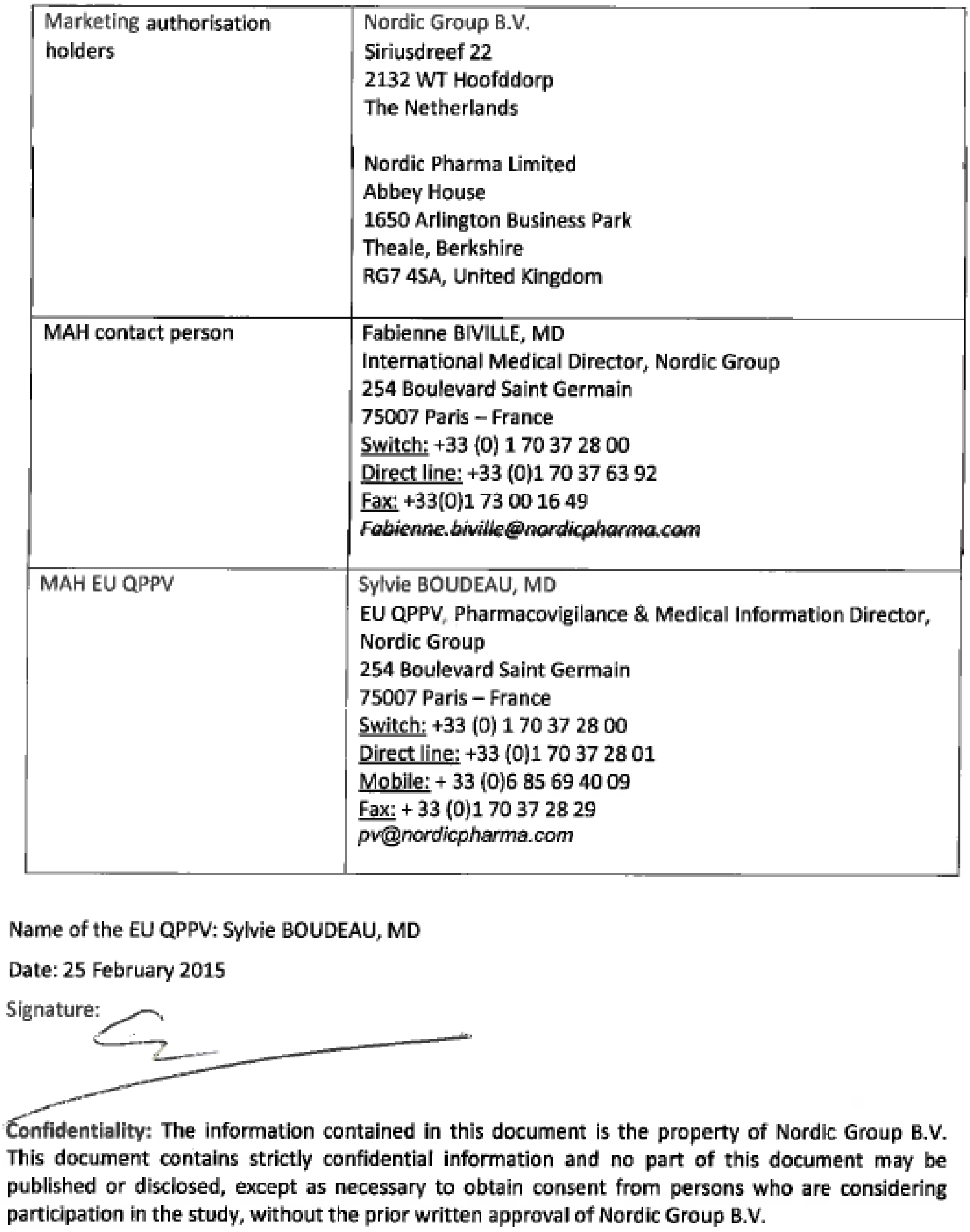
Title	**Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin** Short title: "Nordic Aprotinin Patient Registry"
Protocol version identifier	NG-APRO-PASS-01.3
Date of last version of protocol	11 March 2015
EU PAS register number	Study not registered yet
Active substance	ATC code: B02AB01 Aprotinin
Medicinal product	TRASYLOL 10,000 KIU/ml, injectable solution Aprotinin 10,000 KIU/ml Injection BP
Product reference	AT: 15663 BE: BE108631; BE197294 DE: 34579.00.00 DK: 13857 EL: 77760301 ES: 60.067 FI: 12264 FR: NL 17428; NL 20868; NL 21354 HU: OGYI-T-5393/01 LU: 1998095267 NL: RVG 05312 PL: 10965; 10966; 10967 PT: 8416941; 3481884; 3481983 SE: 8177 SI: 5363-I-1120/13 UK: PL 05827/0015
Procedure number	EMEA/H/PSP/j/0004
Marketing authorisation holder(s)	Nordic Group B.V. Nordic Pharma Limited
Joint PASS	Yes
Research question and objectives	In order to monitor the pattern of use of Nordic Aprotinin, this Registry has been set up. Its purpose is to record utilisation information on patients at cardiac surgery centres exposed to Nordic Aprotinin when it becomes available to the market. This Registry is a risk minimisation measure as described in the current Risk Management Plan.
Countries of study	AT, BE, DE, DK, EL, ES, FI, FR, HU, LU, NL, PL, PT, SE, SI, UK. *This list is likely to be modified in the coming years*
Author	Fabienne BIVILLE, MD International Medical Director, Nordic Group 254 Boulevard Saint Germain 75007 Paris – France

