Analysis Plan for the NORA Study

Introduction:

This analysis plan integrates analyses suggested by the investigators as well as requests by regulatory authorities and the independent Safety Monitoring and Advisory Council (SMAC).

The primary objective of this one-arm, non-comparative study is to investigate the frequency of insertion-, localization and removal-related events.

In principle, three different sets of analyses could be provided:

1) the 'as treated' (AT) population and
2) the 'intention to treat' (ITT) population
3) the 'per protocol' population

However, in this one-arm study AT and ITT populations will be almost identical. A woman who is included in the study will only be exposed to one treatment (Nexplanon). Therefore, the true exposure (AT) will be identical with the intended exposure (ITT). The only theoretical exception would be a woman where no insertion attempt is made although the woman agreed to participate. The inclusion of those women into the ITT analysis set would dilute the rate of insertion- and removal-related adverse events. I.e., the ITT analysis would slightly underestimate the risk associated with the use of Nexplanon. Therefore, an ITT analysis will not be done.

Also 'per protocol' analyses will not be done, because 1) there are no medical inclusion and exclusion criteria in this non-interventional study, and 2) protocol violations against non-medical inclusion and/or exclusion criteria (such as enrollment of a woman who refuses to sign the informed consent form) will lead to immediate exclusion of the participant. Therefore, the results of the 'per protocol' analysis would be identical with the AT analysis.

It is conceivable that women, who had a previous implant (repeat / consecutive users previously using Implanon or Norplant) might differ in their reporting of adverse events and might be at lower risk for insertion, localization and or removal associated events from women who never used a hormonal implant before (first-time users). Therefore, the analyses will include three analysis subsets:

1) all users
2) first-time users ("starter")
3) repeat/consecutive users

Section A of this statistical analysis plan will provide a description of the population (total study population and stratified by first time users and repeat/consecutive users) and the availability of follow-up information. Three of the tables in this section (Tables A3a, A3b, A4) have the HCP as unit, not the woman.

Section B shows descriptive tables of baseline characteristics and potential prognostic factors in the different user cohort

Section C shows descriptive tables of the outcomes of interest. 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.
Potential prognostic factors for the outcomes of interest include e.g. age (< 30 y vs. ≥30), BMI (<30 vs. ≥30), user status (first time users vs. repeat users), experience of healthcare professional with Implanon insertions in the past year (<10/y vs. >=10/y) and Nexplanon insertions in total (<5 NXPL vs. >=5 NXPL). The cut-off point regarding experience of the healthcare professional were chosen arbitrary, sensitivity analyses with different cut-off points will done. Additional prognostic factors and classification categories might be added on request of regulatory authorities or the Safety Monitoring and Advisory Board.

This statistical analysis plan will be the basis for the final analysis of the data at study end.

The bi-annual interim report will show data reflected in the tables A1, A3-4, B1-13, C1, C3-11, depending on the status of the study – no data on localization / removal and post-removal questions are expected during the first year of the study.

At study end all tables in the B section will be used to compare characteristics of women who remain during follow-up vs. those who are who dropped out before removal or were Lost to Follow-up.
In case of Loss to FU and drop out before removal exposure to Nexplanon will be based on the last available FU information.

Number of missing answers will be presented in the tables but percentages and confidence intervals will be based on the total number of non-missing answers.

List of abbreviations

AT	As Treated
BMI	Body Mass Index
CI	Confidence Interval
FU	Follow-up
HC	Hormonal Contraceptive
HCP	Health Care Professional
ITT	Intention to Treat
L/R	Localization / Removal
Miss	Missing
n	Number
NXPL	Nexplanon
OC	Oral Contraceptive
PI	Pearl Index (pregnancies per 100 WY)
RR	Relative Risk
(S)AE	(Serious) Adverse Event
WY	Women Years (one WY = 365.25 days of exposure)

Section A: Number of study participants, User Status and Follow-up

Table A1. Number of women included in the study (Date of analysis: . . .)

Table A1-1 - Women included in the study by user Type, Complete Cohort

	n	%
First time users		
Repeat/Consecutive users		
Total number at baseline		

Table A2. Drop-outs and loss to follow-up (Date of analysis: . . .)

