Product: SCH 900415
Protocol: P 08290

NORA

Nexplanon Observational Risk Assessment Study

STUDY PROTOCOL

STUDY ID NUMBER **ZEG2011_03**

PROTOCOL DATE

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15-Jul 2011

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PROTOCOL APPROVAL DATE	**15 JUL 2011**
START OF STUDY PARTICIPANT ENROLLMENT	**October 2011**
LAST FOLLOW-UP	**October 2017**
FINAL REPORT	**February 2018**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ADB	Administrative Database
ATC	Anatomical Therapeutic Chemical Classification System
ß-hCG	Beta Human Chorionic Gonadotropin
CT	X-ray Computerized Tomography
DIMDI	German Institute for Medical Documentation and Information
EDC	Estimated Date of Conception
ENG	Etonogestrel
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiological Practice
GxP	General term for Good Practice quality guidelines and regulations applicable in the field of drug development (GPP, GEP, GMP etc.)
HCP	Health Care Professional
ICD10	International Classification of Diseases
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corporation
NGIA	Next Generation Implanon Applicator
OPS	Operations and Procedures Classification System
SAE	Serious Adverse Event
SDB	Study Database
SMAC	Safety Monitoring and Advisory Council
US	United States
US PI	US Package Insert
USS	Ultrasound Scanning
WHO	World Health Organization
ZEG	Berlin Center for Epidemiology and Health Research (Zentrum für Epidemiologie und Gesundheitsforschung Berlin)

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1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

Implanon® is a subdermal contraceptive implant containing the progestogen etonogestrel. It provides contraceptive protection for three years and has been marketed since 1998. Nexplanon (etonogestrel radiopaque implant) contains the same active ingredient as Implanon® but differs from Implanon® by the addition of barium sulfate and the use of a Next Generation Implanon Applicator (NGIA). Nexplanon has been developed to further facilitate correct insertion of the implant by using the NGIA, and to extend the diagnostic modalities for localization of the implant by making it radiopaque and hence visible via X-ray imaging and X-ray Computerized Tomography (CT). Following approval in the United States, the Funder intends to completely phase out Implanon® and replace it with Nexplanon.

Since the market introduction of Implanon®, the Funder has received reports related to the insertion, localization and removal of the implant. The Funder collects and follows up information on insertion-, localization- and removal-related events. The overall flow of information for such spontaneously reported events in association with Nexplanon will be the same as the procedure followed for Implanon®.

1.2 STUDY RATIONALE

This observational study is being conducted as a post-approval regulatory commitment for the FDA. This study will include US women using Nexplanon. The objective of the study is to characterize the frequency of specific insertion-, localization- and removal-related events and clinically significant consequences thereof among Nexplanon users in the US during standard clinical practice.

1.3 STUDY SETTING

The study will be conducted by the Berlin Center for Epidemiology and Health Research (ZEG).

The study will be overseen by an independent committee of experts, *the Safety Monitoring and Advisory Council,* who will review the study data every 6 months and on request of the Principal Investigator.

2. STUDY OBJECTIVES

The primary objective of the study is to characterize the frequency of specific insertion-, localization- and removal-related events and clinically significant consequences thereof among Nexplanon users in the US during standard clinical practice.

Specific insertion-, localization- and removal-related events to be studied are:
- incorrect insertion (including unrecognized non-insertion, partial insertion and deep insertion)
- palpability of the implant at insertion and removal
- localization of non-palpable implant
- difficult removals

Clinically significant consequences of insertion-, localization- and removal related events to be studied are:
- pregnancy due to unrecognized non-insertion of the implant
- injury to neurovascular structures in the arm
- hospitalization and/or surgical procedures for localization and/or removal

Secondary objectives are:
- to monitor the occurrence of pregnancy and pregnancy outcomes
- to describe the reasons for (premature) discontinuation of Nexplanon
- to describe the baseline characteristics of Nexplanon users

3. INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This is a large, US-based, descriptive, prospective, non-interventional, observational cohort study that follows a single cohort. The cohort consists of new users of the contraceptive implant Nexplanon. The study will use a non-interference [1] approach to provide standardized, comprehensive and reliable information on implant use in the US during standard clinical practice.

[1] i.e., 1) all patients who have a newly inserted Nexplanon implant are eligible for enrollment if they give their informed consent, and 2) patient recruitment should not (significantly) influence the physicians' prescribing behavior

Women will be recruited through Health Care Professionals (HCPs) who have completed the Nexplanon Clinical Training Program. NORA has no specific inclusion or exclusion criteria. All women prescribed a new Nexplanon implant are eligible for study participation provided they are capable of understanding the major aspects of the study, can complete the self-administered questionnaire in English and are willing to sign an informed consent form. Women under 18 years of age at study entry are eligible for study participation providing they have a parent/guardian countersign their consent forms.

After study entry, study participants will be followed for a period of 42 months for insertion-, localization- and/or removal-related events or clinically significant consequences thereof. Data will be captured via a series of self-administered questionnaires. At baseline both the HCP and study participant will complete a questionnaire designed to capture background medical and gynecological information as well as specific information related to the implant insertion procedure. Study participants will then be followed 6 monthly, receiving the final follow-up questionnaire 6 months after removal of the implant - up to a maximum of 42 months after insertion[2]. The 6 monthly *follow-up questionnaire* will gather information on significant and/or serious adverse events (including the occurrence of pregnancy and symptoms related to possible neurovascular injury in the arm of insertion), the study participants general health and localization and/or removal procedures. When localization and/or removal procedures have been performed, the study participant's HCP will be asked to complete a *localization/removal questionnaire* regarding outcomes of the procedure.

Data analysis will mostly be undertaken via point-estimates of the prevalence and event rates as well as their 95% confidence intervals. The impact of potential prognostic factors (e.g. BMI, age, experience of HCP) will be analyzed using multivariate regression models and/or stratified analyses.

The study will be overseen by an independent Safety Monitoring and Advisory Council (SMAC) with an unconditional grant from Merck Sharp & Dohme Corp.

