POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

Title	**Post-authorisation observational safety study to examine the effectiveness of risk minimization measures in place in persons with an Anapen® prescription**
Protocol version identifier	Version 3.0
Date of the last version of protocol	30 July 2025
EU PAS register number	Study will be registered upon approval of the protocol
Active substance	Adrenaline (Epinephrine, ATC code: C01CA24) Pharmacotherapeutic groups: Cardiac stimulants excl. Cardiac glycosides; Adrenergic and dopaminergic agents
Medicinal product	Anapen®
Product reference	Anapen® 150 micrograms in 0.3 ml solution for injection in a pre-filled syringe. CIP 3400936157361 Anapen® 300 micrograms in 0.3 ml solution for injection in a pre-filled syringe. CIP 3400936157422 Anapen® 500 micrograms in 0.3 ml solution for injection in a pre-filled syringe. CIP 3400930166116
Procedure number	Anapen® 150: Mutual Recognition Procedure n° PT/H/1189/001/MR Anapen® 300: Mutual Recognition Procedure n° PT/H/1189/002/MR Anapen® 500: Decentralized Procedure n° PT/H/1189/003/DC
Marketing authorisation holder(s)	**MAH for France** Bioprojet Pharma 9, rue Rameau - 75002 PARIS - France
Joint PASS	No
Research question and objectives	Bioprojet Pharma provides healthcare professionals with educational materials with the aim of ensuring that patients and relatives use adrenaline auto-injectors successfully. The objectives of this study are to assess the real-life effectiveness of the risk minimization measures associated with Anapen® at the time of dispensation by the pharmacist, in measuring the patients' and relatives' knowledge on how to use Anapen® prior to its use.
Country of the study	France
Author	Christine JUHEL (Ph. D) christine.juhel@groupecen.com

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Bioprojet Pharma 9, rue Rameau - 75002 PARIS - France
MAH contact person	Estelle LANGLOIS e.langlois@bioprojet.com

PARTICIPATION TO THE STUDY – CONFIDENTIAL AGREEMENT

Information contained in this protocol is confidential and is the property of Bioprojet Pharma.

This protocol contains all necessary details to perform the study. Each participating pharmacist should ensure strict compliance with the protocol. The participating pharmacist should in no case be a source of protocol modification without having previously obtained Bioprojet Pharma's permission. Respect of the inclusion criteria should be documented by the participating pharmacist on the data collection questionnaire. Participating pharmacists should take all possible measures to complete the study within the time allocated.

Access to all information provided by Bioprojet Pharma may be given to all involved collaborators under the supervision and responsibility of the participating pharmacist. People taking note of this information should be informed of their confidential nature; they must respect confidentiality without restrictions.

The contents of this protocol cannot be used for other non-interventional study or clinical study and will not be disclosed to any other person or entity without prior written authorization of Bioprojet Pharma. The commitment does not apply to the disclosure required by law or governmental regulation; nevertheless, Bioprojet Pharma should be informed prior to such disclosure.

Bioprojet Pharma may terminate the study at any time, this discontinuation may be motivated or not.

Additional information that could be added to this protocol is also confidential and property of Bioprojet Pharma; it must remain confidential such as the content of this protocol.

APPROVAL FORM – STUDY PROTOCOL

Post-authorisation observational safety study to examine the effectiveness of risk minimization measures in place in persons with an Anapen® prescription (Anapen® PASS)

SPONSOR

Benoit DE GERMINY Signature: Date:

Medical and Economic Director Bioprojet Pharma

Martine LE GALL Signature: Date:

Head of Clinical Development Bioprojet Pharma

Jean-Stéphane JULIEN Signature: Date:

Responsible Pharmacist Bioprojet Pharma

Marlène VELLAR Signature: Date:

EU-QPPV Bioprojet Pharma

CRO

Christine JUHEL Signature: Date:

Medical Director CEN

COORDINATING INVESTIGATOR SIGNATURE PAGE – STUDY PROTOCOL

Post-authorisation observational safety study to examine the effectiveness of risk minimization measures in place in persons with an Anapen® prescription (Anapen® PASS)

The study will be conducted in compliance with the following protocol and will be carried in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11 and following revisions). EMA/95098/2010 and applicable local regulatory requirements in the participating country.

I give my complete agreement on this protocol which gives all necessary information to conduct this study. I hereby accept to coordinate this study.

COORDINATING INVESTIGATOR

Pharmacist Signature: Date:

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AAI	Adrenaline Auto-Injector
ADR	Adverse Drug Reaction
AE	Adverse Event
ANSM	National Agency for the Safety of Medicines and health products
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures - human
CHMP	Committee for Human Medicinal Products
CRF	Case Report Form
CRO	Contract Research Organization
CSP	French Public Health code
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	The electronic ENCePP E-register of studies
GDPR	General Data Protection Regulation
HCP	Healthcare Professionals
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

3. RESPONSIBLE PARTIES

The main responsible parties are presented in Table 1.

Table 1: List of the main responsible parties

Responsible Party	Name and Affiliation
Sponsor	Bioprojet Pharma 9, rue Rameau - 75002 PARIS - France
Principal/Coordinating Investigator	Pharmacist
Contract Research Organization (CRO)	CEN 18, rue Pauline Kergomard - 21000 DIJON - France

4. ABSTRACT

Title

Post-authorisation observational safety study to examine the effectiveness of risk minimization measures in place in persons with an Anapen® prescription

Version 3.0 30 July 2025

Author: Christine JUHEL

Rationale and background

Anaphylaxis is an acute, life-threatening, systemic allergic reaction associated with various triggers, clinical presentations and levels of severity. It is imperative that adrenaline is immediately administered as soon as signs and symptoms of anaphylaxis appear. Adrenaline Auto-Injectors (AAI) are the first-aid treatment. Any problem with the administration of adrenaline could result in significant hazard to the patient due to the emergency nature of the condition that AAI is intended to treat. In the worst scenario, this could result in a failure to deliver adrenaline and, in emergency, leading to a fatal outcome for the patient if he is not supported by a care service.

In 2014, the EMA carried out a review of adrenaline auto-injectors following concerns that available devices may deliver adrenaline under the skin instead of into a muscle, and this may delay response to treatment. Usability assays and reports have led to improve the safety of disposable self-injection devices (Weinhold 2018, Kessler 2019, EMA 2015): *i.e.*, needle length, the way AAI works, intuitive use etc. Multi-incident analyses have identified factors contributing to the lack of efficacy due to errors in the use of self-injection devices, or accidental injection (Schwirtz 2012, Cohen 2017, Posner 2017, Sasaki 2018, Weinhold 2018, EMA 2015): *i.e.*, angle at which the device is placed, strength used to activate the device, how well the user follows instructions for injection or recognizes concomitant symptoms requiring injection. Several studies have shown that regular patient education and training can minimize user errors and the resulting lack of efficacy of AAI (Segal 2012, Sirin Kose 2020, Kadivec 2021). These studies have highlighted that education should not be limited to the patient but disseminated in community setting to effectively prevent accidental injections, laceration or, lack of efficacy due to mishandling. All these points have been taken up by the EMA's Committee for Human Medicinal Products (CHMP). The CHMP concluded that training of the user is of paramount importance. The companies that market adrenaline auto-injectors have therefore been asked to develop more effective educational material for patients, as well as for healthcare professionals, to ensure their optimal use. This includes a training device with which patients can practice; audio-visual material to show in detail how the device is to be used; and a checklist for prescribers to ensure that sufficient information is given to the patient before they use the auto-injector. The product information of adrenaline auto-injectors has also been updated with further warnings and precautions, including a recommendation that patients should be prescribed two auto-injectors which they should always carry along and a recommendation for family members, carers or teachers to be trained on how to use the auto-injector. The CHMP also concluded that further data should be generated to better understand how adrenaline penetrates body tissues when given with auto-injectors. The assessment report (25 June 2015 under articles 31 and 32 of Directive 2001/83/EC European Parliament and

Council / ref#EMEA/H/A-31/1398) was sent to the European Commission which endorsed it and issued a legally binding decision (C2015/5886 14Aug2015) that is valid throughout the EU.