Marketing authorisation holders



Marketing authorisation holders	Nordic Group B.V. Siriusdreef 22 2132 WT Hoofddorp The Netherlands Nordic Pharma Limited Abbey House 1650 Arlington Business Park Theale, Berkshire RG7 4SA, United Kingdom
MAH contact person	Fabienne BIVILLE, MD International Medical Director, Nordic Group 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 63 92 Fax: +33(0)1 73 00 16 49 *Fabienne.biville@nordicpharma.com*
MAH EU QPPV	Sylvie BOUDEAU, MD EU QPPV, Pharmacovigilance & Medical Information Director, Nordic Group 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 28 01 Mobile: + 33 (0)6 85 69 40 09 Fax: + 33 (0)1 70 37 28 29 *pv@nordicpharma.com*

Name of the EU QPPV: Sylvie BOUDEAU, MD

Date: 25 February 2015

Signature:

Confidentiality: The information contained in this document is the property of Nordic Group B.V. This document contains strictly confidential information and no part of this document may be published or disclosed, except as necessary to obtain consent from persons who are considering participation in the study, without the prior written approval of Nordic Group B.V.

Responsible parties

Contact persons within MAH

Fabienne BIVILLE, MD International Medical Director 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 63 92 Fax: +33(0)1 73 00 16 49 *fabienne.biville@nordicpharma.com*	Thomas LANDEMAINE, PhD International Project Manager, TRASYLOL® 254 Boulevard Saint Germain 75007 Paris – France Switch : +33 (0) 1 70 37 28 00 Direct line: + 33(0)1 70 37 63 93 Fax: +33(0)1 73 00 16 49 *thomas.landemaine@nordicpharma.com*
Sylvie BOUDEAU, MD EU QPPV, Pharmacovigilance & Medical Information Director, Nordic Group 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 28 01 Mobile: + 33 (0)6 85 69 40 09 Fax: + 33 (0)1 70 37 28 29 *pv@nordicpharma.com*	Alan GUIVARC'H Pharmacovigilance and Medical Information manager 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 28 01 Mobile: + 33 (0)6 81 72 53 40 Fax: + 33 (0)1 70 37 28 29 *alan.guivarch@nordicpharma.com* *or pv@nordicpharma.com*

External expert consultant

Christopher SPEIRS, MSc MRCP FFPM
Director of Harefield Pharmacovigilance Limited
Fetcham Park House
Lower Road
Fetcham KT22 9HD - United Kingdom
cspeirs@harefieldpv.com

Data Management

Dendrite Clinical Systems Ltd
The Hub, Station Road
Henley-on-Thames
Oxfordshire
RG9 1AY
United Kingdom
Phone: +44 1491 411 288
Fax: +44 1491 411 377
E-Mail: info@e-dendrite.com
http://www.e-dendrite.com/

Principal Investigator

The Principal Investigator is Professor Stefan De Hert (Department of Anesthesiology, Ghent University Hospital, Belgium)

Coordinating Investigators for each participating country

The list of Coordinating Investigators is not defined yet, as the final list of countries is not defined yet and the launch in most countries is expected Q3 2015. Nordic is currently discussing with experts in this field about this. A national coordinator will be defined before launch in each concerned country. The list of coordinating Investigators, including contact details, will be kept as a stand-alone document and updated in each study report /PSUR.

Monitoring

In accordance with local needs, CRO can be involved in training of the healthcare professionals that will use the Registry ("end-users") and monitoring. In other countries, this will be performed by Nordic.

Abstract

Name of MAHs	NORDIC GROUP BV NORDIC PHARMA LIMITED
Name of finished product	TRASYLOL® 10,000 KIU/ml, injectable solution Aprotinin 10,000 KIU/ml Injection BP
Name of active ingredient	Aprotinin
Short title of the Study	Nordic Aprotinin Patient Registry
Full title of the Study	Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin
Protocol No.	NG-APR-PASS-01.3
Date of last version of protocol	11 March 2015
Author	Fabienne BIVILLE, MD Nordic Group B.V. International Medical Director
Rationale and background	This study is being conducted as part of an agreed European Risk Management Plan (EU RMP), condition of the Nordic Aprotinin marketing authorisation

Research question and objectives	This Nordic Aprotinin Patient Registry is a non-interventional Post Authorisation Safety Study as defined in the Guideline on GVP Module VIII – Post-authorisation safety study (EMA/813938/2011 Rev 1). The study is part of the European Risk Management Plan for Nordic Aprotinin as required by CHMP. The Registry is intended to record utilisation information on virtually all patients at cardiac surgery centres exposed to Nordic Aprotinin in participating countries in Europe beginning from the day that Nordic Aprotinin becomes available to the market, and continuing for at least three years thereafter. To have access to Nordic Aprotinin, cardiac surgery centres have to commit to enrol in the Registry. The primary objectives of the Registry are to: 1. Monitor the pattern of use and record utilisation information: o the proportion of patients exposed to aprotinin in accordance with the authorized indication 2. Measure the incidence of the following adverse events: o death and the distribution of the primary cause of death o thromboembolic events; the total and individual incidence of myocardial infarction, stroke and other thromboembolic events recorded o incidence of renal dysfunction defined as a rise in creatinine from pre-operative to post-operative levels of > 0.5 mg/L, and the incidence of renal dialysis o the numbers having an anaphylactic response to aprotinin 3. Measure the effectiveness of risk minimisation measures as described in the RMP and close monitoring of adherence to the SmPC recommendations: o the proportion of patient receiving heparinisation monitoring as recommended in the SmPC o the proportion of patients with a post-operative renal dysfunction defined as a rise in creatinine from pre-operative to post-operative levels of > 0.5 mg/L or requiring dialysis known to have received aminoglycoside antibiotics o the proportion of patients exposed to aprotinin without the use of test dose (or antibody test) o the proportion of patients administered with the recommended posology The secondary objectives of the Registry are to: 1. Estimate the contribution of suspected risk factors to adverse events: o the proportion of patients with total and individual thrombotic events who did not receive heparinisation monitoring as recommended in the SmPC (regarding the risks related to heparinisation monitoring)