3.2 TREATMENT

Nexplanon

[2] The product life of Nexplanon is 36 months. Final follow-up will occur 6 months after the scheduled removal date to capture late removals (37-42 months), in-treatment pregnancies occurring in the final month(s) of Nexplanon use and injury to neurovascular structures of the arm due to Nexplanon removal.

3.3 SELECTION OF STUDY POPULATION

In the US Nexplanon can only be inserted by HCPs who complete the Nexplanon Clinical Training Program. Approximately 700 HCPs will be recruited in collaboration with the Funder's Clinical Training Program for Nexplanon. Approximately 7,100 women will be recruited through HCPs who have completed the Nexplanon Clinical Training Program. Women will be considered for enrollment in this study after the participating HCP has determined that Nexplanon use is appropriate. All women who are eligible for study inclusion are to be asked by their HCP if they are willing to participate in the study. Due to the non-interventional nature of the study, the possibility of study participation should not be discussed with the woman before both HCP and the woman agree upon the prescription and insertion of Nexplanon. The HCP is to explain the nature of the study, its purpose and associated procedures and the expected duration of follow-up for each woman prior to her entry into the study. Each woman is to have ample opportunity to ask questions and must be informed about her right to withdraw from the study at any time without disadvantage and without having to provide reasons for her decision. This information will be provided on an informed consent and data privacy form which must be signed by all study participants. These documents are to be approved by the relevant local Ethics Committees and the relevant Data Privacy Offices, if applicable.

At any time during the study, study participants may choose to discontinue the use of Nexplanon. All study participants, regardless of when their implant is removed, will receive a final follow-up questionnaire 6 months after removal of the implant – up to a maximum of 42 months after insertion – to capture any events related to the removal procedure as well as any in-treatment pregnancies that are diagnosed after the removal of the implant.

3.4 STUDY ENDPOINTS

3.4.1 Specific insertion- localization- and removal related events

Although it is expected that complications with the insertion, localization and/or removal of Nexplanon are rare, occasionally the insertion, localization and/or removal of the implant may not be successful. Insertion should be carried out following the insertion procedure as described in detail in the US Package Insert (US PI). Nexplanon should only be inserted by HCPs that have completed the Clinical Training Program for Nexplanon. Incorrect insertion techniques may result in insertion-, localization- and removal-related events, such as an unrecognized non-insertion, partial insertion, deep insertion, difficulties in

palpating or localizing the implant, migration of the implant and difficulties during removal of the implant.

The events listed below concern the specific insertion-, localization- and removal-related events to be studied as the primary objectives of the NORA study.

Unrecognized non-insertion

If the implant was accidentally not inserted into the arm of the study participant (failed insertion) and this was not noticed at the time of insertion, it is called an unrecognized non-insertion. Unrecognized non-insertions can only be confirmed with certainty by a negative ENG blood test.

Unrecognized non-insertions will be captured by obtaining data on a negative blood ENG measurement via the *localization/removal questionnaire*.

Partial insertion

If, during the insertion of Nexplanon, the needle is not inserted to its full length, if the purple slider of the applicator is not completely moved to the back or if the applicator is not kept in the same position while unlocking the purple slider and moving it to the back, the implant will not be properly inserted. This will result in a partly visible implant protruding from the skin. Partial insertion will be captured on the *baseline insertion questionnaire* by asking whether any issues were encountered during the insertion procedure (e.g. implant is partly visible, difficulty sliding needle to its full length into skin).

Deep insertion

Nexplanon should be inserted sub-dermally (i.e. just under the skin) on the inner side of the non-dominant upper arm approximately 8-10 cm above the medial epicondyle. If, during insertion, the applicator is not kept in the correct position, the implant may be inserted too deep (e.g. intramuscular or within the fascia). Deep insertions may cause neural or vascular injury and may also lead to migration of the implant. Moreover, when the implant is inserted into the deep tissue layers, it may not be palpable and the localization and/or removal may be difficult.

Deep insertions will be captured via either the *baseline insertion questionnaire* or the *localization/removal questionnaire*. It should be recorded on the *baseline insertion questionnaire* whether the needle was inserted in the correct position and the location of the implant at insertion. Further details on the location of the

implant may also be ascertained from ultrasound, X-ray, CT or MRI reports where appropriate.

Palpability of the implant at insertion and removal

When inserted correctly, the presence of the implant can be verified by palpating both ends of the implant.

Palpability of the implant is captured by recording palpability of the implant at insertion on the *baseline insertion questionnaire* and by recording palpability of the implant on the *localization/removal questionnaire* and the *follow-up questionnaire*.

Localization of a non-palpable implant

The methods used to confirm the presence and location of a non-palpable implant (e.g. two-dimensional X-ray, CT scan, ultrasound scanning (USS), magnetic resonance imaging (MRI) or measuring the blood etonogestrel (ENG)) will be captured by recording the localization efforts on the *localization/removal questionnaire*. In rare cases related primarily to either a deep insertion or to external forces such as manipulation of the implant or contact sports, the implant may migrate from the insertion site. Implant migration may complicate the localization and removal of the implant. If migration is suspected, this will be captured via the *localization/removal questionnaire*. Further details on the location of the implant may also be ascertained from ultrasound, X-ray, CT or MRI reports where appropriate.

Difficult removals

A difficult or unsuccessful removal of an implant may be caused by an implant being inserted into the deep tissue layers, migration of the implant, and presence of fibrotic tissue around the implant or unrecognized non-insertion.

Difficult removals will be captured on the *localization/removal questionnaire* by asking whether any complications (including unrecognized non-insertion) occurred during implant removal.

3.4.2 Clinically significant consequences of insertion-, localization- and removal-related events

Pregnancy due to unrecognized non-insertion of the implant
See Section 3.4.3

Injury to neurovascular structures in the arm
Nexplanon implants inserted into the deep tissue layers may result in neural or vascular injury. Removal of a deeply inserted implant should be undertaken with caution in order to prevent injury to neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.