Bioprojet Pharma markets AAIs containing either 150, 300 or 500 mcg of adrenaline, under the brand name of Anapen® or Chenpen® depending on the country of marketing.

The CHMP recommendations have been fulfilled and detailed in the last revision of the sponsor Risk Management Plan (RMP, version 4.1 submitted on 2023/02/21). Safety concerns are summarized as follows:

- Important potential risks: serious allergic reaction to sodium metabisulfite content and serious cardiovascular adverse reaction in predisposed patients,
- Important identified risks: device failure, accidental injection and lack of efficacy (due to wrong handling or lack of efficacy when no wrong handling or device failure was reported).

To prevent device failure, accidental injection and lack of efficacy due to wrong handling, Bioprojet Pharma has developed a duo-pack containing two auto-injectors (named as "Anapen® box" in this protocol) and education material for healthcare professionals (HCPs) and patients or relatives that contains key safety information and messages. The current educational materials consist of:

- a prescriber's checklist to facilitate correct and sufficient instruction of patients about the device and optimal way of using it,
- a small card leaflet to patients “How to use AAI Anapen®?”,
- an instructional video,
- and an Anapen® Trainer.

To support further preventive actions in the future, intensified follow-up of post-marketing data is essential to clearly distinguish between device failure (technical problems) and handling error. In addition to routine pharmacovigilance activities, proactive data collection is requested.

To respond to the CMDh recommendation to conduct a study to examine the effectiveness of the risk minimization measures in place, Bioprojet Pharma has designed the present Post-Authorisation Safety Study (PASS) which is submitted to the French Authority (ANSM) through a national procedure.

Research question and objectives

When prescribing an AAI, healthcare professionals inform patients, as well as their relatives when present, on how to recognize the warning signs of anaphylaxis, on how to use the AAI and, give post-injection instructions. Because it is imperative to have an operational AAI at any time, they also explain the importance of carrying two AAI at any time, checking the validity of the AAI and being compliant with good storage recommendations. Bioprojet Pharma provides healthcare professionals with educational materials to help them inform/train AAI users with the aim of ensuring that patients and relatives use adrenaline auto-injectors successfully.

The objectives of this study are to assess the real-life effectiveness of the risk minimization measures associated with Anapen® i.e., to assess patients’ and relatives' knowledge on how to use Anapen® when the product is dispensed at the pharmacy, rather than after it has been used, given the nature of the RMMs in place for Anapen®, which consist exclusively of educational materials designed to train patients and relatives on the correct use of the auto-injector prior to its use, given also the expected low proportion of Anapen® use compared to the number of prescriptions for which these measures should be applied, as well as the anticipated difficulty of collecting information on the use of the product in life-threatening emergency situation.

Primary objective and outcome

The primary objective is to assess the effectiveness of the risk minimization measures associated with Anapen® at the time of delivery by the pharmacist, in measuring the patients’ and relatives' knowledge on how to use Anapen® prior to its use.

The injection will be simulated using Anapen® Trainer. Injection ability measurement will be standardized using a specific grid. The grid will list each action and distinguish minor errors that may affect the quality of the injection process without undermining its potential effectiveness from major errors that can lead to failure/inefficiency of the injection. Number of errors will be listed for each participant and the percentage of participants able to use the device correctly without major error will be calculated. Possibly, the percentages of participants able to use the device correctly will be assessed according to the participants’ level of education (*i.e.* knowledge of educational materials *vs.* lack of prior access).

Secondary objectives and outcomes

The secondary objectives are to describe the participant education with Anapen® provided by healthcare professionals, the use of the disposable educational materials and the level of knowledge of the good practice for Anapen® using.

Knowledge and understanding will be controlled using a questionnaire based on the main items of the prescriber's checklist and patient educational materials. The questionnaire will be carried out by the participant himself (patient or patient's relative).

The percentage of participants aware or not of the following categories of items will be calculated:

- Anaphylaxis symptoms: identifying the warning signs requiring adrenaline injection;
- Instructions on the management of Anapen® in daily practice: always carrying two Anapen®, checking validity and drug solution integrity, replacement, storage conditions;
- Post-injection instructions: call emergency services, when to consider a second injection, what to do while waiting for emergency services or in case of adverse events;
- Conduct to adopt in case of accidental injection.

Possibly, secondary outcomes will be assessed according to participants' level of education (*i.e.* knowledge of educational materials *vs.* lack of prior access).

Study design

This study is an observational, prospective, multicentric, national, study. Primary data are collected via surveys.

The most relevant way to meet the primary objective is to assess the users' ability to perform a correct injection using a Trainer as they are expected to do in a situation of emergency. To this end, assessment of the use of Anapen® Trainer is chosen as primary outcome. Because anaphylaxis risk management is not limited to the injection of adrenaline, the level of knowledge of Anapen® users regarding symptoms of anaphylaxis, Anapen® daily practice, post-injection instructions and, conduct in case of accidental injection will be assessed as secondary outcomes.

In France, AAIs are generally prescribed by the patient's doctor, allergist, general practitioner (GP), ear nose throat (ENT) specialist, pediatrician or by a physician at emergency department discharge in case of hospitalization. As mentioned in the guidelines of French learned societies (French Society of Emergency Medicine or SFMU, French Allergology Society or SFA, French Speaking Group in Pediatric Intensive Care and Emergency or GFRUP, and French Pediatric Pneumology and Allergology Society or SP²A) (Gloaguen, 2016), these prescribers HCPs play a key role in educating patients with high risk of anaphylaxis and their relatives. To stick to the real-world conditions and, taking into account the patient pathway, a study in pharmacies seems the most suitable and relevant approach to achieve the objectives of the study.

Given the importance of a good knowledge and understanding of anaphylaxis and first-aid treatment, this study is not limited to patients but also to relatives since they can be in charge of the administration. For this reason, adults who come to the pharmacy with a prescription for an Anapen® box, whether the prescription is for themselves or for a relative, could be included.

This study, which plans to include 400 participants (patients or relatives), would require the enrolment of approximately 100 pharmacies spread over the national territory for a better representativeness of the target population.

Population

The target study population will be all individuals complying with the following inclusion criteria:

- Adult person;
- Person who has been informed and who does not oppose to participate ("non-opposition" according to French provisions for observational studies);
- Person with Anapen® prescription (first or renewal) for himself/herself or for a relative;
- Person to whom the pharmacist has issued an Anapen® box in the current practice of pharmacy;
- Person participating to this study for the first time.

There are no exclusion criteria in the study.

Variables

A case report form (CRF) on duplicate paper will be developed to collect the following data:

- Participant characteristics,
- A short description of Anapen® prescription and dispensing conditions,
- Responses to questionnaires measuring:
    - The participant's ability to use Anapen® Trainer, by completion of a specific grid by the pharmacist (Primary effectiveness variables);
    - The previous training and use of Anapen® and related education supports (Secondary effectiveness variables);
    - The knowledge and understanding of anaphylaxis symptoms requiring adrenalin injection, Anapen® daily practice recommendations, post-injection instructions and, conduct in case of accidental injection (Secondary effectiveness variables).

Main categories of data are detailed in the following section and the blank CRF is presented in Annex 1A (French version) and Annex 1B (English version).

Data sources

The source of information for the study will be the data collected by the pharmacist dispensing Anapen® and participants' self-reported questionnaire.

Study size

The sample size calculation is based on the required number of participants with Anapen® prescription who make a major error using the Anapen® Trainer. Based on an arbitrary estimate of 7% of the participants failing to correctly use the Anapen® Trainer, with an alpha risk of 0.05 and a margin of error of 2.5%, the number of participants needed, given by the formula $0.07 \times 0.93 \times (1.96)^2 / (0.025)^2$, is 400.

The inclusion period will last until the recording of 400 participant's CRF with complete primary outcome.

Data analysis

Descriptive statistics will be employed to analyze the data. In brief, statistics for continuous variables will include mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages. In addition, for all variables, a 95% confidence interval will be estimated.