	○ the proportion of patients with anaphylactic reactions who had previously been exposed to aprotinin (solution or fibrin sealant containing aprotinin) in the last 12 months 2. Estimate information concerning: ○ the proportion of pregnant and lactating women ○ the proportion of patients undergoing repeat isolated CABG ○ the proportion of patients having a concomitant use of drugs that affect haemostasis (including antiplatelet therapy) and/or non-VKA oral anticoagulant considered as active at time of surgery and relating safety outcomes when aprotinin is used in those patients ○ the proportion of patients over 75 years of age and outcomes: the proportion of these patients requiring re-operation for bleeding; the mortality rate 3. Estimate optional information according to the national legislation of the countries involved: ○ the proportion of patients exposed to aprotinin for cardiothoracic surgery which indications are outside isolated cardiopulmonary bypass graft surgery ○ the proportion of patients exposed to aprotinin in the paediatric population ○ the proportion of patients exposed to aprotinin for indications other than cardiothoracic surgery
Study design	The Nordic Aprotinin Patient Registry is a multicentre, non-interventional Post Authorisation Safety Study with active surveillance via patient exposure registry. Nordic will supply Nordic Aprotinin only to centres that perform cardiac surgery on cardio-pulmonary bypass and which commit to enrol in the Nordic Aprotinin Patient Registry (participating centres). The Nordic Aprotinin Patient Registry is designed to be easy-to-use and to fit with standard clinical practice. The Registry is intended to record utilisation information on virtually all patients at cardiac surgery centres exposed to the product beginning from the day that Nordic Aprotinin becomes available to the market, and continuing for at least three years thereafter. Nordic will provide appropriate training and support to facilitate implementation of the Registry at all participating centres. Nordic will encourage all participating centres to treat only patients conforming to the authorised indications for Nordic Aprotinin. According to the national legislation of the countries involved, Nordic will carefully monitor the number of cases in which Nordic Aprotinin is given to patients having surgery outside the authorised use and will collect data on these patients via the Registry (use outside cardiac surgery is expected to be negligible due to the limitation

	of supply to cardiothoracic centres) however if there is any such use, it will be monitored carefully and discussed in the PSUR. The proposed Registry will provide information on the number of patients who receive Nordic Aprotinin by centre, indication (cardiac surgical procedure, indication features) for which Nordic Aprotinin was administered, and the conditions of use, including dose and adherence to instructions for administration in the approved SmPC. Interim and progress reports will be provided to the PRAC (and the National Competent Authorities if required) and will include summary tables of analyses of patterns of use.
Study population	All patients exposed to Nordic Aprotinin at all participating cardiac surgical centre fulfilling criteria of the restricted distribution in participating countries in Europe.
Variables	The content of the Registry follows the template of the reports of the European Association for Cardio-Thoracic Surgery (EACTS) with additional data assessment relevant to the specific needs for recording the use and safety monitoring, including haemostatic monitoring, of the use of aprotinin. The collection of data is therefore divided into Key Pages and non-key pages. The Key Pages include the Key Data: patient demography and all of the major outcomes of identified or potential hazards in the use of aprotinin, that includes adverse drug reactions such as allergic reactions, renal dysfunction and its relationship to aminoglycoside antibiotics, coagulation control and the use of heparin and the major outcomes of renal failure, myocardial infarction, stroke and other thrombotic effects. Those Key Data allow answering the research question and objectives of this study. The Key Pages are the following: - Initial Registry data (patient demography) - Operation - Antiplatelet and anticoagulant therapy considered to be active at operation - Aprotinin use - Intra-operative coagulation and blood loss monitoring in the operating room - Transfusion (intra-operative and post-operative) - Post-operative - Post-discharge follow-up Only adverse drug reactions, which are suspected to be associated to Nordic Aprotinin should be reported by the Investigator to Nordic Pharmacovigilance via the Routine pharmacovigilance reporting ways (such as phone, email, fax) or via the Registry and its link with Nordic Pharmacovigilance department. The information regarding these adverse drugs reactions is processed, entered into the Nordic Safety Database, assessed and reported to the Competent Authorities, if applicable, according to the regulation in force. Those adverse drugs reactions will also be discussed in PSUR according to the regulation in force. A close monitoring will be performed for risks mentioned in the RMP. All other safety information (not suspected to be associated to Nordic Aprotinin) will be included by the Investigator in the electronic case report form (eCRF). This information will be recorded in the Registry and reviewed on a continuing basis allowing recognition of any pattern that may be of cause for concern of a particular