Neural and vascular injury will be captured on the *baseline insertion questionnaire and follow-up questionnaires* by asking for symptoms and complications during and shortly after the insertion*, as well as* after the removal procedure on the *localization/removal questionnaire*. Furthermore, the transient or persisting nature of these symptoms will be elucidated.

Symptoms suggestive of neurovascular injury include:

- paraesthesia, hypoaesthesia, numbness, hyperaesthesia, or dysaesthesia in the arm where Nexplanon has been inserted/removed
- neuralgia in the arm where Nexplanon has been inserted/removed
- (partial) sensory and/or motor loss in the arm where Nexplanon has been inserted/removed
- major hemorrhage, thrombosis, phlebitis in the arm where Nexplanon has been inserted/removed

When a study participant reports the occurrence of any of these symptoms, the HCP will be asked for more details and verification of possible injury to neurovascular structures in the arm.

Hospitalization and/or surgical procedures for localization and/or removal
Under routine conditions the HCP will remove Nexplanon as a minor surgical procedure in his or her office. In case that a more complex surgical procedure is required to localize and/or remove the implant, this information will be captured on the localization/removal questionnaire. The HCP will be able to specify the reason for-, the type of- and the outcome of the surgical intervention. The HCP can also indicate whether the surgical procedure was performed under local or general anesthesia.

All unplanned hospitalizations will be captured as SAEs (see Section 7). In addition, in case the study participant was hospitalized for localization and/or

removal procedures, this information will be captured on the localization/removal questionnaire. The HCP will be able to specify the reason for hospitalization.

3.4.3 Pregnancy

Nexplanon will be effective and protect against pregnancy immediately if inserted at the right time. The recommended time of insertion is based on each woman's natural cycle or previous method of contraception.

A study participant can report the occurrence of a pregnancy on the 6-monthly *follow-up questionnaire*. The last *follow-up questionnaire* will be sent 6 months after removal (up to 42 months after insertion) of the implant to capture pregnancies diagnosed after implant removal but with an estimated date of conception (EDC) within the in-treatment period of Nexplanon. In case of an in-treatment pregnancy the study participant will be followed until the pregnancy outcome is determined.

Confirmation of self-reported pregnancies is important to avoid misclassification of pregnancies. During the use of Nexplanon a woman's bleeding pattern is likely to change. Absent bleeding may be misinterpreted as the early signs of conception. If a study participant reports a pregnancy, confirmation of pregnancy will be obtained from her HCP. A pregnancy is considered to be confirmed if diagnosed by beta human chorionic gonadotropin (ß-hCG) measurement or ultrasound.

<u>Classification of confirmed pregnancies</u>
Pregnancies in study participants using Nexplanon may occur due to reasons other than insufficient contraceptive action. This could relate to an incorrect insertion technique, resulting in unintentionally not inserting Nexplanon or inserting Nexplanon outside the recommended time frame resulting in insufficient contraception for a certain period. In addition, a study participant may be pregnant at the time of insertion.

Each pregnancy is classified after thoroughly evaluating all available information. If necessary, follow-up information will be requested.

Confirmed pregnancies will be categorized as:

1) Pre-treatment pregnancies
   Pregnancies with an estimated date of conception before the implant insertion
2) In-treatment pregnancies

Pregnancies with an estimated date of conception within the in-treatment period, i.e. from the day of implant insertion up to and including the day of implant removal

3) Post-treatment pregnancies
Pregnancies with an estimated date of conception after the in-treatment period; post-treatment pregnancies will be further categorized into those occurring 1-7 days, 8-14 days and >14 days after removal
4) Non-insertion pregnancies: Pregnancies due to unrecognized non-insertion of the implant (ENG blood test is negative)

The process of pregnancy confirmation and pregnancy categorization is presented in Figure 1, page 16.

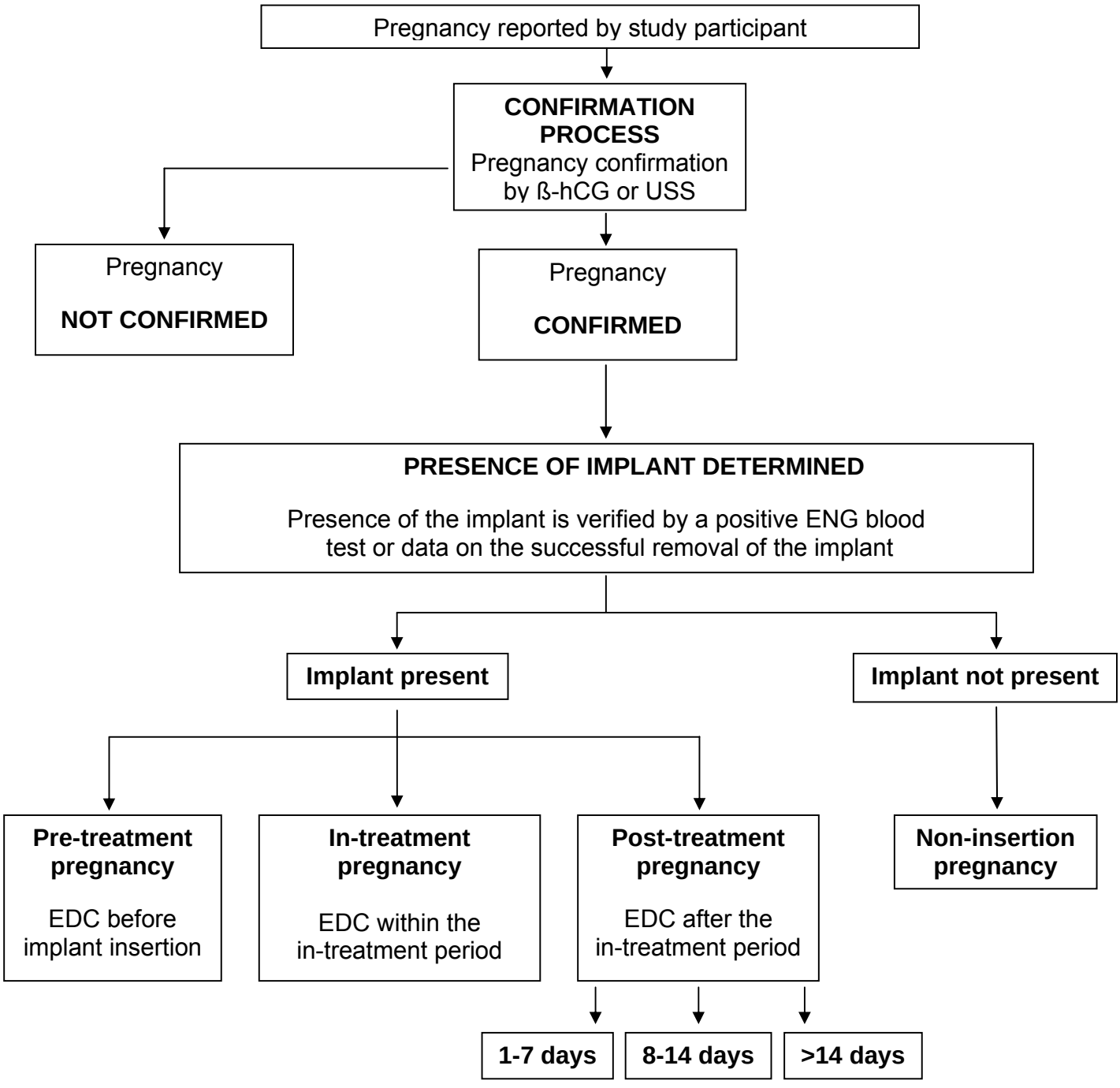
Follow-up of confirmed pregnancies:

For all pregnancies, follow-up will take place during the event validation process. When a study participant reports a pregnancy, she and her HCP will be contacted and asked to provide information surrounding the pregnancy and its relationship to implant use. Specific questions will be asked regarding the date the pregnancy was diagnosed, the diagnostic method used to confirm conception, the estimated gestational age, the estimated date of conception, the use of concomitant medication, pregnancy outcome (delivery, induced abortion, spontaneous abortion) and actions taken with the implant (continuing or removed).

For all confirmed pregnancies where fetal exposure to ENG may have taken place, the study participant will be contacted after the expected date of delivery to obtain relevant details about the delivery and the health of the baby. This will not apply when the pregnancy was discontinued (induced or spontaneous abortion) or when, according to the pregnancy categorization, the pregnancy was due to unrecognized non-insertion (no fetal exposure to ENG). The diagnosing and/or treating physician will be contacted for clarification and validation of the information received from the study participant in case of reported health problems of the baby.

See page 16 (Figure 1) for the process of confirmation and categorization of pregnancies.

Figure 1: Process of confirmation and categorization of pregnancy



EDC	estimated date of conception
ß-hCG	beta human chorionic gonadotropin
USS	ultrasound

3.4.4 Reasons for (premature) discontinuation of Nexplanon

The reason for removal of the implant will be captured via the *follow-up questionnaire*. The study participant should identify the reason for removal of the implant in the questionnaire (i.e. 3 years of use has elapsed, desire pregnancy, pregnancy occurred or other reasons, e.g. side effects; the study participant is asked to further specify the reason).

3.4.5 Description of Nexplanon users' baseline characteristics

The baseline characteristics of Nexplanon users including contraceptive history, medical and gynecological history as well as socio-demographic details will be captured through the *baseline insertion questionnaire.*

3.4.6 Monitoring of Significant and Serious Adverse Events

Significant and/or serious adverse events[3] that occur during or shortly after Nexplanon use will be captured via the 6 monthly *follow-up questionnaire* and the *localization/removal questionnaire.* Study participants will also be asked open-ended questions regarding hospitalization, surgery and/or illness.

3.5 DATA COLLECTION AND STUDY PROCEDURES

The study will be divided in two phases: the insertion phase and the follow-up phase with four different questionnaires used during the study.

Insertion phase:	Baseline Insertion Questionnaire, completed by HCP and study participant
Follow-up phase:	Follow-up Questionnaire, completed by study participant
	Localization/Removal Questionnaire, completed by HCP
	Post-removal Questionnaire, completed by study participant

The *insertion phase* includes a *baseline insertion questionnaire* for both the HCP and study participants which is filled out at the time of implant insertion. The *follow-up phase* includes sending a 6-monthly *follow-up questionnaire* to study

[3] Significant and/or serious adverse events include the occurrence of pregnancy and symptoms suggestive of possible neurovascular injury to the arm which may have occurred during either the insertion *or* removal of the implant

participants for up to 36 months post implant insertion (i.e. at 6, 12, 18, 24, 30, 36 month post-insertion) and a *post-removal questionnaire* sent 6 months after the scheduled implant removal (36 + 6 = 42 months). If study participants have their implant removed before 36 months, the regular follow-up phase will stop and the *post-removal questionnaire* will be sent 6 months after the stated removal date. The follow-up phase also includes contact with the HCP after localization and/or removal of the implant (42 months after insertion or as soon as the study participant reports a localization/removal procedure). Follow-up contacts are calculated in calendar months following the initial insertion visit.

The participating HCPs are requested to follow-up the study participants in accordance with the procedures they generally use for monitoring women with newly inserted contraceptive implants. The instructions given in the US PI should be followed.

Study flow chart

Procedures/Questionnaires	**Pre-insertion**	**Inser-tion**	**Follow-up [months]**						
			6	**12**	**18**	**24**	**30**	**36**	**42**
Informed consent/Privacy Rule Authorization	●								
Baseline insertion questionnaire (HCP and Study participant)		●							
Follow-up questionnaire (Study participant)*			●	●	●	●	●	●	●
Localization/Removal questionnaire (HCP)			○	○	○	○	○	○	●†
Post-removal questionnaire (Study participant)			○	○	○	○	○	○	●

* study participants will be followed 6 monthly for 42 months or until the implant is removed.
All study participants, regardless of when their implant is removed, will receive a final follow-up questionnaire 6 months after removal of the implant – up to a maximum of 42 months after insertion

○ questionnaire sent at this time point if implant is removed prematurely (i.e. prior to 36 months)

† at 42 months after insertion, or earlier in case the implant has been removed prematurely, i.e. the localization/removal questionnaire will be send to the HCP as soon as localization and/or removal efforts have been recorded on the follow-up questionnaire.