A detailed statistical analysis plan describing the planned analysis and the approach for handling missing data will be developed prior to the data review.

Milestones

Milestone	Estimated planned date
Start of data collection	2 months after approval of the Ethics Committee (Q4-2025)
End of data collection	It is anticipated that analytical dataset will be completely available 3 months after the end of the study (last patient Q4-2026) (Q1-2027)
Registration in the EU PAS register	After approval of the Ethics Committee (Q4-2025)
Final report of study results[1]	6 months after the end of data collection (Q2-2027)

[1] *Timing of final report includes the following:*

- *Data Review Board (DRB): 1 month after the end of data collection*
- *Statistical Analysis Report (SAR): 1 month after the DRB*
- *First draft of the final report writing: 2 months after the SAR*
- *Final report review and approval: 2 months after the writing of the first draft of final report*

5. AMENDMENTS AND UPDATES

Version	Date	Description
2.0	18 February 2025	Update of the milestones and update of the role of the investigator to better comply with the risk minimization measures in place and SmPC regarding educational responsibilities.
3.0	30 July 2025	Clarifications on research objectives

6. MILESTONES

The planned estimated dates for study milestones are detailed in Table 2.

Table 2: Milestones

Milestone	Estimated planned date
Start of data collection	2 months after approval of the Ethics Committee (Q4-2025)
End of data collection	It is anticipated that analytical dataset will be completely available 3 months after the end of the study (last patient Q4-2026) (Q1-2027)
Registration in the EU PAS register	After approval of the Ethics Committee (Q4-2025)
Final report of study results[1]	6 months after the end of data collection (Q2-2027)

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- *Final report review and approval: 2 months after the writing of the first draft of final report*

7. RATIONALE AND BACKGROUND

Anaphylaxis is an acute, life-threatening, systemic allergic reaction associated with various triggers, clinical presentations and levels of severity. It is imperative that adrenaline is immediately administered as soon as signs and symptoms of anaphylaxis appear. Adrenaline Auto-Injectors (AAI) are the first-aid treatment. Any problem with the administration of adrenaline could result in significant hazard to the patient due to the emergency nature of the condition that AAI is intended to treat. In the worst scenario, this could result in a failure to deliver adrenaline and, in emergency, leading to a fatal outcome for the patient if he is not supported by a care service.

In 2014, the EMA carried out a review of adrenaline auto-injectors following concerns that available devices may deliver adrenaline under the skin instead of into a muscle, and this may delay response to treatment. Usability assays and reports have led to improve the safety of disposable self-injection devices (Weinhold 2018, Kessler 2019, EMA 2015): *i.e.*, needle length, the way AAI works, intuitive use etc. Multi-incident analyses have identified factors contributing to the lack of efficacy due to errors in the use of self-injection devices, or accidental injection (Schwirtz 2012, Cohen 2017, Posner 2017, Sasaki 2018, Weinhold 2018, EMA 2015): *i.e.*, angle at which the device is placed, strength used to activate the device, how well the user follows instructions for injection or recognizes concomitant symptoms requiring injection. Several studies have shown that regular patient education and training can minimize user errors and the resulting lack of efficacy of AAI (Segal 2012, Sirin Kose 2020, Kadivec 2021). These studies have highlighted that education should not be limited to the patient but disseminated in community setting to effectively prevent accidental injections, laceration or, lack of efficacy due to mishandling. All these points have been taken up by the EMA's Committee for Human Medicinal Products (CHMP). The CHMP concluded that training of the user is of paramount importance. The companies that market adrenaline auto-injectors have therefore been asked to develop more

effective educational material for patients, as well as for healthcare professionals, to ensure their optimal use. This includes a training device with which patients can practice; audio-visual material to show in detail how the device is to be used; and a checklist for prescribers to ensure that sufficient information is given to the patient before they use the auto-injector. The product information of adrenaline auto-injectors has also been updated with further warnings and precautions, including a recommendation that patients should be prescribed two auto-injectors which they should always carry along and a recommendation for family members, carers or teachers to be trained on how to use the auto-injector. The CHMP also concluded that further data should be generated to better understand how adrenaline penetrates body tissues when given with auto-injectors. The assessment report (25 June 2015 under articles 31 and 32 of Directive 2001/83/EC European Parliament and Council / ref#EMEA/H/A-31/1398) was sent to the European Commission which endorsed it and issued a legally binding decision (C2015/5886 14Aug2015) that is valid throughout the EU.

Bioprojet Pharma markets AAIs containing either 150, 300 or 500 mcg of adrenaline, under the brand name of Anapen® or Chenpen® depending on the country of marketing.

The CHMP recommendations have been fulfilled and detailed in the last revision of the sponsor Risk Management Plan (RMP, version 4.1 submitted on 2023/02/21). Safety concerns are summarized as follows:

- Important potential risks: serious allergic reaction to sodium metabisulfite content and serious cardiovascular adverse reaction in predisposed patients,
- Important identified risks: device failure, accidental injection and lack of efficacy (due to wrong handling or lack of efficacy when no wrong handling or device failure was reported).

To prevent device failure, accidental injection and lack of efficacy due to wrong handling, Bioprojet Pharma has developed a duo-pack containing two auto-injectors (named as "Anapen® box" in this protocol) and education material for healthcare professionals (HCPs) and patients or relatives that contains key safety information and messages. The current educational materials consist of:

- a prescriber's checklist to facilitate correct and sufficient instruction of patients about the device and optimal way of using it,
- a small card leaflet to patients “How to use AAI Anapen®?”,
- an instructional video,
- and an Anapen® Trainer.

Clear instructions with pictograms describing how to use Anapen® are provided in the patient information leaflet, summary of product characteristics (https://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=66223317&typedoc=R) and in the small card leaflet to patients “How to use AAI Anapen®?”. An instructional video is also available on Bioprojet website (https://www.bioprojet.com/portfolio_page/anapen/) and in France on National Competent Authority website (https://ansm.sante.fr/tableau-marr/adrenaline-3). Patients are encouraged to consult it at any time.

In order for patients and/or their relatives to be familiar with the use of Anapen®, Anapen® Trainers are available to Healthcare Professionals, patients and/or their relatives to practice correct activation. Anapen® Trainers are clearly identified, and the users are informed to maintain Anapen® Trainers away from Anapen® auto-injectors to avoid accident and use of Trainer instead of Anapen® auto-injector. Instructions on how to use Anapen® Trainer are available, Anapen® Trainer leaflet.

To support further preventive actions in the future, intensified follow-up of post-marketing data is essential to clearly distinguish between device failure (technical problems) and handling error. In addition to routine pharmacovigilance activities, proactive data collection is requested.

To respond to the CMDh recommendation to conduct a study to examine the effectiveness of the risk minimization measures in place, Bioprojet Pharma has designed the present Post-Authorisation Safety Study (PASS) to be conducted in France where Anapen® is most prescribed (2024, 80% of the total number of dispensations across Italy, Germany, Spain, Ireland and France were made by French pharmacies). This study is submitted to the French Authority (ANSM) through a national procedure.

8. RESEARCH QUESTION AND OBJECTIVES

When prescribing an AAI, healthcare professionals inform patients, as well as their relatives when present, on how to recognize the warning signs of anaphylaxis, on how to use the AAI and, give post-injection instructions. Because it is imperative to have an operational AAI at any time, they also explain the importance of carrying two AAI at any time, checking the validity of the AAI and being compliant with good storage recommendations. Bioprojet Pharma provides healthcare professionals with educational materials to help them inform/train AAI users with the aim of ensuring that patients and relatives use adrenaline auto-injectors successfully.

The objectives of this study are to assess the real-life effectiveness of the risk minimization measures associated with Anapen® i.e., to assess patients' and relatives' knowledge on how to use Anapen® when the product is dispensed at the pharmacy, rather than after it has been used, given the nature of the RMMs in place for Anapen®, which consist exclusively of educational materials designed to train patients and relatives on the correct use of the auto-injector prior to its use, given also the expected low proportion of Anapen® use compared to the number of prescriptions for which these measures should be applied, as well as the anticipated difficulty of collecting information on the use of the product in life-threatening emergency situation.