	hazard in the overall use of Nordic Aprotinin or at the level of an individual country or centre. All safety information will be included in the interim and final study reports of the Registry which will be submitted to the PRAC (and other Competent Authority if required) via PSUR.
Data sources	The data source is an electronic registry that can be accessed worldwide through a web portal, working with all web browsers and designed to collect uniform data on patients exposed to Nordic Aprotinin. Data which is collected during routine clinical practice will be entered into the eCRF.
Study size	Based on likely prescription rates Nordic estimates that at least 12,000 patients are expected to be enrolled in the Registry over the 3-year period
Data analysis	All data analyses will be performed by Dendrite Clinical Systems together with Nordic after the Key Data are completed. Analysed data will be reviewed by an Independent Data Safety Monitoring Committee, involving at least four (4) national coordinating investigators. The analysis of data from the Registry will be descriptive, and all information will be reported in summary tables. Summary data will be provided for all variables collected and the data will be reported overall, by country, and if required by centre. The intention is to focus on those variables most pertinent to assessing compliance with approved labelling and instructions for appropriate use, including use of heparin and monitoring of anticoagulation. The data will also be reviewed for any safety signals. The outcomes to be included in each report will include at least: death, myocardial infarction, renal failure with and without aminoglycoside use, stroke and other embolic or thrombotic event, blood loss (requiring transfusion, requiring re-operation), blood product transfusion and anaphylaxis. Analysis of each outcome will be presented by: country, age categories, sex, presence of anti-platelet agents active at time of operation, cardiac by-pass and operative type. Other variables may be included as considered appropriate by an Independent Data Safety Monitoring Committee or as requested by the PRAC. Overall reports will be synchronised with PSUR scheme and timelines.
Planned milestones	Study start: planned for Q2 2015 Recruitment completed: planned mid-2018 Interim reports: 6 months, 1 year and 2 years after launch Last data collection: mid-2018 Report of study: 6 months after the end of Data collection (prospective collection). The Registry will operate for at least three years beginning with Nordic Aprotinin's return to the market in Europe, and the decision to terminate the Registry will be taken based on agreement with the PRAC.

Annex 1. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

encepp

European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

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

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

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

Study title:
Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin

Study reference number:
NG-APRO-PASS-01

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

Comments:

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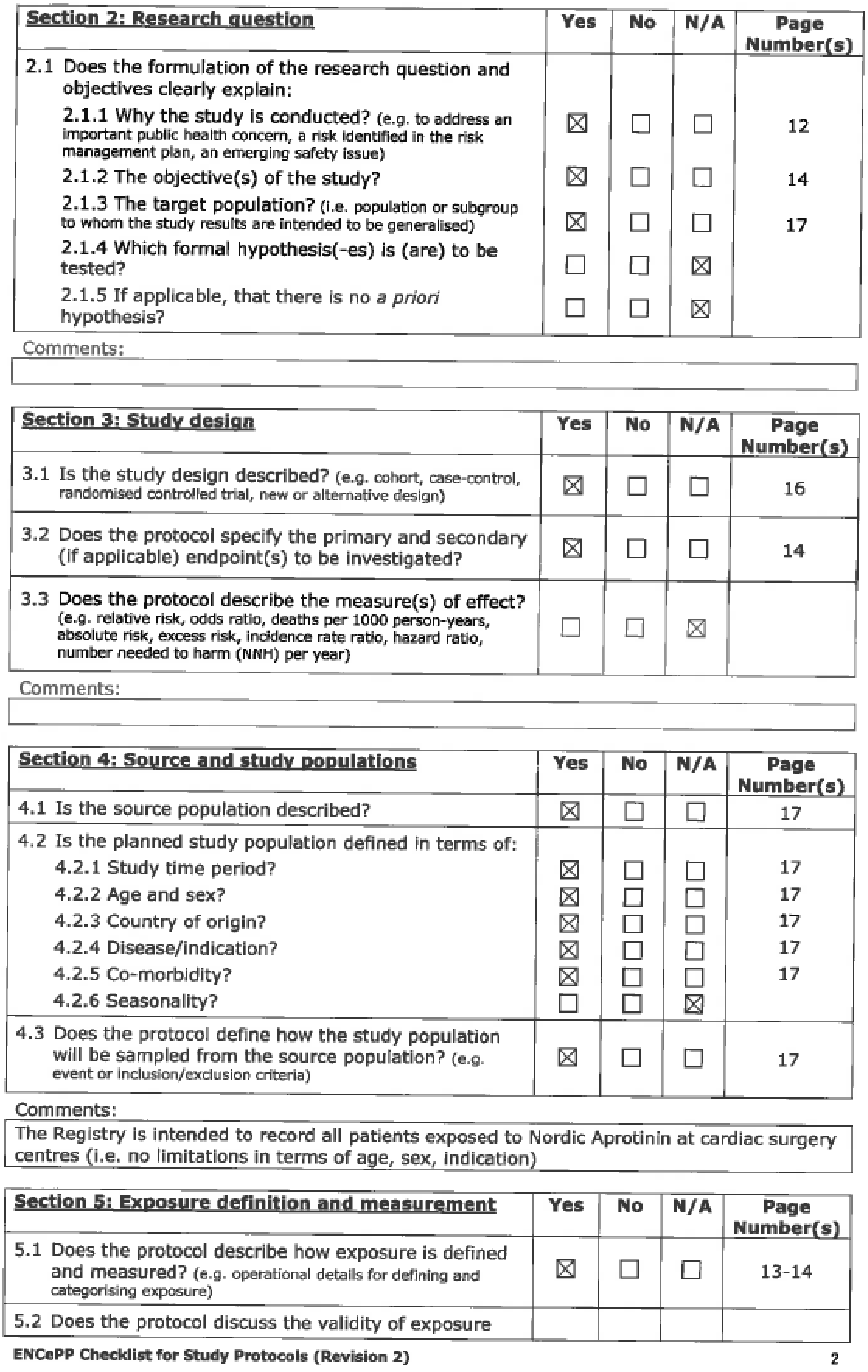
[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.



Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	12
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

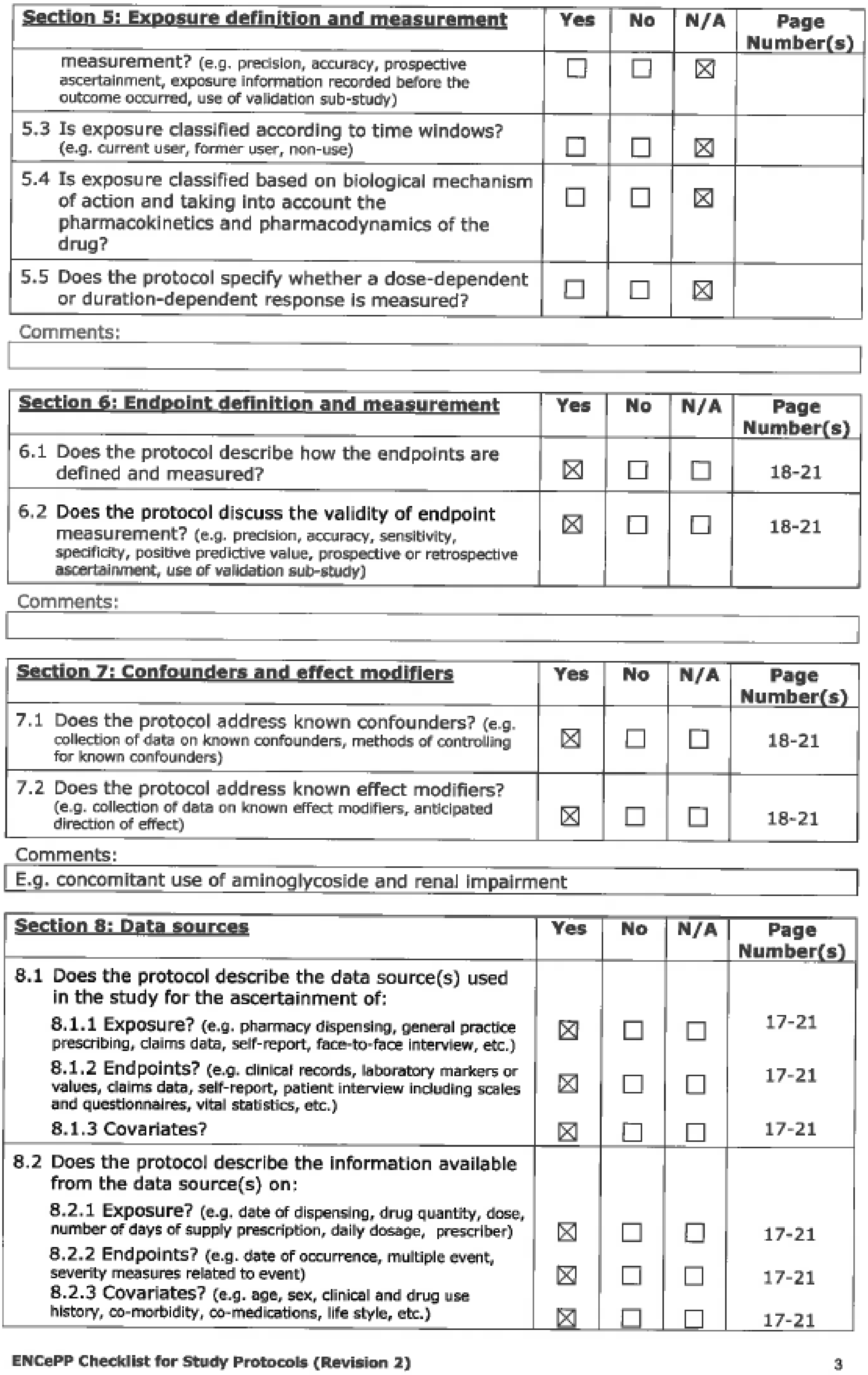
Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	17
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?	☒	☐	☐	17
4.2.5 Co-morbidity?	☒	☐	☐	17
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	17

Comments:

The Registry is intended to record all patients exposed to Nordic Aprotinin at cardiac surgery centres (i.e. no limitations in terms of age, sex, indication)

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	13-14
5.2 Does the protocol discuss the validity of exposure				

ENCePP Checklist for Study Protocols (Revision 2) 2



Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18-21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	18-21

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	18-21
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	18-21

Comments:

E.g. concomitant use of aminoglycoside and renal impairment

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	17-21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	17-21
8.1.3 Covariates?	☒	☐	☐	17-21
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	17-21
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17-21
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17-21

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21

Comments:

All patients exposed to Nordic Aprotinin are intended to be included

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	22-23
10.2 Is the choice of statistical techniques described?	☒	☐	☐	22
10.3 Are descriptive analyses included?	☒	☐	☐	22
10.4 Are stratified analyses included?	☒	☐	☐	22
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	22-23
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	24
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	22
11.3 Are methods of quality assurance described?	☒	☐	☐	24
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	23-24
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	30