3.5.1 Baseline insertion questionnaire

On the day of the implant insertion, both the study participant and her HCP will complete questions on a *baseline insertion questionnaire*. This self-administered questionnaire contains questions on the date of insertion, timing of implant

insertion (e.g. relative to day of the menstrual cycle, previous contraceptive use or abortion/delivery), insertion site, any potential complications or difficulties specific to the insertion procedure, outcome of insertion, implant palpability after insertion and if not palpable, the actions taken to confirm the presence of the implant. Furthermore, the study participant will be asked for specific information regarding her general state of health, history of previous contraceptive use, medical and gynecological history, height and weight, medication history as well as any immediate symptoms/problems she has noticed in the implant arm since the insertion procedure. At baseline the addresses, email addresses and phone number of the study participant as well as a second contact (relative or friend) and her HCP details are collected. In compliance with data protection regulations names, addresses and phone numbers are to be documented on a separate sheet and stored separately in a locked cabinet.

3.5.2 Follow-up questionnaire

After completing the *baseline insertion questionnaire* in the HCP's office, study participants will be sent up to 7 *follow-up questionnaires*. In addition study participants will have the option to answer the questions via an online survey. A follow-up assessment for each study participant is scheduled 6, 12, 18, 24, 30, 36 and 42 months after insertion of the implant. The last follow-up is planned 6 months after the scheduled removal of Nexplanon (36 months) in order to capture any late removals, any complications due to the removal procedure and to capture in-treatment pregnancies diagnosed after removal of the implant. At any time during the study, study participants may choose to discontinue the use of Nexplanon. All study participants, regardless of when their implant is removed, will receive a final follow-up questionnaire 6 months after removal of the implant – up to a maximum of 42 months after insertion (i.e. *the post-removal questionnaire*). The *follow-up questionnaire* contains questions on whether any actions have been taken to localize the implant, whether any attempts were made to remove the implant, whether removal has been successful, whether the study participant experienced any symptoms in the arm in which Nexplanon has been inserted (including, if applicable, a question to further specify those symptoms), reasons for implant discontinuation or switching to another contraceptive if applicable, and the occurrence of pregnancy or SAEs. If a study participant records that she has had the Nexplanon implant removed or attempts have been made to localize or remove the implant (successful or unsuccessful), she will be asked to fill in the name and address of the HCP involved in localization and/or removal of the implant. Her nominated HCP will be sent a *localization/removal questionnaire* regarding the localization and/or removal procedure. If a study participant reports the occurrence of pregnancy or the

occurrence of an significant and/or serious adverse event, she will be contacted to confirm the details and her nominated treating physician may be contacted for details on the pregnancy or significant/serious adverse event.

3.5.3 Localization/Removal questionnaire

If a study participant reports that the implant has been localized and/or removed, the HCP who was involved in the (attempted) localization and/or (attempted) removal of the implant will be asked to complete a self-administered *localization/removal questionnaire.* The questionnaire elucidates information on the date of localization and/or removal, the occurrence of specific localization- and/or removal-related events, difficulties with localization and/or removal of the implant, hospitalization due to localization/removal (if any), whether surgical intervention was required and the outcome of the localization and/or removal. Over the course of the study, the *Localization/Removal questionnaire* may be filled out several times for a single study participant if, after the localization procedure, the HCP and study participant decide not to remove the implant.

3.5.4 Validation and adjudication of self-reported events

The self-administered questionnaire used by study participants is a very sensitive tool which captures almost all serious clinical outcomes[4]. From a methodological point of view, it captures a much higher proportion of relevant outcomes than methods relying on events reporting by the prescribing physician (e.g. gynecologist). However, laypersons can misinterpret symptoms, preventive treatments (e.g., anticoagulatory treatment to prevent venous thromboembolism) and diagnostic measures leading to a significant difference between the number of events reported and the number that are confirmed by validation of the ZEG team. Therefore, validation of the self-reported events is of utmost importance.

Validation of self-reported events is undertaken by the Investigator (ZEG) and begins at the level of ZEG's local research team with a review of all study

[4] Dinger JC, Heinemann LAJ, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: Final results from the European Active Surveillance study on Oral Contraceptives (EURAS-OC) based on 142,475 women-years of observation. Contraception 2007, 75: 344-354.

Bourgeois FT, Porter SC, Valim C, Jackson T, Cook EF, Mandl KD. The Value of Patient Self-report for Disease Surveillance. J Am Med Inform Assoc. 2007 Nov-Dec;14(6):765-71.

Ming ME, Levy RM, Hoffstad OJ, Filip J, Gimotty PA, Margolis DJ. Validity of patient self-reported history of skin cancer. Arch Dermatol. 2004 Jun;140(6):730-5.

participant reported “events.” Potential serious outcomes are reported to ZEG Berlin on a continuing basis and validated by ZEG’s Event Validation Team.

If an event is reported by a study participant, the study participant’s symptoms and signs related to the event and, if possible, the diagnosis as perceived by the patient are recorded. The name and address of the relevant physician (attending physician, physician responsible for the follow-up treatment on discharge from hospital or primary care physician) should be provided by the study participant.

Follow-up questionnaires containing information on potential significant and/or serious adverse events are immediately passed on to the Event Validation Team at ZEG. If information is unclear or missing, the study participant will be contacted via phone, e-mail or other means. For many serious outcomes it will be necessary to contact the diagnosing and/or treating physician for clarification and validation of the information received from the patient. Contact with the study participant and/or HCP for further clarification of the self-reported event will be undertaken for all outcomes of interest and in particular specific issues related to the insertion and removal of the implant. This includes collecting all pregnancy related information and information regarding unplanned hospitalizations. If the study participant does not mention the reasons for hospital admission on the questionnaire, she is contacted in order to ensure that she was not hospitalized in connection with a study endpoint.