Table A2-1 Complete Cohort

		Follow-up							
	Baseline	**FU1**	**FU2**	**FU3**	**FU4**	**FU5**	**Localization / Removal FU**	**Post removal FU**	**Total**
No of women with available information per period									
No of women who got their Implant removed (%)									
No of drop outs (%)									
No. of women who are lost to follow-up (%)									

Table A2-2 First time users only (format see Table A2-1)
Table A2-3 Repeat/Consecutive users only (format see Table A2-1)

Table A3. Number healthcare professionals by categories of experience in Implanon/Nexplanon insertions (Date of analysis: . . .)

Table A3 a Implant insertions in the past year

Implanon insertions in the past year	**N**	**%**
<5 in the past year		
>=5 - <10 in the past year		
>= 10 in the past year		
Miss#		
Total		

Table A3 b Total number of Nexplanon insertions

Total number of Nexplanon insertions	**N**	**%**
<5		
>=5 - <10		
>= 10		
Miss#		
Total		

number of missing answers are presented, percentages based only on the total number of non-missing answers

Table A4. Educational background of Healthcare Professional (Date of analysis: . . .)

	N	%
Nurse		
Nurse Practitioner		
Gynecologist		
Other*		
Miss#		
Total		

*If another educational background of HCP shown in the "Other" category accounts for more then 1% of the Nexplanon insertions in the study, it will be listed in a separate category
number of missing answers are presented, percentages based only on the total number of non-missing answers

Section B: Demographics

Table B1. Age (y), weight (lb) and BMI at study entry (Date of analysis: . . .)

Table B1-1 Complete Cohort

	NXPL
Age, Mean [SD]	
Age, Minimum	
Age, Percentile 5	
Age, Percentile 25	
Age, Median	
Age, Percentile 75	
Age, Percentile 95	
Age, Maximum	
Weight, Mean [SD]	
Weight, Minimum	
Weight, Percentile 5	
Weight, Percentile 25	
Weight, Median	
Weight, Percentile 75	
Weight, Percentile 95	
Weight, Maximum	
Weight, Miss	
BMI, Mean [SD]	
BMI, Minimum	
BMI, Percentile 5	
BMI, Percentile 25	
BMI, Median	
BMI, Percentile 75	
BMI, Percentile 95	
BMI, Maximum	
BMI, Miss	

Table B1-2 First time users only (format see Table B1-1)
Table B1-3 Repeat/Consecutive users only (format see Table B1-1)

Table B2. Age and BMI distribution (Date of analysis: . . .)

Table B2-1 Complete Cohort

	n	%	95% CI
Age category			
<20			
20-29			
30-39			
40-49			
>=50			
TOTAL			
BMI category			
BMI <20			
BMI >=20 & <25			
BMI >=25 & <30			
BMI >=30 & <35			
BMI >=35			
Miss#			
TOTAL			
Weight category			
<88 lb			
88-<110 lb			
110-<132 lb			
132-<154 lb			
154-<176 lb			
176-<198 lb			
198-<220 lb			
>= 220 lb			
Miss#			
TOTAL			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Table B2-2 First time users only (format see Table B2-1)

Table B2-3 Repeat/Consecutive users only (format see Table B2-1)

Table B3. Proportion of Women who have ever been pregnant, had a delivery in the last 12 months, and who had Miscarriage / Abortion in the last 12 months

(Date of analysis: . . .)

Table B3-1 Complete Cohort

	n	%	95% CI
Ever pregnant			
Yes			
No			
Miss#			
Delivery within the last 12 months			
Yes			
No			
Miss#			
Miscarriage / Abortion within the last 12 months			
Yes			
Of which			
First trimester miscarriage / abortion			
Second trimester miscarriage / abortion			
No			
Miss#			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Table B3-2 First time users only (format see Table B3-1)

Table B3-3 Repeat/Consecutive users only (format see Table B3-1)

Table B4. Age at menarche, number of live births (Date of analysis: . . .)