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	25-26
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	25-26
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	25-26

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	26-27
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	26-27
13.3 Have data protection requirements been described?	☒	☐	☐	26-27

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10-11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	31
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	31

Comments:

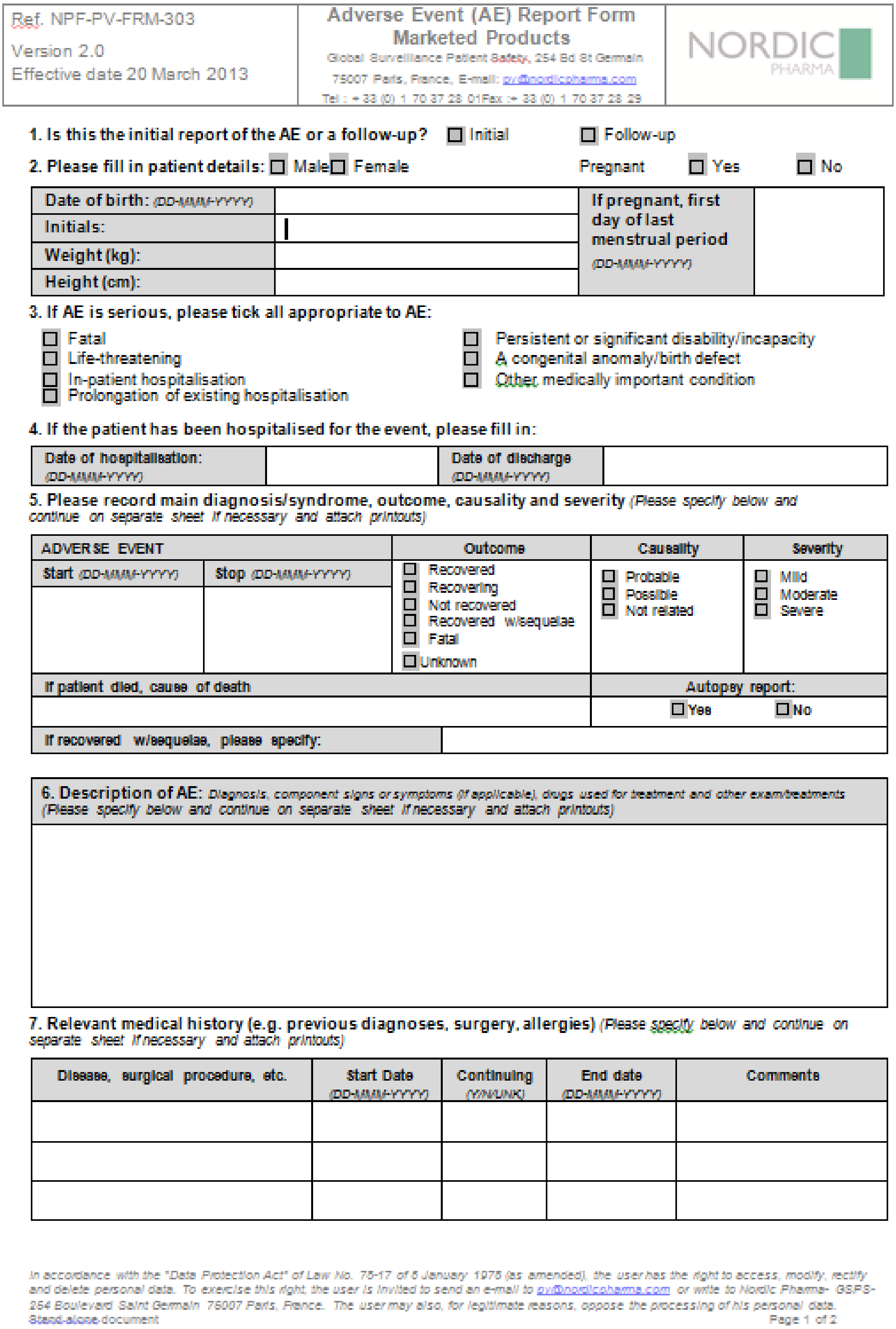
Name of the main author of the protocol: Boivine Fabienne

Date: 25/2/2015

Signature:

Annex 2. Additional information

Adverse Event Report Form



Ref. NPF-PV-FRM-303 Version 2.0 Effective date 20 March 2013	**Adverse Event (AE) Report Form Marketed Products** Global Surveillance Patient Safety, 254 Bd St Germain 75007 Paris, France, E-mail: pv@nordicpharma.com Tel : + 33 (0) 1 70 37 28 01Fax :+ 33 (0) 1 70 37 28 29	NORDIC PHARMA

1. Is this the initial report of the AE or a follow-up? ☐ Initial ☐ Follow-up

2. Please fill in patient details: ☐ Male ☐ Female Pregnant ☐ Yes ☐ No

Date of birth: *(DD-MMM-YYYY)*		**If pregnant, first day of last menstrual period** *(DD-MMM-YYYY)*	
Initials:			
Weight (kg):			
Height (cm):			

3. If AE is serious, please tick all appropriate to AE:

- ☐ Fatal
- ☐ Life-threatening
- ☐ In-patient hospitalisation
- ☐ Prolongation of existing hospitalisation
- ☐ Persistent or significant disability/incapacity
- ☐ A congenital anomaly/birth defect
- ☐ Other medically important condition