Under routine medical conditions, diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs are classified by ZEG’s Event Validation Team as “confirmed” or “not confirmed” according to a predefined algorithm (see Appendix 1). Confirmed events are further differentiated into ‘definite events’ and ‘probable events’. Alongside the predefined algorithms outlined in Appendix 1, ZEG will develop a standard set of questions for the Event Validation Team to use when conducting interviews or gathering source documentation on the primary outcomes of interest.

At study end, the investigator’s classification of insertion-, localization- and removal-related events will be compared to the results of an independent medical adjudication process. A board, consisting of three independent medical experts, will review all available information on the reported primary outcomes. The adjudication board will have access to all information available to ZEG including questionnaires, transcripts of telephone conversations, medical reports and case summaries. In cases where the investigator’s and the adjudicators’ classification

differ, the adjudicators' classification will supersede the investigator's classification. The following adjudication procedure will be used:

1) Independent adjudication by the individual specialists
2) Documentation of the individual assessments
3) Comparison of the individual assessments
4) Discussion of "split decisions" among the adjudicators without enforcement of a unanimous decision
5) Independent re-adjudication of the discussed cases by the individual adjudicators
6) Documentation of the individual assessments

Based on this procedure six different classification strategies will be possible

I. Classification of the reported event as confirmed if all adjudicators classify the event as confirmed before the discussion of "split decisions" took place (i.e., the decision is based on step 2 of the six-step procedure described above)

II. Classification of the reported event as confirmed if all adjudicators classify the event as confirmed after discussion of "split decision" takes place (i.e., the decision is based on step 6 of the six-step procedure described above)

III. Classification of the reported event according to the assessment of the majority of adjudicators before the discussion of "split decision" takes place (i.e., "majority vote" based on step 2 of the six-step procedure described above)

IV. Classification of the reported event according to the assessment of the majority of adjudicators after discussion of "split decision" takes place (i.e., majority classification based on step 6 of the six step procedure described above)

V. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed before the discussion of split decisions took place (i.e., "worst case decision" based on step 2 of the six-step procedure described above)

VI. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed after the discussion of split decisions took place (i.e., "worst case decision" based on step 6 of the six-step procedure described above)

The final analysis will be based on strategy V (worst case decision without discussion of split decisions) because it represents the most conservative approach. Alternative analyses will be possible on request of the SMAC or regulatory authorities.

3.5.5 Loss to Follow-up

For the successful conduct of the NORA study it is of utmost importance to ensure low loss-to-follow-up (LTFU). LTFU refers to women who are lost to the follow-up procedures at some stage during the study and from that time-point forward their whereabouts is unknown making it impossible to collect further relevant information such as exposure to Nexplanon and adverse events. It is conceivable that the incidence of serious adverse events is higher among women who are lost to follow-up compared to study participants who are in regular follow-up. In contrast, drop-out refers to women who choose to leave the study prematurely. On leaving the study their exposure to Nexplanon and health status is known. As different HCPs may be involved in the insertion and removal of the implant, regular contact with the study participant (the constant factor) will reduce potential LTFU occurring when a study participant changes her HCP. In order to further minimize LTFU a multi-faceted, four-level follow-up process will be established. If the study participant does not answer the initial follow-up letter or email, she receives up to two reminder letters/emails. In case the study participant does not respond, the study participant will be called. If necessary the contact persons (e.g. mother, friend, and/or physician) that the study participant listed at baseline will be called and asked for the study participant's current mailing address and telephone number. If contact is still not successful, national and international phone and e-mail directories as well as electronic social networks are searched in order to obtain her new contact details. The 4th level follow-up procedures include a formal address inquiry using commercially available databases and an inquiry with the state and national death registries. Overall, the aim should be to keep the loss-to-follow-up to less than 10.0%. Based on ZEG's experience it is expected that the final loss to follow-up will be approximately 7%.

3.6 DATA MANAGEMENT

3.6.1 Databases

Two different databases are used for data collection; the administrative database (ADB) and the study database (SDB).

The ADB is provided by ZEG to the local research team in Toledo, Ohio. HCP details, as well as patient data, can be entered and maintained on this database.

The SDB is validated according to GxP[5] rules. It contains all questionnaire data including baseline data and all subsequent follow-ups. ZEG regularly performs cross-check and verification checks on the data and any inconsistencies or unanticipated answers are sent to the local research team for further clarification.

From the questionnaire data, event data is derived from the SDB. All disease diagnoses are coded using the ICD10 (International Classification of Diseases). ZEG also uses additional codes for the coding of events that are of specific interest (e.g. partial and non-insertion of implant).

Concomitant medication is coded using WHO ATC-Codes. Surgical procedures are coded using the modified operation and procedure coding list (OPS) provided by DIMDI (German Institute for Medical Documentation and Information). All other relevant information will be coded by a ZEG specific, highly standardized coding system (ZEG Coding Dictionary). All clinical outcomes of interest are additionally described in a case narrative, the “case summary”.

3.6.2 Data Flow

When questionnaires are received from study participants, all pages are counted and the questionnaire is date-stamped. Questionnaires are to be checked for correct study participant identification numbers, missing pages, legibility, and incomplete information on the questionnaires. Missing pages, illegible or missing information are requested from the study participants prior to data entry of the respective questionnaire.

Baseline information is immediately checked to ensure the study participant meets minimum eligibility criteria. Standard checks are based on the ZEG Plausibility Dictionary. Based on data entry guidelines detailed in the NORA Working Procedures and training sessions provided by ZEG, the questionnaire data is entered in the Study Database (SDB) by the US research team. The SDB is transferred to ZEG, Berlin on a monthly basis.

