oncologist, pulmonologists, urologists) who have prescribed or managed at least one patient with atezolizumab in routine clinical practice will be recruited to participate in this study. To minimise selection bias, a panel of registered physicians will be used to randomly invite physicians. All participants will provide informed consent and data will be anonymous when presented to Roche.

Variables

The variables and structure of the questionnaire will be as follows:

A. Informed acceptance to participate (date and tick box)

B. Screening: eligibility

C. Demographics and HCP practice information:

- Country
- Age group (<30, 30-45, 46-65, >65)
- Gender (male/female)
- Type of setting (office based, hospital based, both)
- Specialty (oncologist, pulmonologist, urologist)
- Experience: years working with oncology patients

- Past experience with atezolizumab: Time since last contact with a patient receiving atezolizumab, participation in an atezolizumab clinical trial, number of patients treated with atezolizumab in the last 12 months

D. Main questionnaire domains (in the order presented in the questionnaire - knowledge and behaviour are responded by all completers while receipt, understanding and use include filtering questions):

- Knowledge: awareness, identification, monitoring and management of IrADRs and awareness of the need to report them.
- Behaviour around identification, monitoring and management of IrADRs.
- Receipt of the HCP Guide and PAC.
- Understanding of the HCP Guide.
- Use of the HCP Guide and PAC i.e. whether physicians read and refer to the HCP Guide, inform patients of the risks associated with atezolizumab, complete and hand out the PAC to patients.

Data Sources

A panel will be used to identify physicians to participate in the survey.

The survey is a primary data collection study conducted through an on-line questionnaire. Responses will be collected through an on-line electronic data capture (EDC) system that will be used to create the study database for analytical purposes.

Study Size

The survey will aim to include approximately 300 physicians with completed questionnaires across the participating countries, to allow precisions of ±5.8% to ±3.6% for correct responses of 50-90%, respectively.

Data Analysis

The statistical analyses will be further detailed in the Statistical Analysis Plan (SAP).

The study will aim to address the following primary endpoints:

- **Receipt:** Percentage of respondents that report having received the HCP Guide and PAC.
- **Knowledge:** Percentage of respondents that correctly answered each knowledge sub-question. An individual physician score will be calculated as the proportion of all knowledge sub-questions with correct responses.

Secondary endpoints include:

- **Understanding:** Percentage of respondents that report having understood the HCP Guide.
- **Use:** Percentage of respondents that report having read or used the HCP Guide and PAC. An individual physician score will be calculated as the proportion of all use questions with correct responses.
- **Behaviour:** Percentage of respondents that correctly answered each behaviour sub-question. An individual physician score will be calculated as the proportion of all behaviour sub-questions with correct responses.

Each endpoint will be considered successful if the percentage/score is ≥70%. Results will be presented, overall, by country and by specialty.

Additionally, the level of knowledge and behaviour (overall scores and individual questions) consistent with key safety messages (including the need to report IrADRs)

according receipt and use of the aRMMs will be calculated. Knowledge and behaviour results will be described in physicians who received the aRMMs and those who did not and in users and non-users separately. No formal hypothesis will be tested. Results will be presented, overall, by country and by specialty.

Milestones

Start Date of Study:
The study start date will be the date of the first data collection: the date from which information from the first physician is recorded in the study database. The planned start date is January-March 2019.

End of Study
The end of the study will be the date from which the last data collected from the last physician is recorded in the study database. The planned end of study date is June-August 2019.

Length of Study
This study will last approximately 5 months after site selection.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the MAH or designee.

The Scientific Responsible will seek Counsel / Consultancy for the Protocol and succeeding amendments with his/her competent Ethics Committee.

Substantial protocol amendments/updates so far: none

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Registration of final PRAC approved protocol in the EU PAS register	Nov 2018
Start of data collection*	Jan - Mar 2019
End of data collection	Jun - Aug 2019
Final report of study results	Sep - Dec 2019
Registration of the results in the EU PAS register	TBD, after final PRAC recommendation as per CHMP opinion
Publication of study results	Apr - Jun 2020

*The data collection period may vary by country, but it is planned to fall within the 9-18 months period from each country launch.

6. RATIONALE AND BACKGROUND

TECENTRIQ® (atezolizumab) is an Fc-engineered, humanized, monoclonal antibody targeting human programmed death-ligand 1 (PD-L1) on tumour-infiltrating immune cells and tumour cells.

On 21 September 2017, TECENTRIQ® received marketing authorisation from the European Commission for the treatment of adult (≥18 years of age) patients with locally advanced or metastatic urothelial cancer (UC) after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression $\geqslant$ 5% as well as for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab. TECENTRIQ® is due to become available throughout the EU according to country-specific timelines.

The following important safety risks associated with the use of atezolizumab were identified to require additional risk minimisation measures (aRMMs): immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, and infusion related reactions (IRRs).

The aim of the atezolizumab aRMMs (Guide for Healthcare Professionals [HCP Guide] and patient alert card [PAC]) is to minimise the adverse consequences of these adverse reactions by increasing the physicians' awareness of IrADRs to facilitate early detection and prompt treatment.

As a requirement linked to the atezolizumab Risk Management Plan (RMP), Roche as the MAH, shall ensure that in each EU member state where atezolizumab is marketed all physicians who are expected to prescribe atezolizumab are provided with a brochure to inform them on how to recognise, monitor and manage side effects related to atezolizumab. particularly IrADRs. Patients should be given a PAC with information about the risks of atezolizumab, and instructions on when to contact their doctor if they experience symptoms (Table 1).

Table 1. aRMMs for atezolizumab and key messages agreed in the EU-RMP

aRMMs	Target population	Key messages
Patient Alert Card - PAC	Patients Prescribing physician HCPs to whom patients would present the card	• Atezolizumab can cause serious side effects during or after treatment, that need to be treated immediately. • Description of the main signs and symptoms of IrADRs • Warning message for patients on the importance of consulting their doctor immediately if they develop any of the listed signs and symptoms and not to treat themselves. • Importance of notifying their treating physician immediately if symptoms occur, persist or worsen • Reminder to carry the PAC at all times and to show it to all HCPs who may treat them. • Prompt to enter contact details of the treating physician • Message for other HCPs treating the patient at any time, including emergencies, that atezolizumab is being used.
Guide for healthcare professionals – HCP Guide	Prescribing Physicians: oncologists, pulmonologists, urologists	• Relevant information including signs and symptoms to recognise IrADRs associated with atezolizumab. • Details for each significant IrADR requiring treatment on how to minimise adverse consequences through appropriate monitoring and management. • Reminder to distribute the PAC to all patients receiving treatment with atezolizumab and advise them to show it to any HCP who may treat them. • Reminder to treating physicians to educate patients/caregivers about the signs and symptoms of IrADRs. • Reminder to treating physicians to educate patients/caregivers of the importance to report side effects immediately to the physician.