4. If the patient has been hospitalised for the event, please fill in:

Date of hospitalisation: *(DD-MMM-YYYY)*		**Date of discharge** *(DD-MMM-YYYY)*	

5. Please record main diagnosis/syndrome, outcome, causality and severity *(Please specify below and continue on separate sheet if necessary and attach printouts)*

ADVERSE EVENT		Outcome	Causality	Severity
Start *(DD-MMM-YYYY)*	**Stop** *(DD-MMM-YYYY)*	☐ Recovered ☐ Recovering ☐ Not recovered ☐ Recovered w/sequelae ☐ Fatal ☐ Unknown	☐ Probable ☐ Possible ☐ Not related	☐ Mild ☐ Moderate ☐ Severe
If patient died, cause of death			**Autopsy report:**	
			☐ Yes ☐ No	
If recovered w/sequelae, please specify:				

6. Description of AE: *Diagnosis, component signs or symptoms (if applicable), drugs used for treatment and other exam/treatments (Please specify below and continue on separate sheet if necessary and attach printouts)*

7. Relevant medical history (e.g. previous diagnoses, surgery, allergies) *(Please specify below and continue on separate sheet if necessary and attach printouts)*

Disease, surgical procedure, etc.	Start Date (DD-MMM-YYYY)	Continuing (Y/N/UNK)	End date (DD-MMM-YYYY)	Comments

In accordance with the "Data Protection Act" of Law No. 78-17 of 6 January 1978 (as amended), the user has the right to access, modify, rectify and delete personal data. To exercise this right, the user is invited to send an e-mail to pv@nordicpharma.com or write to Nordic Pharma- GSPS- 254 Boulevard Saint Germain 75007 Paris, France. The user may also, for legitimate reasons, oppose the processing of his personal data.

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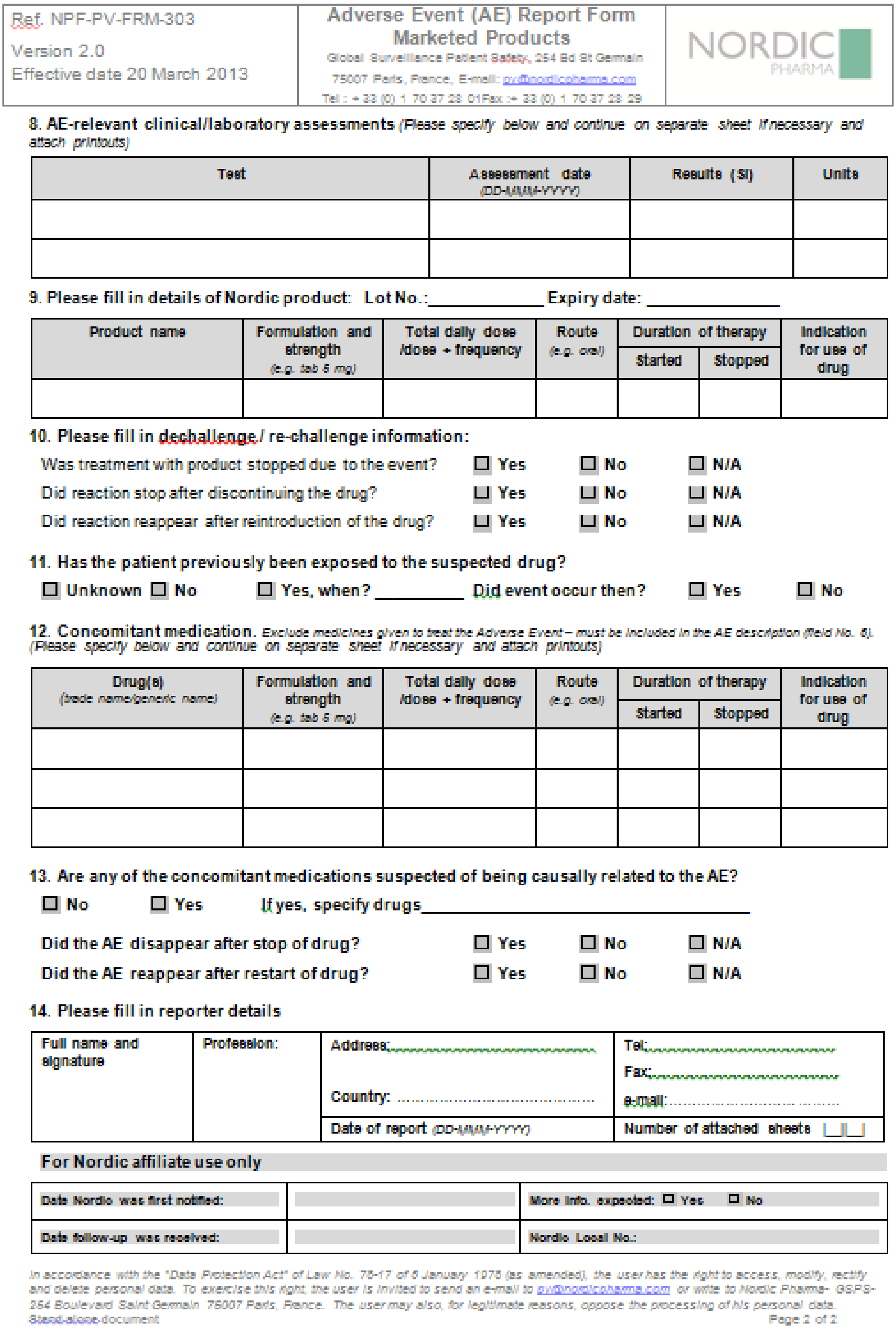