Data is entered by double data entry via formatted entry screens designed to reflect the appearance of the questionnaire. Discrepancies between first and second data entry are identified by comparison of the two entry files within the statistical software SAS. The decision on the true entry is done by the

[5] General term for Good Practice quality guidelines and regulations applicable in the field of drug development (GPP, GEP, GMP etc.)

responsible data manager at ZEG. This may require direct contact with the study participant who filled in the questionnaire. Corrections will be made to the questionnaire only after contact with the study participant or her treating physician (cf. section 3.5.4 'Validation and adjudication of self-reported events'). All corrections are dated and initialed by the data manager who received the relevant new information (e.g., via direct contact or by a copy of medical reports/documents). The incorrect questionnaire entry will be crossed out; however, it must remain legible, and the correct entry will be placed next to it. The reason for any correction of medical data on the questionnaire must be documented.

Quality control of entered data will be supported by SAS plausibility programs which include range, coding, missing and date checks as well as cross-reference (consistency) checks between variables.

The above mentioned quality control measures apply also to online questionnaires. However, most plausibility checks are conducted electronically during data entry by the study participant, and double data entry is not necessary as the online questionnaires do not require a manual data transfer.

3.6.3 Database Freeze/Lock

For each biannual interim analysis, beginning 12 months after study start, and for the final analysis the database is frozen at a predefined time point. The database will be cleaned within 4 weeks of the database freeze. After the final freeze (approximately 4 months after the last removal questionnaires have been sent to the HCPs), no additional incoming data is entered in the database – this database will represent the final data source for all analyses. Safety copies are made of each database, so that all calculations can be repeated if necessary.

3.7 STATISTICAL METHODS

3.7.1 Statistical analysis plan

A detailed statistical analysis plan will be developed by ZEG. This plan will include methodological details as well as a comprehensive set of mock tables for the presentation of the study results. The final analysis plan will be approved by the independent SMAC before the first patient is recruited. Changes to this document are to be approved by the SMAC.

Characterization of the frequency of specific insertion-, localization- and removal-related events among Nexplanon users under standard clinical practice will mostly be undertaken via point-estimates of the event rate as well as 95%

confidence intervals. The impact of potential prognostic factors will be analyzed using multivariate regression models and/or stratified analyses.

3.7.2 Sample size

The sample size of this study is based on the following considerations.

I. It is anticipated that due to the new applicator design (cf. section 1.1) the rate of insertion- and removal-related adverse events will be substantially lower for Nexplanon compared with Implanon®. Based on limited evidence from clinical trials this rate is expected to be approximately 1%. Partial insertions will most-likely represent the majority of insertion-related adverse events. The rate of "other" insertion-related events and removal-related events is expected to be below 1%.

II. The vast majority of insertion- and removal-related adverse events will not be life-threatening nor will they lead to permanent or significant disability/incapacity. Therefore it is not deemed necessary to power the study for the assessment of very rare insertion-/removal-related events. The statistical analysis will focus on adverse events that occur in 1 out of 1000 insertions/removals or greater.

III. It is expected that about 22% of recruited study participants will drop-out of the study and a further 7% will be lost to follow-up over the 42 month study period (see below). Therefore, the precision for insertion-related events will be higher compared to removal-related events. The sample size should be sufficient to estimate the risk of insertion as well as removal-related events with reasonable precision.

A reasonable precision for an event rate of 0.01 (1 out of 100 insertions/removals) is a point estimate accuracy of approximately +/- 30%. The 95% confidence interval for an event rate of 0.010 should therefore be in the range of 0.007 and 0.013. Consequently approximately 5000 insertions/removals are needed to achieve this accuracy (see below). Based on the investigators experience it is expected that 7100 insertions are needed to gain valid data on 5000 removals. The expected number of evaluable study participants per follow-up is shown in Table 1.

Table 1: Expected Number of Evaluable Study Participants per Follow-up

Follow-up period	Cumulative Drop-out Rate	Cumulative Loss to Follow-up	No. of Study Participants
Baseline	n/a	n/a	7,100
6m	5.0%	4.0%	6,461
12m	8.0%	5.0%	6,177
24m	14.0%	6.0%	5,680
36m	20.0%	6.5%	5,310
42m	22.0%	7.0%	5,041

Table 2 shows the 95% confidence intervals for insertion and removal related event rates between 0.010 and 0.001 for the calculated number of 7100 study participants.

Table 2: Clopper-Pearson 95% Confidence Intervals for insertion and removal related events based on 7100 Study Participants

Event Rate	Insertion-related Events 95% Confidence intervals based on 7100 insertions	Removal-related Events 95% Confidence intervals based on 5000 removals
0.01000	0.00781 – 0.01260	0.00743 – 0.01316
0.00300	0.00186 – 0.00458	0.00168 – 0.00494
0.00100	0.00040 – 0.00206	0.00032 – 0.00233

In summary: valid data on 7100 insertions and 5000 removals should be sufficient for a reasonable assessment of the risks associated with insertion and removal of Nexplanon including events that occur in 1 out of 1000 insertions/removals. In case that a specific event is not observed in 7100 insertions and 5000 removals the upper limits of the 95% confidence intervals for

the event rates would be 0.00052 and 0.00074, respectively i.e., it could be assumed that the true event rate is lower than 1 out of 1000 insertions/removals.

However, precise power calculations based on actual drop-out rates should be done on the basis of follow-up data before the end of the recruitment phase. If these calculations do not confirm the assumed drop-out rates the Safety Monitoring and Advisory Council may discuss the need to adapt number of study participants.

4. ETHICAL CONDUCT OF THE STUDY AND PROTECTING STUDY PARTICIPANT PRIVACY

4.1 INSTITUTIONAL REVIEW

The study will only start after all relevant legal, administrative and ethical requirements (including all requirements regarding the enrollment of minors) have been fulfilled. Information on the identity of the patients and treating physicians will be kept separated from the clinical information throughout the study. All relevant US data protection laws will be followed. The study protocol will be submitted to the Western Institutional Review Board (Olympia, US state of Washington) for approval.