8.1. PRIMARY OBJECTIVE AND OUTCOME

The primary objective is to assess the effectiveness of the risk minimization measures associated with Anapen® at the time of delivery by the pharmacist, in measuring the patients' and relatives' knowledge on how to use Anapen® prior to its use.

The injection will be simulated using Anapen® Trainer. Injection ability measurement will be standardized using a specific grid. The grid will list each action and distinguish minor errors that may affect the quality of the injection process without undermining its potential effectiveness from major errors that can lead to failure/inefficiency of the injection. Number of errors will be listed for each participant and the percentage of participants able to use the device correctly without major error will be calculated. Possibly, the percentages of participants able to use the device correctly will be assessed according to the participants' level of education (*i.e.* knowledge of educational materials *vs.* lack of prior access).

8.2. SECONDARY OBJECTIVES AND OUTCOMES

The secondary objectives are to describe, the participant education with Anapen® provided by healthcare professionals the use of the disposable educational materials and the level of knowledge of the good practice for Anapen® using.

Knowledge and understanding will be controlled using a questionnaire based on the main items of the prescriber's checklist and patient educational materials. The questionnaire will be carried out by the participant himself (patient or patient's relative).

The percentage of participants aware or not of the following categories of items will be calculated:

- Anaphylaxis symptoms: identifying the warning signs requiring adrenalin injection;
- Instructions on the management of Anapen® in daily practice: always carrying two Anapen®, checking validity and drug solution integrity, replacement, storage conditions;
- Post-injection instructions: call emergency services, when to consider a second injection, what to do while waiting for emergency services or in case of adverse events;
- Conduct to adopt in case of accidental injection.

Possibly, secondary outcomes will be assessed according to participants' level of education (*i.e.* knowledge of educational materials *vs.* lack of prior access).

9. RESEARCH METHODS

9.1. STUDY DESIGN

This study is an observational, prospective, multicentric, national, study. Primary data are collected via surveys.

The most relevant way to meet the primary objective is to assess the users' ability to perform a correct injection using a Trainer as they are expected to do in a situation of emergency. To this end, assessment of the use of Anapen® Trainer is chosen as primary outcome. Because anaphylaxis risk management is not limited to the injection of adrenaline, the level of knowledge of Anapen® users regarding symptoms of anaphylaxis, Anapen® daily practice, post-injection instructions and, conduct in case of accidental injection will be assessed as secondary outcomes.

In France, AAIs are generally prescribed by the patient's doctor, allergist, general practitioner (GP), ear nose throat (ENT) specialist, pediatrician or by a physician at emergency department discharge in case of hospitalization. As mentioned in the guidelines of French learned societies (French Society of Emergency Medicine or SFMU, French Allergology Society or SFA, French Speaking Group in Pediatric Intensive Care and Emergency or GFRUP, and French Pediatric Pneumology and Allergology Society or SP²A) (Gloaguen, 2016), these prescribers HCPs play a key role in educating patients with high risk of anaphylaxis and their relatives. To stick to the real-world conditions and, taking into account the patient pathway, a study in pharmacies seems the most suitable and relevant approach to achieve the objectives of the study.

Given the importance of a good knowledge and understanding of anaphylaxis and first-aid treatment, this study is not limited to patients but also to relatives since they can be in charge of the administration. For this reason, adults who come to the pharmacy with a prescription for an Anapen® box, whether the prescription is for themselves or for a relative, could be included.

This study, which plans to include 400 participants (patients or relatives), would require the enrolment of approximately 100 pharmacies spread over the national territory for a better representativeness of the target population.

9.2. SETTING

9.2.1. PARTICIPANT ELIGIBILITY

The target study population will be all individuals complying with the following inclusion criteria:

- Adult person;
- Person who has been informed and who does not oppose to participate (“non-opposition” according to French provisions for observational studies);
- Person with Anapen® prescription (first or renewal) for himself/herself or for a relative;
- Person to whom the pharmacist has issued an Anapen® box in the current practice of pharmacy;
- Person participating to this study for the first time.

There are no exclusion criteria in the study.

9.2.2. ENROLMENT OF PARTICIPANTS AND PHARMACIES

Participants

Adults coming to the pharmacy with a prescription for an Anapen® box, whether this prescription is for themselves or for a relative, and willing to participate could be enrolled after having been duly informed and given their oral consent (“non-opposition”).

Pharmacies

An estimation of 100 pharmacies spread over the national territory will participate as investigation sites. In each pharmacy, the pharmacist who will be designated as the site's principal investigator will be trained on the study requirements, in particular on filling out the CRF.

9.2.3. STUDY DURATION

Start of the study: first participant included;

End of the study: last participant included;

Estimated total duration of the study:

- Inclusion period: one year;
- Maximum participation time of each participant: single visit of approximately one hour after obtaining the oral consent of the participant duly informed.

9.3. VARIABLES

A case report form (CRF) on duplicate paper will be developed to collect the following data:

- Participant characteristics,
- A short description of Anapen® prescription and dispensing conditions,
- Responses to questionnaires measuring:
    - The participant's ability to use Anapen® Trainer, by completion of a specific grid by the pharmacist (Primary effectiveness variables);
    - The previous training and use of Anapen® and related education supports (Secondary effectiveness variables);
    - The knowledge and understanding of anaphylaxis symptoms requiring adrenalin injection, Anapen® daily practice recommendations, post-injection instructions and, conduct in case of accidental injection (Secondary effectiveness variables).

Main categories of data are detailed in sections 9.3.1 to 9.3.4 and the blank CRF is presented in Annex 1A (French version) and Annex 1B (English version).

9.3.1. DESCRIPTION OF THE PARTICIPANT

When the participant is the beneficiary of the AAI prescription: age, sex, naïve or not regarding Anapen® use, first prescription of Anapen® or not.

When the participant is not the beneficiary of the prescription but a relative: age, sex, naïve or not regarding Anapen® use. Only non-personal data will be collected about the beneficiary: child or adult and first prescription of Anapen® or not.

9.3.2. DESCRIPTION OF PRESCRIPTION CONDITIONS, EDUCATION AND USE OF EDUCATIONAL MATERIALS

Healthcare professional prescriber: allergist, general practitioner (GP), ear nose throat (ENT) specialist, pediatrician, by a physician at emergency department discharge in case of hospitalization or other.

If the participant met a healthcare professional for an Anapen® prescription, previous education by the HCP: having given and provided explanations about the Anapen® instruction for use (small card leaflet to patients), and/or the Anapen® Trainer, and/or encouraging to watch the educational video on managing Anapen® in daily practice. These main items are described in the prescriber's checklist.

Whether or not the participant has met an HCP: having read the Anapen® instruction for use (small card leaflet to patients), and/or having had an Anapen® Trainer, and/or having watched the educational video on managing Anapen® in daily practice.

9.3.3. ASSESSMENT OF TRAINER USE BY THE PHARMACIST

The pharmacist will use the following evaluation grid after asking the participant to use an Anapen® Trainer on himself/herself as if he/she was in a situation of emergency without trying to influence him/her.

Table 3: Evaluation grid

	No	Yes
Step 1: Activation of Anapen®		
- Removing the black needle cap	❑	❑
- Removing the grey safety cap	❑	❑
- Holding the device in fist	❑	❑
- Positioning the device in the right direction (needle towards the skin)	❑	❑
Step 2: Injection		
- Press the device firmly on injection area	❑	❑
- Device placed against the outer thigh	❑	❑
- Pushing the trigger button to hear a click	❑	❑

- Holding in place for 10 seconds	❑	❑
- Gentle massage of the injection site	❑	❑
Step 3: Post-injection instructions		
- Checking the injection indicator (it must be red)	❑	❑
- Covering of the needle with the protective black cap of the needle (cap placed in the right direction, the wide part covers the visible needle)	❑	❑

In this grid, "No" means "Failure", "Yes" means "Success", minor errors are highlighted in green and major errors in orange. However, to avoid bias during assessments, grids provided to the investigators will not be highlighted.