In line with regulatory guidance (e.g. EMA Good Pharmacovigilance Practice [GVP] XVI), the MAH was further asked to propose a Post-Authorisation Safety Study (PASS) to evaluate if the atezolizumab aRMMs are effective in informing physicians of the recognition and management of IrADRs including the need to report IrADRs.

The MAH proposed a physician survey to the EMA to describe receipt of, understanding and use, knowledge and behaviour outlined in the aRMMs among physicians and to assess whether the aRMMs are effective in informing physicians to recognize and manage IrADRs. This study is classified as a PASS and has been designed to meet the requirements of GVP module VIII: 'Post-authorization safety studies' (European Medicines Agency, 2016) and module XVI: 'Risk minimisation measures - Selection of tools and effectiveness indicators' (European Medicines Agency, 2017). This protocol also takes into account the key elements of survey methodology described in Annex I of GVP Module XVI (EMA 2017) in terms of sampling procedures and recruitment strategy; design and administration of the data collection instruments; analytical approach; as well as ethics, privacy, and overall study feasibility.

The results of the survey will be analysed to assess the effectiveness of the aRMMs in fulfilling the objectives. The survey results will be submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) and will also evaluate whether and how further updating the aRMMs should occur and the need and timing of any further evaluation.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. RESEARCH QUESTION

The study aims to address the following research questions:

- Have the atezolizumab HCP Guide and PAC reached the target physician population?
- Are the atezolizumab HCP Guide and PAC understood and used as intended by the target physician population?
- What is the level of knowledge for key messages related to IrADRs in the atezolizumab HCP Guide and PAC by the target physician population?
- What is the level of behaviour consistent with key messages related to IrADRs in the atezolizumab HCP Guide and PAC?
- Is the atezolizumab HCP Guide effective in informing the physician target population of the early recognition and management of IrADRs?

7.2. OBJECTIVES

The primary objective of this study is to assess the receipt of the atezolizumab HCP Guide and PAC for the target physician population and to assess the level of knowledge of key messages related to IrADRs outlined in the atezolizumab HCP Guide and PAC.

The secondary objectives of this study are to assess:

- The understanding of key messages related to IrADRs outlined in the atezolizumab HCP Guide.
- The use of the atezolizumab HCP Guide and PAC.
- The behaviour consistent with key messages related to IrADRs outlined in the atezolizumab HCP Guide and PAC.
- Knowledge according to receipt and use of the atezolizumab aRMMs.

- Behaviour consistent with key messages, according to receipt and use of the atezolizumab aRMMs.

This study will help assess the effectiveness of the atezolizumab aRMMs, with success declared if ⩾ 70% of participating HCPs in the survey confirm receipt, and demonstrate knowledge consistent with the key safety messages. These results, and threshold, will be interpreted in wider context of the secondary objectives and results of individual questions, response rates and recruitment. Additional information from the conduct of the study and externally may be used to help understand the experience with the aRMMs, to determine what actions, if any, should be taken. The rationale for the selection of threshold in this study is presented in Section 8.1.1.

8. RESEARCH METHODS

8.1. STUDY DESIGN

This is a multi-country, one-wave, cross-sectional physician survey, classified as a primary data collection NI-PASS.

The physician survey will be hosted on-line in the language of the participating country and is expected to take approximately 15 minutes to complete. In each country, physicians will be identified according to their specialty (oncologists, pulmonologists, and urologists).

Start Date of Study:

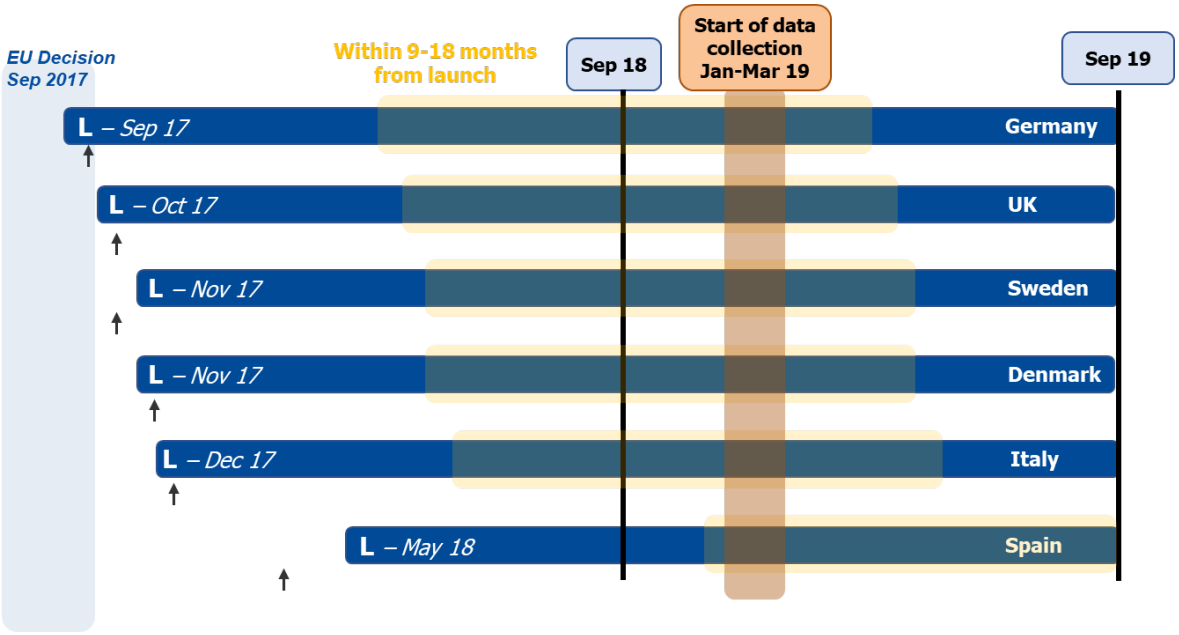
The study start date will be the date of the first data collection: the date from which information on the first study questionnaire is recorded in the study database.

The start of data collection in each country is planned to start within the 9 to 18 months period from each country-specific launch to allow time for uptake of atezolizumab and familiarity and use of the materials by the physicians, but to also assure the start of data collection does not vary greatly between countries. The timing of this evaluation is sufficiently early in the product lifecycle to identify and rectify promptly any aspect of the educational program that might need to be modified.

End of Study:

The end of the study will be the date of the last data collected from the last physician questionnaire recorded in the study database.

Figure 1. Illustration of the study design



Black arrow – Date of distribution of aRMMs; **L** – Date of country-specific launch

8.1.1. Rationale for Study Design

In line with regulatory guidance (e.g. European Medicines Agency, 2017) effectiveness of aRMMs requires an evaluation of the processes and relevant clinical and safety outcomes, where possible. Comparisons of frequency of outcomes before and after the implementation of aRMMs are unfeasible in this evaluation with no reference group available for post-implementation assessment over time.

In the context of the evaluation of process indicators, a survey among physicians is one of the methods most frequently used, and often the only method feasible, to assess receipt, use, knowledge and self-reported behaviour consistent with the messages in aRMMs (Vora et al., 2018). Representativeness and generalization of results to the target population can also be assessed (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, 2017).