Ref. NPF-PV-FRM-303 Version 2.0 Effective date 20 March 2013	**Adverse Event (AE) Report Form Marketed Products** Global Surveillance Patient Safety, 254 Bd St Germain 75007 Paris, France, E-mail: pv@nordicpharma.com Tel : + 33 (0) 1 70 37 28 01Fax :+ 33 (0) 1 70 37 28 29	NORDIC PHARMA

8. AE-relevant clinical/laboratory assessments *(Please specify below and continue on separate sheet if necessary and attach printouts)*

Test	Assessment date *(DD-MMM-YYYY)*	Results (SI)	Units

9. Please fill in details of Nordic product: Lot No.:____________ Expiry date: ____________

Product name	Formulation and strength *(e.g. tab 5 mg)*	Total daily dose /dose + frequency	Route *(e.g. oral)*	Duration of therapy		Indication for use of drug
				Started	Stopped	

10. Please fill in dechallenge / re-challenge information:

Was treatment with product stopped due to the event? ☐ Yes ☐ No ☐ N/A
Did reaction stop after discontinuing the drug? ☐ Yes ☐ No ☐ N/A
Did reaction reappear after reintroduction of the drug? ☐ Yes ☐ No ☐ N/A

11. Has the patient previously been exposed to the suspected drug?

☐ Unknown ☐ No ☐ Yes, when? _________ Did event occur then? ☐ Yes ☐ No

12. Concomitant medication. *Exclude medicines given to treat the Adverse Event – must be included in the AE description (field No. 6). (Please specify below and continue on separate sheet if necessary and attach printouts)*

Drug(s) *(trade name/generic name)*	Formulation and strength *(e.g. tab 5 mg)*	Total daily dose /dose + frequency	Route *(e.g. oral)*	Duration of therapy		Indication for use of drug
				Started	Stopped	

13. Are any of the concomitant medications suspected of being causally related to the AE?

☐ No ☐ Yes If yes, specify drugs______________________________

Did the AE disappear after stop of drug? ☐ Yes ☐ No ☐ N/A
Did the AE reappear after restart of drug? ☐ Yes ☐ No ☐ N/A

14. Please fill in reporter details

Full name and signature	Profession:	Address:............................. Country:	Tel:............................. Fax:............................. e-mail:.............................
		Date of report *(DD-MMM-YYYY)*	Number of attached sheets |__||__|

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Date Nordic was first notified:		More info. expected: ☐ Yes ☐ No
Date follow-up was received:		Nordic Local No.:

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Annex 3 - Details of Nordic Aprotinin Restricted distribution

Nordic Aprotinin will be available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the registry.

In this aim, Nordic (or distributors appointed by Nordic) will establish for each European country where Nordic Aprotinin has a valid Marketing Authorisation, a list of qualified hospitals which can order and receive Nordic Aprotinin.

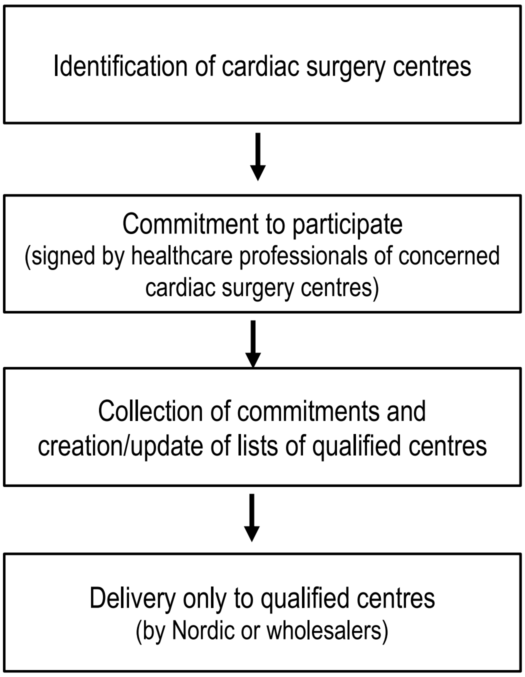
A hospital will be qualified when the following items are fulfilled:

1. The hospital has a cardiac surgery ward, which performs surgery on cardio-pulmonary bypass
2. One or several healthcare professionals of the cardiac surgery ward signed a commitment to fulfil the Aprotinin Patient Registry.

Nordic will make sure that Nordic Aprotinin is delivered only to qualified hospitals.

Controls of deliveries shall be organised regularly and potential corrective actions organised accordingly.

The process is summarized in the flowchart:



Centres identification: Nordic or distributor employees will confirm with healthcare providers that cardio-pulmonary bypass is used in the concerned cardiac surgery centres.

Commitment to participate: Nordic will train end-users of the Aprotinin Patient Registry (healthcare professionals working in cardiac surgery centres) and will ask them to sign a commitment to participate to the Registry (at least one per cardiac surgery centre). Commitments will be collected at national level to create and to update national lists of participating centres.

Qualified centres: A centre will be qualified when (i) identified by Nordic affiliates / Distributors and (ii) has at least one signed commitment.

Delivery: Nordic will supply Nordic Aprotinin only to hospitals qualified in the list. In case Nordic delivers to wholesalers, Nordic will make sure that the wholesalers will deliver the qualified hospitals.

This process is part of the RMP (approved following worksharing procedure NL/H/9007/WS/088) and described in the “Annex 10 - Details of proposed additional risk minimisation measures” of the RMP