9.3.4. PARTICIPANT KNOWLEDGE AND UNDERSTANDING OF ANAPHYLAXIS AND ANAPEN® INSTRUCTIONS

For all participants, the level of knowledge and understanding of the participant regarding anaphylaxis symptoms, management of the auto-injectors in daily practice, post-injection instructions and conduct in case of accidental injection will be evaluated by a self-questionnaire.

9.4. DATA SOURCES

The source of the relevant information for the study objectives will be the primary data collected by the pharmacist dispensing Anapen® and participants' self-reported questionnaire on the symptoms of anaphylaxis, the management of Anapen® in daily practice, post-injection instructions, and conduct in case of accidental injection. All information will be recorded on duplicate paper CRF.

9.5. STUDY SIZE

The sample size calculation is based on the required number of participants with Anapen® prescription who make a major error using the Anapen® Trainer. Based on an arbitrary estimate of 7% of the participants failing to correctly use the Anapen® Trainer, with an alpha risk of 0.05 and a margin of error of 2.5%, the number of participants needed, given by the formula $0.07 \times 0.93 \times (1.96)^2 / (0.025)^2$, is 400.

The inclusion period will last until the recording of 400 participant's CRF with complete primary outcome (the evaluation grid completed at least for major errors).

All 400 participants will be included within a period of approximately one year in about 100 pharmacies in France.

9.6. DATA MANAGEMENT

The database will be developed by a data manager from CEN and programmed using Ennov Clinical software provided by ENNOV CLINICAL.

Paper CRF will be printed on carbonless duplication, then sent to pharmacies.

A data validation plan, integrated into the Data Management Plan (DMP), will describe in detail the checks to be carried out for each variable. All the information required by this observational study must be recorded in the CRF, an explanation must be provided for each missing data. Once entered (double entry by two different operators), the consistency of the data will be checked, and data clarification requests will be sent to pharmacists if needed. All data changes will be traced (Audit trail function) in the Ennov Clinical software.

Data will be examined for validation during data review. Particular attention will be paid to deviations and missing data.

If necessary, data clarification requests will be sent to pharmacists about the discrepancies discussed during the data review meeting. Then the database will be updated accordingly as appropriate.

The data closure process will occur once the data review is approved and will be carried out in accordance with the procedure put in place at CEN. If absolutely necessary, the database can be thawed and then re-frozen, in accordance with the procedure set-up at CEN. The database will be exported by the CEN data

manager then transferred to a SAS (Statistical Analysis System) database for statistical analysis by CEN statisticians.

9.7. DATA ANALYSIS

Considering the observational design of the study is not designed to test specific hypotheses, the statistical analysis will be of descriptive nature. Summary tabulations will be presented and will display the number of observations (N), mean, standard deviation (SD), median, minimum and maximum for continuous variables. Categorical variables will be presented by using, N and frequencies and 95% Confidence Interval.

Missing values will be reported as missing and no imputation will be undertaken.

All analyses will be performed using SAS for Microsoft Windows Operating system software (SAS Institute, Cary, North Carolina, USA) version “9.4”.

9.8. QUALITY CONTROL

This study will be conducted in accordance with the guidelines and regulations described in sections 10.1 (Data protection) and 10.2 (Scientific integrity and ethical aspects), and procedures detailed in section 9.2.

Standard operating procedures of CEN will be used to guide the conduct of the study. These include internal quality audits of the data, consistency of collected data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive research documents, quality control procedures for statistical analysis plan and medical writing.

9.9. LIMITATIONS OF THE RESEARCH METHODS

The main strengths and limitations of the study design are inherent to real-life studies. First, this study plans to include all people with Anapen® prescription who agree to participate and who will have varying levels of experience with Anapen® AAI and anaphylaxis literacy. As a result, non-naïve participants are expected to be more successful in the assessments. In this study, no stratification is planned on whether the participant is naïve or not regarding Anapen® use, the prevalence of the two populations not being clearly defined. However, a subgroup analysis could lead to target Anapen® users for whom it would be desirable to intensify risk minimization measures. Finally, the study is designed as a cross-sectional study (one visit) which means that the remanence of the educational measures will not be evaluated.

9.10. OTHER ASPECTS: STUDY PLAN

After having filled in the characteristics of the participant and HCP prescriber, the pharmacist will ask the participant if he/she has already met an HCP for an Anapen® prescription, and if yes, he/she has been trained by an HCP for the use of Anapen®. And whether or not the participant met an HCP, the pharmacist will ask which educational materials he/she knows and used.

The pharmacist will ask the participant to use an Anapen® Trainer on himself/herself as if he/she was in a situation of emergency without trying to influence him/her.

The pharmacist will have a standard grid (Table 3) in which he/she will note whether the user of Anapen® performs the listed actions leading to proper use of the AAI or not.

Finally, the pharmacist will ask the participant to complete the self-questionnaire intended to assess his/her own knowledge and understanding of anaphylaxis and AAI use.

The pharmacist will record and report (according to the national provisions for Good Pharmacovigilance Practices (ANSM, 2022) and European regulation ((EU) 1235/2010)) any past adverse events/device deficiencies spontaneously reported by the participant (see also section 11).

Table 4: Summary of participant evaluations

	Inclusion / Visit (D0)
Information, oral consent	☑
Eligibility criteria	☑
Characteristics of the participant	☑
Previous education	☑
Trainer use assessment	☑
Completion of the self-questionnaire	☑

10. PROTECTION OF HUMAN SUBJECTS

10.1. DATA PROTECTION

The data recorded during this research will be subject to computerized processing at CEN, responsible for the implementation of data processing in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council relating to the protection of individuals with regard to the processing of personal data and the free movement of such data and amended law n°78-17 of 6 January 1978 relating to data processing, files and freedoms.

This study will be part of the "Reference Methodology" (MR-003) of the French data protection authority (CNIL) pursuant to the provisions of Article 54 paragraph 5 of the amended law n°78-17 relating to information, files and freedoms. This change was approved by decision n°2018-154 of March 3, 2018. The MAH and CEN have signed a commitment to comply with this MR-003.

In accordance with the local legislative regulation, persons (pharmacy staff) having direct access to the source data take all the necessary precautions in order to ensure the confidentiality of the information relating to the products under study, the investigations, the persons who participate in the study and in particular with regard to their identity and to the results obtained. These persons, like the investigators themselves, are subject to professional confidentiality.

To comply with MR-003, CEN will not be able to know any participants' or beneficiaries' personal data in the framework of the study including in the compensation process.

During the study or at its end, data collected on participants will be made pseudonymous and in no case will reveal the names of the people concerned or their contact details. Each participant is identified by a code specific to the study. When the participant is not the beneficiary of the prescription but a relative, only non-personal data will be collected about the beneficiary (child or adult and first prescription of Anapen® or not).

The sponsor ensures that each person who takes part in the research has given their agreement for access to the individual data concerning them and strictly necessary for the quality control of the study.

10.2. SCIENTIFIC INTEGRITY AND ETHICAL ASPECTS

The Sponsor and the investigator(s) undertake that this study will be carried out in accordance with Good Clinical Practices (decision of November 24, 2006; ICH E6 (rev 4) and the Declaration of Helsinki (which can be found in its full version on the website http://www.wma.net)).

This study will be conducted in accordance with the "Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (rev 3)" (EMA 2017), "The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11) (EMA-ENCePP 2010).

In accordance with national provisions (Jardé Law n° 2012-300), this observational study is a Research Involving Human Subjects without risk or constraint, that requires to be ethically evaluated by a national ethics

committee (Committee for the Protection of Persons). Approval of the ethics committee must be notified to the French national competent authority (ANSM).

The start of the investigation will be notified immediately (*i.e.*, as soon as the sponsor or his representative in charge of the study becomes aware of it and approves it) to the ethics committee. The effective date of the start of the study will correspond to the date of the first participant's inclusion.

In accordance with Article R1123-66 of CSP, a notification of the end of the study will be sent to the ethics committee within 90 days following the end of the study, or within 15 days in case of temporary interruption or early termination.