To the extent launch dates of atezolizumab permit, an attempt was made to include a sample of countries (see section 8.2) involving different EU regions and healthcare cultures and systems. Oncologists, pneumologists and urologists were selected as the most appropriate audience to study as they are potential prescribers of atezolizumab, diagnose and manage serious IrADRs and are the chief target of the distribution of the aRMMs.

Current guidance documents do not stipulate ‘a priori’ thresholds to judge the success of aRMMs. The choice of 70% as a cut-off value for all endpoints in this study responds to a combination of: consideration of potential operational challenges inherent to the study

design (i.e. low participation and self-reported practices that rely on recall) and results observed in previous studies of this type (from an analysis of studies in the EU PAS Register, Vora et al., 2018). Preliminary results of a cumulative systematic review and meta-analysis of risk minimisation survey studies (presented at EMA/DIA Information Day, 2017) showed that receipt and use rates among HCPs rarely exceed 80% whereas percentages of correct knowledge of key safety messages mostly lie between 70% and 90%, varying substantially with safety concerns (45% correct knowledge for one risk and 90% for other in the same study). Therefore, to account for this potential variability, 70% is considered a reasonable threshold by the MAH for considering the aRMMs to be effective in this study.

8.2. SETTING

The selection of European countries to be involved in the survey has taken into account the following criteria:

- where atezolizumab has been registered and marketed for at least 9 months at the start of the survey to allow sufficient time for uptake of atezolizumab and familiarity and use of the materials.
- where physicians have been targeted to receive the aRMMs by the start of the survey.
- where atezolizumab availability and market penetration is sufficiently high to allow physician participation.

This study is planned to be conducted in a selection of European countries: UK, Italy, Spain, Germany, Denmark and Sweden (List in Table 2 based on commercial launch). Other countries may be added to meet the study timeline or if recruitment proves challenging. Roche has taken into account the predicted market uptake to preselect the countries and will ensure that the study will be performed in countries where atezolizumab is available and accessible to patients. The choice of study countries also attempted to support the external validity of the study findings, by collectively encompassing a wide range of healthcare systems: general practitioner-based gate-keepers, health insurance as part of the social security system, and mixed.

Table 2: Atezolizumab dates for commercial launch and aRMM distribution in selected countries with highest projected number of patients in EU (source: Roche data on file)

Country	Atezolizumab commercial launch	Distribution of aRMMs
Germany	September 2017	September 2017
UK	October 2017	October 2017
Italy	December 2017	December 2017
Spain	May 2018	March 2018
Denmark	November 2017	November 2017

Country	Atezolizumab commercial launch	Distribution of aRMMs
Sweden	November 2017	October 2017

8.2.1. Centres

Not applicable, as individual physicians from a panel will be targeted and not necessarily involve the centres in which they practice.

8.2.2. Study Population

Physician Identification and Selection

The current target population of the RMMs are physicians that could have potentially received the aRMMs and include oncologist, pulmonologists, and urologist. Physicians will be identified from panels in each country.

A stratified sampling method will be applied with pre-defined quotas based on the number of physicians of each specialty in the distribution list of each participating country (Roche data on file). Random samples of physicians in the panel strata will be invited to participate in the survey and asked to complete the on-line questionnaire until the quota for each stratum is reached, or the list is exhausted.

Physicians will be invited to participate in the survey via email. The survey background and objectives, the contact information for questions, and proposed financial compensation will be explained to them at this stage. The compensation will be based on a Fair Market Value assessment (e.g., time and effort) in each participating country.

An invitation and screening questionnaire will be sent to physicians in the sample. Eligible physicians who agree to participate in the survey will receive a link to access the e-questionnaire. Unresponsive physicians will be sent reminders by email periodically, during the month immediately after the link to access the e-questionnaire was first sent. Unresponsive physicians will be replaced until the target of survey respondents has been reached.

A recruitment database (including the number of physicians invited, screened, eligible, enrolled and completing the questionnaire – See Section 8.7.2.3.2) will be compiled during the recruitment process to document recruitment efforts and used for the description of study conduct.

Additional recruitment approaches may be considered if after a number of attempts recruitment remains challenging.

Eligibility Criteria

Physicians must meet the following criteria for study inclusion:

- Oncologist, pulmonologist or urologist who has prescribed or managed at least one patient with atezolizumab in routine clinical practice.

Physicians who meet any of the following criteria will be excluded from the study:

- Physician used atezolizumab only in clinical trials or in an expanded access programme.
- Physician refuses to participate.
- Physician is a current or former employee of Roche or delegates.

8.2.3. Concomitant Medication and Treatment

Not applicable

8.2.4. Dosage, Administration, and Compliance

Not applicable

8.3. VARIABLES

The survey will examine the effectiveness of the aRMMs targeting physicians about the IrADRs associated with atezolizumab treatment and the early identification and adequate management of IrADRs to minimise these risks.

The survey questionnaire will contain multiple-choice questions with no free text fields (See Appendix 2.1).

The questionnaire will be structured as follows:

A. Informed acceptance to participate (date and tick box)

B. Screening: eligibility

C. Demographics and physician practice information:

- Country
- Age group (<30, 30-45, 46-65, >65)
- Gender (male/female)
- Type of setting (office based, hospital based, both)
- Specialty (oncologist, pulmonologist, urologist)

- Experience: years working with oncology patients
- Past experience with atezolizumab: Time since last contact with a patient receiving atezolizumab, participation in a atezolizumab clinical trial, number of patients treated with atezolizumab in the last 12 months.

D. Main questionnaire domains in the order presented in the questionnaire (knowledge and behaviour are responded by all completers while receipt and use include filters):

- Knowledge: awareness, identification, monitoring and management of IrADRs and awareness of the need to report them.
- Behaviour around identification, monitoring and management of IrADRs.
- Receipt of the HCP Guide and PAC.
- Understanding of key messages in the HCP Guide.
- Use of the HCP Guide and PAC i.e. whether physicians read and refer to the HCP Guide, inform patients of the risks associated with atezolizumab, complete and hand out the PAC to patients.

Appendix 2.2 includes a table correlating the main questionnaire domains and endpoints with the specific question numbers.

8.4. DATA SOURCES

8.4.1. Collection of Data on the Questionnaire

The survey is a primary data collection study conducted through an on-line questionnaire. Responses from physicians will be collected through an on-line electronic data capture (EDC) system that will be used to create the study database for analytical purposes. No patient data will be collected in this study.

The survey questionnaire will be self-administered and can be completed at the participants' convenience. Although participants will be advised to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and, at a later time, pick up where they left off, if necessary. Participants will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the respondent using the web or other sources to influence answers to questions. Participants will also not be allowed to access the questionnaire once it has been submitted. Additionally, response options presented in a list will be randomized to minimise positional bias.

The physician questionnaire completion is estimated to take approximately 15 minutes.

A paper version of the physician questionnaire will first be developed in English, translated into the languages of the participating countries and culturally adapted among a sample of each targeted physician in each country, for comprehension, consistency and the appropriateness of medical terms. HCP comments will be implemented in the final version.