4.2 INFORMED CONSENT

Study participants will sign informed consent forms after reading a study participant information sheet and discussing the study with the participating HCP. The HCP will describe the purpose of the study, the non-interventional character of the study, timing and expected content of follow-up phase, and the collection of alternative contact information. Consent will include permission to contact treating physicians to follow up on specific safety outcomes related to the primary and secondary objectives of the study. Study participants will be informed that ZEG's study team will contact them during the follow-up phase to ask a predefined set of safety related questions or to update alternative contact information. Answers to these questions will remain anonymous when forwarded to Merck or the SMAC.

Study participants will be asked to provide personal contact information (e.g., telephone number, home and e-mail address) and information regarding alternative contacts (e.g., relative, friend, physician) in case they cannot be reached. In the event that a study participant cannot be reached during the follow-up phase, the study team will attempt to reach an alternative contact to re-establish contact with the study participant. Study participants may be contacted between two follow-up

points to confirm that their personal contact information is correct. Study participants will receive a honorarium of 10 US$ for each baseline and follow-up questionnaire they return to the study team.

Study participants retain the right to withdraw their consent at any time during the study.

5. PUBLICATIONS

The results of this study will be published. In accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical studies in a public registry as a condition for publication, the study will be registered in the U.S. National Institutes of Health's protocol registration database (http://ClinicalTrials.gov) and the ENCePP Study Database (http://www.encepp.eu).

6. STUDY MANAGEMENT

This study will be conducted in accordance with

- 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2007
- 'Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the International Epidemiological Association (IEA) European Federation in 2007
- ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, 2010
- The ethical principles that have their origin in the Declaration of Helsinki.

7. REPORTING OF SERIOUS ADVERSE EVENTS AND PREGNANCIES

ZEG's medical event validation team will perform a causality assessment for all serious adverse events. ZEG will report all confirmed serious adverse events related to the use of a MSD product within 2 business days to the Funder. These serious adverse events include events related to the use of ENG or the insertion/localization/removal of Nexplanon. A physician on the ZEG study team will assess the likelihood of a causal relationship to the implant use for each serious adverse event in accordance with a predefined algorithm (cf. Appendix 2). In addition, ZEG will report all confirmed pregnancies within 2 business days to the Funder. All confirmed pregnancies where fetal exposure to ENG may have

taken place during a certain period of the pregnancy will be followed up for final outcome and reported (cf. Figure 1). Overall, the handling of adverse events will follow Volume 9A of 'The Rules Governing Medicinal Products in the European Union (part I, section 7).

ZEG will not monitor whether the Funder meet its obligation to report these events to the relevant Health Authorities according to (inter)national rules.

8. SAFETY MONITORING AND ADVISORY COUNCIL

This study will maintain scientific independence and will be governed by an independent Safety Monitoring and Advisory Council (SMAC). This committee is independent and separate from the aforementioned event validation adjudication committee. SMAC has full scientific authority over the study. MSD (Whitehouse Station, NJ, U.S.A.) will provide an unconditional grant. The Berlin Center for Epidemiology and Health Research (ZEG), Germany and its research team will be accountable to SMAC in all scientific matters.

The SMAC members will be international experts in relevant scientific fields (e.g., epidemiology and gynecology). The members will receive remuneration of expenses and an honorarium to compensate for loss of potential earnings during their work for SMAC. The members will not be involved in or paid for the operational conduct of the study.

9. SIGNATURES

9.1 FUNDER'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

9.2 PRINCIPAL INVESTIGATOR

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practices, Good Epidemiological Practice, the ENCePP code of conduct and the ethical principles that have their origin in the Declaration of Helsinki. I also agree to report all information or data in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, registration in the U.S. National Institutes of Health's protocol registration database or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE

10 ATTACHMENTS

APPENDIX 1: VALIDATION OF SELF-REPORTED EVENTS

- Definite Event:

  Confirmed by diagnostic measures with high specificity (e.g., ultrasound, X-ray or CT for migration/deep insertion of Nexplanon, ENG assay for non-insertion, phlebography for DVT, spiral CT for pulmonary embolism, cerebral MRT for cerebrovascular accidents, ECG with typical ST segment elevation for acute myocardial infarction, histology for cancers)

- Probable Event:

  Absence of confirmation by a diagnostic measure with high specificity, but clinical diagnosis confirmed by a health professional or supported by diagnostic tests with low specificity (such as the medical report of migration of Nexplanon without objective measurement, D-dimer for VTE, typical ECG/blood gas tests for PE). These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis, long-term anticoagulant therapy). However, if the attending physician confirms that the diagnosis is correct, the event will be classified as a probable event even if specific treatment was not given.

- Event not confirmed:
  - Diagnosis reported by the patient is excluded by diagnostic procedures
  - A different medical condition is diagnosed by the attending physician
  - The study participant did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

Definite and probable events will be classified as ‘confirmed events’.

APPENDIX 2: CAUSALITY ASSESSMENT

Categories (Code)	Definition
no (1)	The time course between insertion/removal of Nexplanon and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of Nexplanon in the occurrence/worsening of the adverse event exists.
unlikely (2)	The time course between insertion/removal of Nexplanon and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of Nexplanon, its drug substance class or the insertion/removal procedures provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known and/or regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of Nexplanon, the drug substance class or the insertion/removal procedures, but another cause is much more probable and/or another cause is confirmed and involvement of Nexplanon in the occurrence/worsening of the adverse event is unlikely.
possible (3)	Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of Nexplanon or the substance class, or the insertion/removal procedures but another cause just as likely to be involved is also known or although the pharmacological properties of Nexplanon, the substance class or knowledge about the insertion/removal procedure provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation.
probable (4)	The properties of Nexplanon or of the substance class and/or the course of the adverse event after dechallenge and, if applicable, after rechallenge and/or specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of Nexplanon in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.
definite (5)	The properties of Nexplanon or of the substance class and the course of the adverse event after dechallenge and, if applicable, after rechallenge and specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of Nexplanon in the occurrence/worsening of the adverse event and no indication of other causes exists.