10.3. PATIENT INFORMATION AND CONSENT

Informed consent will be collected for each participant agreeing to collect personal data, take part in the Anapen® Trainer use assessment and complete the self-questionnaire. According to article L1122-1-1 of the of French Public Health Code (CSP) the consent means no objection for research mentioned on 3° of the article L1121-1 of CSP. The informed consent from the beneficiary is not required when the participant is not the beneficiary of the prescription but a relative as no personal data will be collected about the beneficiary.

The collection of oral consent ("non-opposition") will be mentioned in the patient information letter and the CRF by the pharmacist. The consent will be asked after the participant has taken the time to read the written information note and the pharmacist has answered all of the participant's questions about the study. The content of the information note will be compliant with article L1122-1 of CSP.

10.4. COMPENSATION

Participants will receive an allowance to compensate for the time they devote to their participation in the study (answering the pharmacist's questions, participation in the Trainer evaluation and completion of the self-questionnaire). The amount of the allowance will be proportional to the constraint and must be approved by the ethics committee.

Pharmacists will be paid nominal incentives to compensate their time in:

- Participation in remote kick-off meetings;
- Participant information and time for CRF completion.

The amount will be commensurate with the time needed and the payment method will be compliant with the national provisions ("Anti-gift legislation").

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is not designed to proactively collect data on individual adverse events. This study falls under the French law relating to non-interventional research involving the human person. Consequently, adverse events (AE), including adverse drug reactions (ADR), suspected adverse drug reactions, device deficiency, special situations (*i.e.*, misuse, overdose, abuse, pregnancy, quality defect, etc.), should be declared according to the national provisions for Good Pharmacovigilance Practices (ANSM, 2022) and European recommendations "Module VI – Management and reporting of adverse reactions to medicinal products" (EMA, 2017) regulation ((EU) 1235/2010), as soon as the pharmacist becomes aware of them.

Throughout the study, pharmacists could be informed of any AE, device deficiency or special situations mentioned above, reported spontaneously by a participant. Healthcare professionals (*i.e.* pharmacists) must report one or other of these events, preferably via the national spontaneous reporting system: portal for reporting adverse health events of the French Ministry of Health (https://signalement.social-sante.gouv.fr), or by contacting the Regional Pharmacovigilance Center on which they depend.

In addition to the routine reporting circuit, if CEN is aware of pharmacovigilance information via CRF, direct contact with pharmacists, etc., these reports will be exchanged with the Marketing Authorization Holder *(i.e.* sponsor of this study).

Pharmacists can be solicited to provide additional information, when requested.

These safety reports should be summarized in the relevant study reports by the Marketing Authorization Holder *(i.e.* sponsor of this study).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The summary of the final study report will be transmitted according to the local regulation within 1 year after the end of the study or within 3 months following the temporary interruption or early termination.

Study protocol and final report(s) will be available on the EU PAS Register (ENCePP), submitted to the regulatory authority or included in regulatory communications in line with the risk management plan, Periodic Safety Update Report (PSUR) and other regulatory timeframes and requirements.

Study results will be considered for publication and communication at appropriate scientific meetings.

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14. ANNEX 1. ADDITIONAL INFORMATION

Annex 1A CASE REPORT FORM (FRENCH VERSION)

Code participant : I__I__I__I-I__I__I PARTIE A COMPLETER PAR LE PHARMACIEN Page **1** sur **5**

INCLUSION DANS L'ETUDE

Date : I__I__I/I__I__I/202I__I

Vous confirmez avoir remis à la personne la lettre d'information, lui avoir laissé le temps de la lire, avoir répondu à ses questions, qu'elle ne s'est pas opposée à sa participation à l'étude et qu'elle a donné son accord au traitement de ses données à caractère personnel selon les finalités poursuivies :
☐ Oui

Si la réponse « Oui » n'est pas cochée, la personne ne peut pas être incluse dans l'étude.

CRITERES DE SELECTION

Vérification des critères de sélection :
☐ Personne majeure
☐ Personne qui a été informée et qui ne s'oppose pas à participer
☐ Personne qui dispose d'une prescription d'Anapen® (première prescription ou renouvellement) pour elle-même ou pour un proche
☐ Personne à laquelle vous avez délivré une boite d'Anapen® en pratique courante officinale
☐ Personne participant pour la première fois à cette étude

Si les cinq cases ci-dessus ne sont pas cochées, la personne ne peut pas être incluse dans l'étude, **vous ne devez pas poursuivre le recueil des données**.

PARTICIPANT A L'ETUDE

La prescription d'Anapen® est :
☐ Une primo prescription
☐ Un renouvellement

Le participant est :
☐ Le bénéficiaire de la prescription d'Anapen®
☐ Un proche du bénéficiaire de la prescription d'Anapen® → Le bénéficiaire de la prescription est un :
☐ Enfant
☐ Adulte

Age du participant : I__I__I ans

Sexe du participant : ☐ Homme ☐ Femme

Le participant a-t-il déjà procédé à une auto-injection ou une injection sur un tiers d'Anapen® : ☐ Non ☐ Oui

PRESCRIPTEUR

Spécialité du médecin ayant délivré cette ordonnance d'Anapen® :
☐ Allergologue
☐ Généraliste
☐ ORL
☐ Pédiatre
☐ Urgentiste
☐ Autre : _____

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Code participant : I__I__I__I-I__I__I PARTIE A COMPLETER PAR LE PHARMACIEN Page **2** sur **5**

EVALUATIONS DU PARTICIPANT PAR LE PHARMACIEN

Compléter les questions ci-dessous en interrogeant le participant à l'étude.

FORMATION ANTERIEURE A L'UTILISATION CORRECTE, LE STOCKAGE ET L'ENTRETIEN D'ANAPEN®

Avez-vous déjà rencontré un professionnel de santé pour une prescription d'Anapen® **:**

☐ Non → Compléter l'**encadré n°1** ci-dessous

☐ Oui → Compléter l'**encadré n°2** ci-dessous

Encadré n°1

Avez-vous déjà :

→ Consulté la brochure « Comment utiliser l'auto-injecteur d'adrénaline Anapen® » : ☐ Non ☐ Oui

→ Disposé d'un trainer Anapen® (stylo de démonstration sans adrénaline ni aiguille) : ☐ Non ☐ Oui

Si Oui : Avez-vous manipulé une ou plusieurs fois le trainer : ☐ Non ☐ Oui

→ Visionné la vidéo d'utilisation de l'auto-injecteur Anapen® : ☐ Non ☐ Oui

Encadré n°2

Un professionnel de santé vous a-t-il déjà :

→ Appris à utiliser correctement l'auto-injecteur Anapen® : ☐ Non ☐ Oui

→ Expliqué pourquoi vous devez toujours avoir en permanence 2 auto-injecteurs Anapen® : ☐ Non ☐ Oui

→ Formé aux conditions de conservation d'Anapen® : ☐ Non ☐ Oui

→ Expliqué les consignes à suivre après avoir utilisé Anapen® : ☐ Non ☐ Oui

→ Remis la brochure « Comment utiliser l'auto-injecteur d'adrénaline Anapen® » : ☐ Non ☐ Oui

Si Oui : Avez-vous consulté cette brochure : ☐ Non ☐ Oui

→ Remis un trainer Anapen® (stylo de démonstration sans adrénaline ni aiguille) : ☐ Non ☐ Oui

Si Oui : Vous a-t-il expliqué que le trainer et les auto-injecteurs Anapen® doivent être conservés séparément : ☐ Non ☐ Oui

Avez-vous manipulé une ou plusieurs fois le trainer : ☐ Non ☐ Oui

→ Incité à visionner la vidéo d'utilisation de l'auto-injecteur Anapen® : ☐ Non ☐ Oui

Si Oui : Avez-vous déjà visionné cette vidéo : ☐ Non ☐ Oui

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EVALUATION VIA UN TRAINER DE LA MANIPULATION DE L'AUTO-INJECTEUR ANAPEN®

Remettez au participant un trainer (dans sa boite avec la notice « Comment utiliser Anapen® trainer ») et demandez-lui de l'utiliser **sur lui-même** comme il le ferait avec un stylo Anapen® pour un traitement d'urgence des symptômes d'un choc anaphylactique.
Sans influencer le participant et en le regardant manipuler le trainer Anapen®, cochez « Non » ou « Oui » en face des questions ci-dessous.