The translated versions of the questionnaire from English into local language will be done using the ´forward and back-translation´ method (from English into local language and then from local language into English) to ensure an accurate translation. This will be done by a certified translator.

8.5. DATA COLLECTED DURING THE OBSERVATION PERIOD

The data collection period will last approximately 16 to 20 weeks. The variables listed in Section 8.3 will be collected.

The survey will be conducted by [redacted], which is specialised in observational studies and surveys. [redacted] has a proprietary validated EDC system and platform for observational studies and surveys, which will be used to construct the e-questionnaire. [redacted] will ensure sufficient number of physicians are invited to reach the recruitment target of 300 physicians. The survey will collect data in an anonymous way.

8.5.1. Data Collected at Study Completion

Not applicable

8.5.2. Safety Data Collection

Not applicable

8.6. STUDY SIZE

8.6.1. Determination of sample size

The approach to the study sample size for the survey is governed by the assumed percentage of physicians who correctly respond to the questions and the acceptable precision around this assumed estimate but also takes into account practical considerations (i.e. feasibility of recruiting the sample). The sample size determination is based on the Clopper-Pearson method for exact binomial probabilities.

The proportions of interest (p) are the proportions mentioned under specific objectives below. As p is not known in advance, different percentages have been used to inform

precisions for different sample sizes i.e. the largest sample size for a specified margin of error.

The study aims to include approximately 300 physicians with completed questionnaires across the participating countries. With a sample size of 300 physicians (Table 3), the statistical precision around the estimate would be ±5.8% to ±3.6% for correct responses of 50-90%, respectively. 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 300 respondents, all completed responses received by the cut-off will be included in the analysis.

Table 3: Sample size obtained for various precisions and various proportions

Sample Size	% Correct responses	Statistical Precision (%)
100	50%	±10.2%
100	60%	±10.0%
100	70%	±9.4%
100	80%	±8.3%
100	90%	±6.4%
200	50%	±7.1%
200	60%	±7.0%
200	70%	±6.6%
200	80%	±5.8%
200	90%	±4.4%
300	50%	±5.8%
300	60%	±5.7%
300	70%	±5.3%
300	80%	±4.7%
300	90%	±3.6%
400	50%	±5.0%
400	60%	±4.9%
400	70%	±4.7%
400	80%	±4.1%
400	90%	±3.1%

8.6.2. Sample distribution

The ideal approach for sample distribution would require a proportional split of the 300 physicians according to the usage of the product in each country. However, due to the large variance of the number of physicians using atezolizumab in the targeted countries such an approach would result in small numbers of participants in the smaller countries (such as Denmark).

Therefore, a minimum of 10 valid questionnaires per country is planned. Provisional numbers are provided in Table 4.

Table 4: Provisional distribution of the countries involved in the survey according to a target sample size of 300 HCP analysable questionnaires.

Country	Target No. of Oncologists Pulmonologist/Urologists
Germany	90
Italy	70
UK	60
Spain	40
Denmark	20
Sweden	20
Total	**300**

Note that the achievement of the target in some of these countries may be challenging. In such cases, [redacted] will aim to achieve the overall target through over recruitment in other countries.

8.7. DATA MANAGEMENT

[redacted] will be responsible for data management of this study, including quality checking of the data.

All methods and procedures involved in each data management step are described in a Data Management Plan (DMP).

Data collected from the online questionnaire is hosted on [redacted] Servers. Daily backup is performed to prevent any data loss or damage.

Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted.

All documentation pertaining to the study, including electronic records will be retained by [redacted] for a maximum of 3 months after the end of the study, in accordance with [redacted] Standards. All study documents will be transferred to Roche thereafter and stored for an additional 25 years. At Roche the data will be stored in an electronic trial master file according to SOPs.

In addition to the online questionnaires, the feasibility and recruitment process will be registered in an excel database and managed by the study operations staff involved in the recruitment of participants. A unique code will be assigned to each physician, which will be used to link the questionnaire with the recruitment database. The unique code will be held by [redacted].

8.7.1. Electronic Data Capture

Questionnaires will be maintained in the EDC system. Data backups for data stored at [redacted] servers and records retention for the study data will be consistent with [redacted] standard procedures. [redacted] will comply with the Agreement between MAH and [redacted] regarding the archiving and record management procedures.

8.7.2. Source Data Documentation

Not applicable

8.8. DATA ANALYSIS

8.8.1. Safety Analyses

Not applicable

8.8.2. Interim/Final Analysis and Timing of Analyses

No interim analysis will be performed.

The statistical analyses will be described and further detailed in a Statistical Analysis Plan (SAP). The final SAP version will include (empty) table shells to be populated for the final study report (FSR).

General considerations:

The statistical analysis will be conducted using SAS 9.3 (or higher) statistical software (SAS, Cary, North Carolina, USA.). All programmes will undergo an independent quality check.

Statistical analyses will be mainly descriptive. Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, median, interquartile range, minimum and maximum.

Categorical variables will be described as the total number and relative percentage per category.

Confidence intervals of 95% will be evaluated, when relevant.

The number of missing data will be indicated. Since missing values are expected to be few and distributed at random, no replacement or imputation will be performed. Missing values will not be considered in the denominators for proportions.

For physician questionnaire measures, results will be stratified by country and physician's specialty.

Results may be weighted according to the distribution of physicians in the general population by country and specialty.

8.8.3. Primary Analysis

To address the primary objective, the total number of physicians with valid responses to all relevant questions and the percentage of physicians with a positive response for the below endpoints will be calculated. Results will be presented, overall, by country and by specialty:

Receipt: Percentage of respondents that report having received the educational materials. Receipt will be considered successful if the percentage of physicians who recall receiving the HCP Guide is ≥70%, and if the percentage of physicians who recall receiving the PAC is ≥70%. The main sources of the atezolizumab aRMMs (e.g. MAH representatives, company website, congresses) will also be described.

Knowledge: Percentage of respondents that correctly answered each knowledge sub-question. An individual physician score will be calculated as the proportion of all knowledge sub-questions with correct responses. A mean score will be calculated to summarise individual physician scores. The level of knowledge will be considered successful if the mean knowledge score is ≥70%.

The questions that will be used to address each specific endpoint are presented in Appendix 2.2.

8.8.4. Secondary Analysis

Understanding: Percentage of respondents that report having understood the key information in the HCP Guide. Understanding will be considered successful if the percentage of physicians who report having understood the HCP Guide among those who report having read it is ≥70%.

Use: Percentage of respondents that report having used the aRMMs i.e. whether physicians read and referred to the HCP Guide, informed patients of the risks associated with atezolizumab, completed and handed out the PAC to patients, counselled patients

to carry the PAC with them. An individual physician score will be calculated as the proportion of all use questions with correct responses. A mean score will be calculated to summarise individual physician scores. Use will be considered successful if the mean use score is ≥70%, and if the percentage of physicians who report reading the HCP Guide among those who reported having received it is ≥70%. Reasons for not reading the HCP Guide, and reasons for not providing and not completing the PAC will be described.