Grille d'évaluation	Non	Oui
Etape n°1 : Activation du stylo Anapen®		
- Retrait du bouchon noir protecteur de l'aiguille :	☐	☐
- Retrait du bouchon gris de sécurité :	☐	☐
- Prise en main du stylo dans le poing :	☐	☐
- Positionnement du dispositif dans le bon sens (côté aiguille vers la peau) :	☐	☐
Etape n°2 : Injection		
- Appui ferme du dispositif sur la zone d'injection :	☐	☐
- Dispositif positionné sur la face externe de la cuisse :	☐	☐
- Appui sur le bouton déclencheur de façon à entendre un « clic » :	☐	☐
- Maintien en position pendant 10 secondes :	☐	☐
- Massage doux du site d'injection :	☐	☐
Etape n°3 : Procédures post-injection		
- Contrôle de l'indicateur d'injection (il doit être passé au rouge) :	☐	☐
- Recouvrement de l'aiguille avec le bouchon noir protecteur de l'aiguille (bouchon positionné dans le bon sens, la partie large recouvre l'aiguille visible) :	☐	☐

PHARMACOVIGILANCE

Le participant vous a-t-il **spontanément** fait part de l'occurrence d'un évènement devant être rapporté à la pharmacovigilance : ☐ Non ☐ Oui
Si Oui : L'avez-vous déclaré sur le portail de signalement du gouvernement (https://signalement.social-sante.gouv.fr) ou au Centre Régional de Pharmacovigilance dont vous dépendez : ☐ Non ☐ Oui

A COMPLETER PAR L'INVESTIGATEUR

J'atteste que les informations contenues dans ce questionnaire sont complètes, exactes et authentiques.

Date : I__I__I/I__I__I/I__I__I__I__I Signature :

Nom : _____

Prénom : _____

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AUTO-EVALUATIONS PAR LE PARTICIPANT

Les auto-évaluations ci-dessous sont des auto-questionnaires à compléter par le participant qui vient d'être évalué par le pharmacien.

SYMPTOMES DE L'ANAPHYLAXIE

Parmi les symptômes suivants lesquels peuvent vous alerter sur la possible survenue d'une anaphylaxie (une seule case à cocher) :

☐ Saignement nasal, mal de gorge, toux
☐ Difficulté à respirer, gonflement des lèvres, du cou et des paupières, urticaire et démangeaisons, confusion
☐ Déshydratation, fièvre, douleurs thoraciques
☐ Hallucinations, palpitations, maux de tête

CONSIGNES QUOTIDIENNES

Les questions ci-dessous portent sur vos connaissances des bonnes pratiques à mettre en œuvre au quotidien avec Anapen®.

Savez-vous qu'il est nécessaire de :

1. Disposer en permanence de 2 auto-injecteurs Anapen® dans le cas où une seule injection ne suffirait pas à résoudre les symptômes de l'anaphylaxie :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

2. Conserver le trainer (stylo de démonstration sans adrénaline ni aiguille) et les auto-injecteurs Anapen® séparément pour ne pas risquer de les confondre lors d'une situation d'urgence :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

3. Conserver les auto-injecteurs Anapen® à l'abri de la lumière, à une température ne dépassant pas 25°C :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

4. Vérifier régulièrement la fenêtre d'inspection des auto-injecteurs Anapen®. La solution doit être limpide et incolore :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

5. Vérifier régulièrement la date de péremption des auto-injecteurs Anapen® :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

6. Remplacer les auto-injecteurs Anapen® si ces derniers ne peuvent plus être utilisés :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

CONSIGNES POST-INJECTION

Les questions ci-dessous portent sur vos connaissances de la conduite à tenir après une injection d'Anapen®.

Savez-vous qu'il est nécessaire de :

1. Immédiatement après avoir utilisé Anapen® appeler le 15 ou le 112, demander une ambulance et dire « choc anaphylactique » et « injection intramusculaire d'Anapen® » :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

2. Si les symptômes ne s'améliorent pas ou s'aggravent dans les 5 à 15 minutes qui suivent la première injection, procéder à une seconde injection avec un autre auto-injecteur Anapen® :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

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3. En attendant l'ambulance, la personne ayant reçu l'injection doit rester allongée, avec les pieds surélevés pour faciliter la circulation sanguine, ou assise en cas de difficultés respiratoires et une personne doit rester à ses côtés jusqu'à l'arrivée des secours :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

4. Si la personne ayant reçu l'injection est inconsciente, elle doit être allongée sur le côté en position latérale de sécurité :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

5. Si un quelconque effet indésirable se produit après l'injection, le déclarer à un professionnel de santé ou via le portail de signalement des événements sanitaires indésirables du ministère chargé de la santé :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

CONSIGNES EN CAS D'INJECTION ACCIDENTELLE

La question ci-dessous porte sur votre connaissance de la conduite à tenir en cas d'injection accidentelle d'Anapen®.

Savez-vous qu'il est nécessaire de :

1. Consulter immédiatement le service des urgences de l'hôpital le plus proche pour recevoir un traitement en cas d'injection accidentelle :
   ☐ Oui je le savais
   ☐ Non je ne le savais pas

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Annex 1B CASE REPORT FORM (ENGLISH VERSION)

Participant code: I__I__I__I-I__I__I PART TO BE COMPLETED BY THE PHARMACIST Page **1** of **5**

INCLUSION IN THE STUDY

Date: I__I__I /I__I__I /202I__I
Day Month Year

You confirm that you have given to the subject the information letter, left him/her time to read it, answered his/her questions, that he/she has not objected to participating in the study and he/she agreed for the processing of his/her personal data in accordance with the intended purposes:
☐ Yes

If the 'Yes' box is not ticked, then the subject is not allowed to be included in the study.

SELECTION CRITERIA

Verification of the selection criteria:
☐ Adult person
☐ Person who has been informed and who does not oppose to participate
☐ Person with an Anapen® prescription (first or renewal) for himself/herself or for a relative
☐ Person to whom you have issued an Anapen® box in the current practice of pharmacy
☐ Person participating to this study for the first time

If the five boxes above are not ticked, the subject cannot be included in the study, **you should not continue collecting data**.

STUDY PARTICIPANT

The Anapen® prescription is:
☐ A first prescription
☐ A renewal

The participant is:
☐ The beneficiary of the Anapen® prescription
☐ A relative of the beneficiary of the Anapen® prescription → The beneficiary of the Anapen® prescription is:
  ☐ A child
  ☐ An adult

Age of the participant: I__I__I years

Gender of the participant: ☐ Male ☐ Female

The participant has ever performed a self-injection or an injection to someone else of Anapen®: ☐ No ☐ Yes

PRESCRIBER

Specialty of the physician who delivered this Anapen® prescription:
☐ Allergist
☐ General practitioner
☐ Ear nose throat specialist
☐ Pediatrician
☐ Emergency physician
☐ Other: _____

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ASSESSMENT OF THE PARTICIPANT BY THE PHARMACIST

Complete the questions below by questioning the study participant.

PREVIOUS TRAINING IN PROPER USE, STORAGE AND MAINTENANCE OF ANAPEN®

Have you already met a healthcare professional for an Anapen® prescription:
☐ No → Fill in **box 1** below
☐ Yes → Fill in **box 2** below

Box 1

Have you already:
→ Consulted the brochure 'How to use the Anapen® adrenaline auto-injector': ☐ No ☐ Yes
→ Had an Anapen® trainer (demonstration pen with no adrenaline and no needle): ☐ No ☐ Yes
If Yes: Have you handled the trainer one or more times: ☐ No ☐ Yes
→ Watched the Anapen® auto-injector user video: ☐ No ☐ Yes

Box 2

Has a healthcare professional already:
→ Instructed you how to properly use the Anapen® auto-injector: ☐ No ☐ Yes
→ Told you why you should always have 2 Anapen® auto-injectors along with you: ☐ No ☐ Yes
→ Trained you on how to keep Anapen®: ☐ No ☐ Yes
→ Explained to you what to do after using Anapen®: ☐ No ☐ Yes
→ Given you the brochure 'How to use the Anapen® adrenaline auto-injector': ☐ No ☐ Yes
If Yes: Have you consulted this brochure: ☐ No ☐ Yes
→ Given you an Anapen® trainer (demonstration pen with no adrenaline and no needle): ☐ No ☐ Yes
If Yes: Did he/she explain that the Anapen® trainer should be kept separately from the Anapen® auto-injectors: ☐ No ☐ Yes
Have you handled the trainer one or more times: ☐ No ☐ Yes
→ Encouraged you to watch the Anapen® auto-injector user video? ☐ No ☐ Yes
If Yes: Have you already watched this video: ☐ No ☐ Yes

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ASSESSMENT USING A TRAINER OF HOW THE PARTICIPANT HANDLES THE ANAPEN® AUTO-INJECTOR

Give the participant a trainer (in its box with the 'How to use Anapen® trainer' leaflet) and ask him/her to use it **on himself/herself** as they would use Anapen® pen for an emergency treatment of anaphylactic shock symptoms. Without influencing the participant and by watching him/her handling the Anapen® trainer, answer the following questions by ticking 'No' or 'Yes'.

	No	Yes
Step 1: Activation of Anapen®		
- Removing the black needle cap	☐	☐
- Removing the grey safety cap	☐	☐
- Holding the device in fist	☐	☐
- Positioning the device in the right direction (needle towards the skin)	☐	☐
Step 2: Injection		
- Press the device firmly on injection area	☐	☐
- Device placed against the outer thigh	☐	☐
- Pushing the trigger button to hear a click	☐	☐
- Holding in place for 10 seconds	☐	☐
- Gentle massage of the injection site	☐	☐
Step 3: Post-injection instructions		
- Checking the injection indicator (it must be red)	☐	☐
- Covering of the needle with the protective black cap of the needle (cap placed in the right direction, the wide part covers the visible needle)	☐	☐

PHARMACOVIGILANCE

Did the participant **spontaneously** inform you of the occurrence of an event to be reported to the Pharmacovigilance: ☐ No ☐ Yes

If Yes: Have you reported it to the French government reporting portal (https://signalement.social-sante.gouv.fr) or to your local Regional Pharmacovigilance Centre: ☐ No ☐ Yes

TO BE COMPLETED BY THE INVESTIGATOR

I certify that the information contained in this questionnaire is complete, accurate and true.

Date: I__I__I/I__I__I/I__I__I__I__I (Day / Month / Year) Signature:

Last name: _____

First name: _____

SELF-ASSESSMENTS BY THE PARTICIPANT

The self-assessment items below are self-questionnaires to be completed by the participant just assessed by the pharmacist.

SYMPTOMS OF ANAPHYLAXIS

Among the following symptoms which ones can alert you about the possible occurrence of an anaphylactic shock (tick one box only):

☐ Nose bleeding, sore throat, cough
☐ Difficulty in breathing, swollen lips, neck and eyelids, rash and itching, confusion
☐ Dehydration, fever, chest pains
☐ Hallucinations, palpitations, headaches

EVERYDAY INSTRUCTIONS

The statements below cover your knowledge of the good practices to apply daily with Anapen®.

Did you know that you need to:

1. Keep 2 Anapen® auto-injectors with you at any time in case a single injection is not enough to counteract the symptoms of anaphylactic shock:
   ☐ Yes, I knew that
   ☐ No, I didn't know

2. Keep Anapen® trainer (demonstration pen with no adrenaline and no needle) separately from the Anapen® auto-injectors so as not to mix them up in case of an emergency:
   ☐ Yes, I knew that
   ☐ No, I didn't know

3. Keep Anapen® auto-injectors in a dark place, at a temperature not exceeding 25°C:
   ☐ Yes, I knew that
   ☐ No, I didn't know

4. Check the inspection window regularly of Anapen® auto-injectors. The solution should look clear and colourless:
   ☐ Yes, I knew that
   ☐ No, I didn't know

5. Check the expiry date of Anapen® auto-injectors regularly:
   ☐ Yes, I knew that
   ☐ No, I didn't know

6. Replace Anapen® auto-injectors if they no longer can be used:
   ☐ Yes, I knew that
   ☐ No, I didn't know

POST-INJECTION INSTRUCTIONS

The statements below relate to your knowledge of what to do after an Anapen® injection.

Did you know that you need to:

1. Call 15 or 112 (the emergency services) straight after using Anapen®, ask for an ambulance and say 'anaphylactic shock' and 'intramuscular Anapen® injection':
   ☐ Yes, I knew that
   ☐ No, I didn't know

2. If the symptoms do not improve or if they even get worse within 5 to 15 minutes of the first injection, then proceed to a second injection with another Anapen® auto-injector:
   ☐ Yes, I knew that
   ☐ No, I didn't know

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3. While waiting for the ambulance, the person who has received the injection must stay lying down, with their feet up in order to make it easier for the blood to circulate. Or, if he/she has difficulty in breathing sit up, and ask someone to stay with until trained medical personnel take over:
   ☐ Yes, I knew that
   ☐ No, I didn't know

4. If the person who has received the injection is unconscious, then he/she should lie him/her in the side safety position:
   ☐ Yes, I knew that
   ☐ No, I didn't know

5. Report any adverse effect experienced after injection to a healthcare professional or via the Health Department's reporting portal (website):
   ☐ Yes, I knew that
   ☐ No, I didn't know

INSTRUCTIONS IN THE EVENT OF ACCIDENTAL INJECTION

The statement below relates to your knowledge of what to do in case of an accidental Anapen® injection.

Did you know that you need to:

1. Call and seek advice right away from the accident & emergency department of your nearest hospital to be given a treatment in case of an accidental injection:
   ☐ Yes, I knew that
   ☐ No, I didn't know

15. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Post-authorisation observational safety study to examine the effectiveness of risk minimization measures in place in persons with an Anapen® prescription

EU PAS Register® number: Study will be registered upon approval of the protocol
Study reference number (if applicable): Protocol 21-08 / Anapen® / PASS

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]	☒	☐	☐	6.
1.1.2 End of data collection[2]	☒	☐	☐	6.
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6.
1.1.6 Final report of study results	☒	☐	☐	6.

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

Comments:

No progress report(s) and interim report(s) are planned in this study.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.
	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)	☒	☐	☐	7.
	2.1.2 The objective(s) of the study?	☒	☐	☐	8.
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2.
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.5.
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1.
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
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)	☒	☐	☐	11.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2.
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.3.
	4.2.2 Age and sex	☒	☐	☐	9.3.1.
	4.2.3 Country of origin	☒	☐	☐	9.5.
	4.2.4 Disease/indication	☒	☐	☐	9.2.1.
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3.

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Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1.

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (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 categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

The study is designed to evaluate the use of Anapen® Trainer in real-life and not the efficacy of adrenaline. There is no adrenaline injection in this study, and no exposure.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

The study does not aim to validate measurement or assessment method of risk minimization.

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Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.

Comments:

Section 8: Effect measure 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)	☒	☐	☐	9.9.

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.
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)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.
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), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.1.

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Comments:

The study is designed to evaluate the use of Anapen® Trainer in real-life and not the efficacy of adrenaline. There is no adrenaline injection in this study, and no exposure.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5.
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

The study does not aim to validate measurement or assessment method of risk minimization.

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)	☒	☐	☐	9.8.
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.
12.1.2 Information bias?	☐	☒	☐	
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).	☒	☐	☐	9.9.
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

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Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2.
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1.

Comments:

The protocol has not yet been submitted for approval to the ethics committee.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.

Comments:

Name of the main author of the protocol: **Christine JUHEL**

Name: **Martine LE GALL**
Head of Clinical Development Bioprojet Pharma

Date:

Signature:

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