Behaviour: Percentage of respondents that correctly answered each behaviour sub-question. An individual physician score will be calculated as the proportion of all behaviour sub-questions with correct responses. A mean score will be calculated to summarise individual physician scores. The level of behaviour will be considered successful if the mean score is ≥70%.

The level of knowledge and behaviour (mean scores and responses to individual questions) consistent with key safety messages -including the need to report IrADRs-, according to receipt and use of the aRMMs will be calculated. Knowledge and behaviour results will be described in physicians who received the aRMMs and those who did not and in users and non-users separately. No formal hypothesis will be tested. Results will be presented, overall, by country and by specialty.

8.8.5. Other Analyses

Profile of physicians with incorrect answers

The profile of physicians with incorrect answers will be described using all available and relevant characteristics collected in the questionnaire (country, specialty, duration of practice, type of setting) and past experience with atezolizumab.

Analysis of physician participation

Survey responses will be compiled, and the analysis of physician participation will be presented by country and speciality.

The following survey participation sets will be identified and described:

- Invited: Physicians invited to participate i.e. to whom an email has been sent.
- Screened: Physicians who have been reached and completed the screening questions.
- Eligible: Physicians who meet all the eligibility criteria.
- Enrolled: Eligible physicians who accept to participate in the survey.
- Analysis Set: Physicians who complete the survey questionnaire and have valid responses for demographic questions.

These data will be documented in the recruitment database to compare the participating and non-participating physicians' profile to assess the impact of selection bias. The reasons for non-response will be sought.

Participation rates will be calculated and presented by country and specialty.

8.9. QUALITY CONTOL

8.9.1. Study Documentation

The study documentation will be stored in the study master file.

The web questionnaires data will be stored on the survey database for 3 months after study completion and transferred to Roche for extra storage. The data will then be stored for a further 25 years at Roche.

8.9.2. Site Audits and Inspections

Not applicable

8.9.3. Administrative Structure

Not applicable

8.9.4. Data collection, validation and data quality control at [redacted] level

Data will be collected using a web questionnaire.

The survey will be conducted according to [redacted] Standard Operating Procedures (SOPs).

Data will be collected using a validated EDC system. Unit testing and formal validation occur on all appropriate components during the build stage.

Data collected from online questionnaire is hosted on [redacted] Daily backup is performed to prevent any data loss or damage. Questions are programmed to ensure that they are asked in the appropriate sequence. 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 and tested prior to implementation.

8.9.5. Quality control of questionnaires

The questionnaire will be translated from English into local language using the forward and back-translation method to ensure an accurate translation of the local versions of the questionnaire. Translations will be performed by a certified company. The local versions of the physician questionnaire will thereafter be culturally adapted with 3 physicians per country.

8.9.6. Quality control of results

All data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data to include recoding and computing of new variables, stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.

At the results level, a quality check will be done to ensure the quality of the statistical analysis report and results integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.

At the study level, all aspects of the study will be conducted according to the [redacted] SOPs.

8.9.7. Safeguards, security and traceability of contacts

All survey aspects from protocol development to the reporting of the results will be conducted according to the [redacted] SOPs. These SOPs can be consulted on site (8).

8.10. LIMITATIONS OF THE RESEARCH METHOD

The potential for selection bias of physicians participating in a survey is an inherent bias/limitation to any study based on volunteer participation. To quantify any selection bias, the distribution of each stratification criterion of physicians (country, specialty, and the other available characteristics present in the recruitment database) will be compared between participants and non-participants.

An existing panel of HCPs will be used as a source to facilitate identification and recruitment of physicians. The population in panels may be more research active than those not in the panel. However, it also provides a more geographically spread population. Where possible, detailed information about the sites and the distribution of the materials in each country would be obtained (e.g. sent to the department or sent to the physician, which type of specialists in each site are also in the distribution list, how many physicians were targeted in each site) to allow some comparisons with the panel population.

In surveys, the generalisation and external validity of the results is restricted to physicians who have an active email address and willing (and able) to answer a questionnaire online. These physicians may not be fully representative of the whole targeted population.

Among non-response bias, targeted physicians may also have activated filters in their mail box to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the physicians do not check their email box frequently they will not receive the invitation during the recruitment period.

Physician responses may be biased by referral to the materials as they complete the questionnaire. This may be minimized by explaining that responses should be based on assessing what they currently know and that they should not refer to the materials. Measures to minimize physician response bias with online questionnaires are: all questions are programmed to ensure that they are presented in an appropriate sequence, questions must be answered in sequence, skipping ahead to later questions is not permitted, answers cannot be changed once submitted, and skip patterns to questions are clearly indicated. Additionally, response options presented in a list will be randomized to minimise positional bias.

Self-reporting of actions and behaviour may be biased towards positive values. The development of a questionnaire carefully pre-tested before actual study starts aims to minimize such a bias. Non-response of items should be minimised due to the rigorous process of questionnaire development, validation and testing.

Recall bias is an inherent limitation of questions asking about the past.

The size of the study population will allow an acceptable level of precision for the study primary endpoints. However, secondary endpoints and other subgroup analyses will be exploratory and may be unreliable due to the small number of patients in each sub-group. The interpretation of differences between sub-groups will be cautious and only based on descriptive statistics.

8.11. OTHER ASPECTS

Strengths of the research methods:

1. The sampling of physicians follows a stratified random method which helps minimise the likelihood of selection bias due to voluntary participation.

2. The questionnaire includes general questions followed by specific ones in order to limit a learning process during the survey. As the physicians may understand the

right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.

3. The questionnaire is tested for its clarity. It is also checked whether there are questions which would suggest a specific answer for any reason for example social desirability. The translation of the questionnaire is tested before implementation.

4. The study is conducted by an experienced team specialised in the design and conduct of risk minimisation surveys. It follows [redacted] SOPs as well as the methodological guidelines of ENCePP and EMA GVP.

9. PROTECTION OF HUMAN SUBJECTS

9.1. PATIENT DISCONTINUATION

Not applicable

9.2. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional PASS.

Each participating country should locally ensure all necessary regulatory submissions (e.g: IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

9.3. INFORMED CONSENT

Physicians participating in the study have to consent for data collection and need to be informed about the purpose of the survey and their storage of data before completing the online questionnaire. This will be done electronically. [redacted] will ensure that the national and European data protection and ethical requirements are met for the physicians.

9.4. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Each participating country should locally ensure all necessary regulatory submissions (e.g: IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

9.5. CONFIDENTIALITY

The physician's personal data which may be included in [redacted] database will be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the physicians, [redacted] will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Each participating physician will receive a unique link to access the survey. The online survey will be located in a secure web page using https protocol to protect the privacy and integrity of the exchanged data while in transit.

The answers provided will be collected in an anonymous way, and only aggregated data presented as a synthesis will be transmitted to the MAH.

9.6. FINANCIAL DISCLOSURE

Physicians will provide [redacted] with sufficient, accurate financial information in accordance with local regulations to allow the MAH to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests.

Physicians will be offered a compensation for the time spent participating in this survey (that they may refuse). For physicians involved in the physician survey, the time to complete the questionnaire is approximately 15 minutes. The amount of this compensation will be determined according to fair market value standards in each country.

10. MANAGEMENT OF ADVERSE EVENTS

This study is a survey to evaluate the effectiveness of materials implemented as aRMM. This survey does not involve data collection on clinical endpoints on individual patients. Although adverse event information is not being actively solicited via this protocol, physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention either to the MAH of the suspected medicinal product or to the concerned competent authorities via the national spontaneous reporting system.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The protocol, study status updates and report(s) will be included in regulatory communications according to the risk minimisation plan, periodic benefit-risk evaluation reports and other regulatory milestones and requirements.

Regardless of the outcome of a study, the MAH is dedicated to openly providing information on the study to HCPs and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

After completion of the survey, a FSR will be developed and submitted to PRAC, and will serve as a basis for the development of publications and presentations in scientific journals, and press releases. The results and interpretation will be submitted for publication. Abstracts, summaries, presentations and manuscripts will be prepared in line with dissemination guidelines of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors, 2017) and Guidelines for Good Pharmacoepidemiology Practice (ICPE, 2016) to help ensure the quality and integrity of pharmacoepidemiological research and to provide adequate documentation of research methods and results.

The survey has been registered in EU-PAS Register. The study summary results will be posted according to Roche procedures.

12. REFERENCES

EphMRA Code of Conduct. 2017.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) - Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 2017.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 2). 2016.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. 2017.

ICPE. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf 2016;25:2–10.

[redacted]

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2017.

Vora P, Singh V, Artime E, Asiimwe A. A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European Union electronic Register of Post - Authorization Studies 2018:1–12. doi:10.1002/pds.4434.

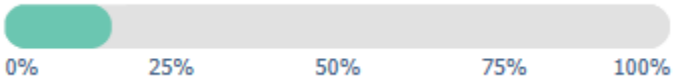
Appendix 1: List of Stand-Alone Documents Not Included in the Protocol

Appendix 2. Physician Questionnaire

Study:

Survey to learn about the management of safety issues of TECENTRIQ® (Atezolizumab) in routine clinical practice in the European Union requested by the EMA

Screening



Thank you for your interest in taking part in this study. The first step is to answer a few upfront questions to help us determine if your background is right for this survey. Please take a few minutes to answer the following questions to see if you are eligible.

Please note the green status bar above will track your progress through the screener questions.

Please know that [redacted] looks to avoid terminated surveys due to screen outs or quota full as much as we can, however it is not always possible. Typically, our studies begin with initial questions to determine which group a respondent falls into. At which point, it is possible that the survey will terminate because the respondent does not fall into a group that is being targeted or because the required number of completed surveys has already been met.

S1 Please select your country:

(please select one answer)

○	Denmark
○	Germany
○	Italy
○	Spain
○	Sweden
○	United Kingdom

S2 Have you ever prescribed or managed a patient with TECENTRIQ® in routine clinical practice?

(please select one answer)

○	Yes, both in routine clinical practice and as part of a clinical trial/expanded access program
○	Yes, only in routine clinical practice
○	No, only in clinical trials or expanded access programs → *We're sorry, but you do not qualify for this particular study. Thank you for your time. You have been terminated on S2.*
○	No, I have never prescribed or managed a patient with TECENTRIQ → *We're sorry, but you do not qualify for this particular study. Thank you for your time. You have been terminated on S2.*

S3 Have you been an employee of Roche or [redacted]?

(please select one answer)

- ○ Yes → *We're sorry, but you do not qualify for this particular study. Thank you for your time. You have been terminated on S3.*
- ○ No

S4 Please select your profile:

(please select one answer)

- ○ Oncologist
- ○ Urologist
- ○ Pulmonologist
- ○ Other → *We're sorry, but you do not qualify for this particular study. Thank you for your time. You have been terminated on S4.*

S5 How old are you?

(please select one answer)

- ○ Younger than 30 years
- ○ 30 to 45 years
- ○ 46 to 65 years
- ○ Older than 65 years

S6 Are you male or female?

(please select one answer)

- ○ Male
- ○ Female

S7 Thank you for your time, you have been selected to participate in this observational study. The [redacted] survey is being conducted to meet a regulatory obligation from the European Medicines Agency (EMA). The purpose of this survey is to learn more about the use of TECENTRIQ® (Atezolizumab) in routine clinical practice. The questionnaire should not take more than 15 minutes to complete, you will receive the web link to access the online questionnaire from an external company, [redacted], who is working on behalf of Roche. We would be grateful if you could complete the questionnaire in 5 days of reception of the link. Please confirm you still agree to participate?

- ○ Yes
- ○ No, could you please indicate the reason:
  - ○ Lack of time →*Thank you very much for your time.*
  - ○ Not interested →*Thank you very much for your time.*

PLATFORM MESSAGE TO INTRODUCE THE LINK TO THE MAIN QUESTIONNAIRE

You recently completed a pre-recruitment questionnaire – [Study [redacted]] – and we would like to thank you for your interest.

We would like to invite you to participate in the main part of the survey that is being conducted to meet a regulatory obligation from the European Medicines Agency (EMA) by [redacted] on behalf of Roche. The purpose of this survey is to learn more about the use of TECENTRIQ® (Atezolizumab) in routine clinical practice. The questionnaire should not take more than 15 minutes to complete.

Text for [country] only: [to fill with the country specific data protection / country specific local regulatory requirements].

Please proceed clicking the survey http://URLxxx.

Your input is highly appreciated.

Main questionnaire

TECENTRIQ® (Atezolizumab) Questionnaire for Physicians

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. Introduction

ASSUMPTIONS:

- Only physicians who have prescribed or managed at least one patient with TECENTRIQ® (atezolizumab) are eligible to participate in this survey.
- The asterisk (*) denotes the correct or the best response(s) in a list of options and will not appear in the final version presented to the Physician.
- An invitation (explaining the project in more detail) will be sent out separately.
- This box ('Assumptions') and the text in *blue* will be hidden in the electronic version of the questionnaire.

First, thank you for agreeing to participate in this study.

This survey is being conducted to meet a regulatory obligation from the European Medicines Agency (EMA). The purpose of this survey is to learn about the management of safety issues of TECENTRIQ® (Atezolizumab) in routine clinical practice. The questionnaire should not take more than 15 minutes to complete.

The survey does not involve any promotional material. You will not be contacted for marketing purposes based on your answers to the survey. Neither the survey sponsor nor its contractors will sell or rent your information.

Confidentiality

Roche is the sponsor for this study will act as the data controller. [redacted] is conducting this study on behalf of the sponsor and will act as the data processor.

[redacted] guarantees, also on behalf of Roche, its commitment to the protection of your privacy and always acting in compliance with its internal procedures and the rules on the protection of personal data.

Roche and [redacted] will process your personal data, for the sole purpose of carrying out the study. The information collected will be entered by you onto an online questionnaire. Your responses will be used only for statistical purposes and will not be disclosed or shared in any personally identifiable form for any other purpose.

Roche and [redacted] will not have access to any personal identifiable information such as name, surname, email, phone number or bank account information.

The data will only be distributed in strictly anonymous form, for example through scientific publications, statistics and scientific conferences.

For any request related to the exercise of your rights of access, correction, deletion or obtaining a copy of your personal information; please contact [redacted]. [redacted] will communicate with Roche, as the controller of the data, or with [redacted], the processor designated by Roche.

Reporting of safety events

While this survey is not designed to collect information on individual adverse events from physicians, if you identify any safety event (adverse events, product complaints and /or other safety findings), including misuse, medication errors, off-label use, overdose, drug abuse, lack of efficacy, suspected transmission of infectious agents, drug exposure during pregnancy/breastfeeding, or occupational exposure that occur in patients treated with TECENTRIQ®, you should report it by email to [redacted].

Please note that you should also report any suspected adverse reactions to the Medicines and National Authorities through the Yellow Card Scheme.
You can complete a Yellow Card online *[adapt to the local regulation]*.

Please confirm your agreement to participate in the current survey below:

○	**Yes**, I agree to participate in this survey.
○	**No**, I do not agree to participate in this survey → *Thank you very much for your time.*

General instructions for completing the questionnaire

- We recommend completing the questionnaire in one sitting (please allow 15 minutes).
- Please do not refer to any of the TECENTRIQ® educational materials before or during the completion of this questionnaire. It does not matter if you are unsure or do not know the answer to a question. This is valuable information in itself.

2. Questions about you and your healthcare practice

In this section, you should answer some questions about yourself.

Q1 In which type of setting do you work most of your time?

(please select one answer)

○	Office based
○	Hospital based
○	Both, office and hospital
○	Other

Q2 For how many years have you managed oncology patients?

(please select one answer)

○	Less than 3 years
○	3 to 5 years
○	6 to 10 years
○	More than 10 years

Q3 How many patients have you ever been involved with in the prescription or management of TECENTRIQ® in routine clinical practice in the last 12 months?

(please select one answer)

○	One → *please write the date of last contact with a patient on TECENTRIQ ®*	→	___/___/___ dd mm yyyy *(If you don't remember the exact date, please specify at least the month and year)*
○	More than one → *please write the date of last contact with a patient on TECENTRIQ®*	→	___/___/___ dd mm yyyy *(If you don't remember the exact date, please specify at least the month and year)*

3. Knowledge about TECENTRIQ®

The purpose of these questions is to understand better physicians´ current knowledge of TECENTRIQ®.

Q4 Which of the following risks are associated with TECENTRIQ®?

	True	False	I don´t know/ Not sure
Neuropathies	○*	○	○
Hepatitis	○*	○	○
Colitis	○*	○	○
Meningoencephalitis	○*	○	○
Pancreatitis	○*	○	○
Pneumonitis	○*	○	○
Endocrinopathies	○*	○	○
Infusion related reactions	○*	○	○
Stomatitis	○	○*	○
Urethritis	○	○*	○
Insomnia	○	○*	○
Amnesia	○	○*	○
The order of the rows displayed will be randomized			

Q5 Which of the following should be complied with?

(please select all answers that apply)

	True	False	I don´t know/ Not sure
Permanently discontinue TECENTRIQ® for any immune-related adverse reactions that requires corticosteroid doses ≤10 mg prednisone or equivalent/day after 12 weeks.	○	○*	○
Rapid tapering of corticosteroids.	○	○*	○
Permanently discontinue TECENTRIQ® for any immune related adverse reaction that persists after treatment modification.	○*	○	○
Permanently discontinue TECENTRIQ® if any Grade ≥3 toxicity occurs a second time.	○*	○	○
Permanently discontinue TECENTRIQ® for Grade 4 immune-related adverse reaction, except for endocrinopathies that are controlled with replacement therapy.	○*	○	○
Monitoring liver function tests and bilirubin before and periodically during treatment with TECENTRIQ®.	○*	○	○
Permanently discontinue TECENTRIQ® if severe diarrhoea / colitis (grade 4) occurs.	○*	○	○
Withhold TECENTRIQ® if hepatitis grade 2	○	○*	○

(please select all answers that apply)

	True	False	I don´t know/ Not sure
occurs (AST/ALT >x3.0–5.0 ULN or bilirubin >x1.5–3.0 ULN), even if they resolve in 2-3 days.			
For grade 2 Infused-Related Reactions (IRR) TECENTRIQ® can be continued with a reduced infusion rate.	○*	○	○
TECENTRIQ® can be resumed while a patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressives.	○	○*	○

The order of the rows displayed will be randomized

Q6 Should all adverse reactions associated with TECENTRIQ® be reported to regulatory agencies, during and at any time after infusion?

(please select one answer)

- ○ Yes*
- ○ No
- ○ Rarely
- ○ I don´t know/ Not sure

4. Hypothetical clinical scenarios of patient treated with TECENTRIQ®

The purpose of these questions is to know how you would manage patients treated with TECENTRIQ® with adverse reactions.

Q7 Please, read each hypothetical case and respond how you would proceed in your routine clinical practice i.e. permanently discontinue or temporarily stop TECENTRIQ®

(please select all answers that apply)

	Permanently discontinue	Temporarily stop	I don´t know/ Not sure
A patient develops dyspnoea, hypoxia and patchy infiltrates on chest x-ray, consistent with immune-related pneumonitis.	○*	○	○
A patient develops new isolated hypothyroidism, without an alternative aetiology, that is corrected by replacement therapy and without the need for corticosteroids or other immunosuppressive therapy.	○	○*	○
A patient develops meningoencephalitis, without an alternative infectious or other aetiology.	○*	○	○

5. Experience with TECENTRIQ®

The purpose of these questions is to evaluate your experience **with the last patient** you managed on TECENTRIQ®.

Q8 Did you counsel/educate your last patient?

(please select one answer for each item)

	Yes	No	I don't remember/ Not sure
About the signs and symptoms of immune related reactions associated with TECENTRIQ®.	○*	○	○
To contact their treating doctor immediately if they experience symptoms of immune-related adverse reactions.	○*	○	○

The order of the rows displayed will be randomized

6. TECENTRIQ® educational materials

The purpose of this section is to know if you have received and used the TECENTRIQ® educational materials.

Q9 Have you received or had access to any of the following materials related to TECENTRIQ®?

	Yes	No	I don´t know/ Not sure
TECENTRIQ® Guide for healthcare professionals	○*	○	○
TECENTRIQ® Patient Alert Card	○*	○	○
TECENTRIQ® Summary of Product Characteristics	○	○	○

If 'Yes' to Guide for healthcare professionals and/or to Patient Alert Card go to Q10 to fill in the column that applies. Otherwise, go to Q20. The order of the rows displayed will be randomized

Q10 How have you received or had access to the TECENTRIQ® educational materials?

(please select all answers that you think apply)	TECENTRIQ® Guide for healthcare professionals	TECENTRIQ® Patient Alert Card
Regular post	☐	☐
Medical / Pharmaceutical representatives	☐	☐
Pharmaceutical company website	☐	☐
National Health Authority website/ National formulary website	☐	☐
e-prescribing prompts	☐	☐
Congresses / symposia	☐	☐
Colleagues	☐	☐
I don´t remember	☐	☐

The order of the rows displayed will be randomize
[Only those participants who have selected 'Yes' in Q9 for the Guide for healthcare professionals should to answer 0 and those participants who have selected 'Yes' in Q9 for the Patient Alert Card should to answer Q15. If 'No' or 'I don´t know/ Not sure' to Q9 for the patient alert card, go to Q20]

Q11 Have you ever read the TECENTRIQ® Guide for healthcare professionals?

(please select one answer)

○	Yes*
○	No → *If 'No' go to Q14*
○	I don't remember → *If 'I don't remember' and those participants who have selected 'Yes' in Q9 for the patient alert card should answer to Q15. If 'No' or 'I don´t know/ Not sure' to Q9 for the patient alert card, go to Q20]*

Q12 How well did you understand the information in the TECENTRIQ® Guide for healthcare professionals?

(please select one answer)

○	I understood the information completely*
○	I have found the material too difficult to understand
○	I did not understand most of the material
○	I did not understand the material at all
○	I don´t remember

Q13 How often did you refer to the TECENTRIQ® Guide for healthcare professionals during the treatment of your last patient on TECENTRIQ®?

(please select one answer)

○	Frequently*
○	Sometimes
○	Rarely
○	I don´t remember

[If 'Yes' to Q9 for the patient alert card and after completing Q13, go to Q15. If 'No' or 'I don´t know/ Not sure' to Q9 for the patient alert card and after completing Q13, go to Q20]

Q14 If you have not read the TECENTRIQ® Guide for healthcare professionals, why did you not read it?

(please select all answers that you think apply)

☐	Somebody else is responsible for dealing with it
☐	I did not know about the existence of it
☐	I haven't had time to read it
☐	I forgot to read it
☐	I consult other material(s) on TECENTRIQ®

☐	I did not think that I would find it useful
☐	Other

[If 'Yes' to Q9 for the patient alert card and after completing Q14, go to Q15. If 'No' or 'I don´t know/ Not sure' to Q9 for the patient alert card and after completing Q14, go to Q20]

Q15 Do you provide the TECENTRIQ Patient Alert Card to patients receiving TECENTRIQ®?

(please select one answer)

○	Yes, to all patients* → *If 'Yes' go to question Q17*
○	Yes, to most patients → *If 'Yes' go to question Q17*
○	Yes, to very few patients → *If 'Yes' go to question Q17*
○	No
○	I don´t remember

Q16 If you do not provide the Patient Alert Card, please specify why

(please select all answers that you think apply)

☐	I am not aware of it
☐	Somebody else is responsible for handing it out
☐	I have not had time to hand it out
☐	I forget to hand it out
☐	I do not think that they would find it useful
☐	I don´t remember
☐	Other

Q17 Do you counsel your patients to carry the Patient Alert Card with them at all times from receiving the first administration to at least 5 months after the last dose of the treatment with TECENTRIQ®?

(please select one answer)

○	Yes, to all patients*
○	Yes, to most patients
○	Yes, to very few patients
○	No
○	I don´t remember

Q18 Do you fill in the Patient Alert Card with your contact details?

(please select one answer)

- ○ Yes, completely* → *If 'Yes' go to question Q20*
- ○ Yes, some of them → *If 'Yes' go to question Q20*
- ○ Yes, very few information → *If 'Yes' go to question Q20*
- ○ Nothing at all
- ○ I don´t remember → *If 'I don't remember' go to Q20*

Q19 If you do not formally fill in the Patient Alert Card, please specify why

(please select all answers that you think apply)

- ☐ I am not aware of them
- ☐ Somebody else is responsible for filling it in
- ☐ I have not had time to fill it in
- ☐ I forget to fill it in
- ☐ I didn't think that they would find it useful
- ☐ I do not remember
- ☐ Other

Q20 Did you read the TECENTRIQ® educational materials just before or during the completion of this questionnaire?

(please select one answer)

- ○ Yes
- ○ No

Thank you for completing the questionnaire!
Your collaboration is greatly valued.

Appendix 2.2 Summary of the Physician survey questions linked to each specific objective.

Summary of the Physician survey questions linked to each specific objective	
Objective	**Question Number**
Receipt of the educational materials	Q9 Q10
Knowledge of key information in educational materials	Q4 Q5 Q6
Behaviour of key information in the educational materials	Q7 Q8
Use of the educational materials	Q11 Q13 Q14 Q15 Q16 Q17 Q18 Q19
Understanding of key information in the educational materials	Q12
Sociodemographic characteristics	S1 S5 S6
Healthcare professionals practice	Q1 Q2 Q3
Screening	S2 S3 S4
Quality control variable	S7 Q20

Appendix 3. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

- 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 section number 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). 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: SURVEY TO EVALUATE THE EFFECTIVENESS OF RISK MINIMISATION MEASURES FOR ATEZOLIZUMAB USE IN THE EUROPEAN UNION

Study reference number: WO40486

1. **Section 1: Milestones**	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5, 3
1.1.2 End of data collection[2]	☒	☐	☐	5, 3
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5

[1] 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.

1. Section 1: Milestones	Yes	No	N/A	Section Number
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

As this is a cross-sectional survey study, no progress or interim reports are planned.

2. Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6, 3
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.0, 8.1.1
2.1.2 The objective(s) of the study?	☒	☐	☐	7.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3, 8.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Comments:

4. Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	3, 8.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	3, 8.1, 8.2
4.2.2 Age and sex?	☒	☐	☐	3, 8.3
4.2.3 Country of origin?	☒	☐	☐	3, 8.1, 8.3, 8.5.2
4.2.4 Disease/indication?	☒	☐	☐	3, 8.3
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.2

Comments:

Cross-sectional design so no patient follow-up.

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

Comments:

NI-PASS Study targeting HCPs only (drug users and exposure are not altered by the study).

6. 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?	☒	☐	☐	3, 8.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3, 8.3

6. Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	3, 8.8.5
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

7. 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 (e.g. healthy user bias)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.3

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.3

Comments:

8. Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	3, 8.4

8. Section 9: Data sources	Yes	No	N/A	Section Number
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	3, 8.4
9.1.3 Covariates?	☒	☐	☐	3, 8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.6.1

Comments:

9. Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7
10.2 Are descriptive analyses included?	☒	☐	☐	8.7
10.3 Are stratified analyses included?	☒	☐	☐	8.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	3, 8.5.1, 8.5.2

Comments:

No exposure-outcome association assessed.

10. Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6, 8.8.4
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:

11. Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.1, 8.5.1

Comments:

12. Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.0

Comments:

13. 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:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____