Table B4-1 Complete Cohort

	NXPL
Age at Menarche, Mean [SD]	
Age at Menarche, Minimum	
Age at Menarche, Percentile 5	
Age at Menarche, Percentile 25	
Age at Menarche, Median	
Age at Menarche, Percentile 75	
Age at Menarche, Percentile 95	
Age at Menarche, Maximum	
Age at Menarche, Miss	
Number of Live Births, Mean [SD]	
Number of Live Births, Minimum	
Number of Live Births, Percentile 5	
Number of Live Births, Percentile 25	
Number of Live Births, Median	
Number of Live Births, Percentile 75	
Number of Live Births, Percentile 95	
Number of Live Births, Maximum	
Number of Live Births, Miss	

Table B4-2 First time users only (format see Table B4-1)

Table B4-3 Repeat/Consecutive users only (format see Table B4-1)

Table B5. Implant History (Date of analysis: . . .)

Table B5-1 Complete Cohort

	n	%	95% CI
Ever contraceptive Implant before study entry			
Yes			
No			
Miss#			
Total duration of Implant use			
<=1 year			
>1 & <=5 years			
>5 & <=10 years			
>10 years			
Miss			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Table B6. Hormonal Contraception History (Date of analysis: . . .)

Table B6-1 Complete Cohort

	n	%	95% CI
Ever OC / HC Use			
Yes			
No			
Miss#			
Number of months since last OC / HC use§			
<=3 months ago			
>3 & <=6 months ago			
>6 & <=12 months ago			
>12 months ago			
Miss#			
Total duration of OC / HC use			
<=1 year			
>1 & <=5 years			
>5 & <=10 years			
>10 years			
Miss#			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

§ For hormonal injections the day the next injection would have been due is used for determination of number of months since last HC use

Table B6-2 First time users only (format see Table B6-1)

Table B6-3 Repeat/Consecutive users only (format see Table B6-1)

Table B7. Smoking Status (Date of analysis: . . .)

Table B7-1 Complete Cohort

	n	%	95% CI
Never smoker			
Current smoker			
Thereof			
Heavy Smoker (>15 cigarettes per day)			
Ex-Smoker			
Thereof			
Heavy Smoker (>15 cigarettes per day)			
Miss#			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Table B7-2 First time users only (format see Table B7-1)

Table B7-3 Repeat/Consecutive users only (format see Table B7-1)

Table B8. Number of Cigarettes (Date of analysis: . . .)

Table B8-1 Complete Cohort

	Current Smoker	Ex-Smoker
Number of Cigarettes, Mean [SD]		
Number of Cigarettes, Minimum		
Number of Cigarettes, Percentile 5		
Number of Cigarettes, Percentile 25		
Number of Cigarettes, Median		
Number of Cigarettes, Percentile 75		
Number of Cigarettes, Percentile 95		
Number of Cigarettes, Maximum		
Number of Cigarettes, Miss		

Table B8-2 First time users only (format see Table B8-1)

Table B8-3 Repeat/Consecutive users only (format see Table B8-1)

Table B9. Educational Level (Date of analysis: . . .)

Table B9-1 Complete Cohort

	n	%	95% CI
Elementary School (at most 5 year)			
Junior High or Middle School (at most 8 years)			
High school (at most 12 years)			
Some college/Associate's Degree/Technical training			
College/University Bachelor Degree			
Post-College/University or higher			
Miss#			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Table B9-2 First time users only (format see Table B9-1)

Table B9-3 Repeat/Consecutive users only (format see Table B9-1)

Table B10. Self-reported history of selected diseases at baseline: Absolute numbers of reports and crude prevalence (%) (Date of analysis: . . .)

Table B10-1 Complete Cohort

	n	%	95% CI
Medical History			
Venous thromboembolism (DVT or PE)			
Myocardial Infarction			
Stroke			
Cancer*			
Other serious diseases			
Operations			

* sub-category will be shown for cancer types with more than 5 reports

Table B10-2 First time users only (format see Table B10-1)

Table B10-3 Repeat/Consecutive users only (format see Table B10-1)

Table B11 **Use of local anesthetic and insertion site** (Date of analysis: . . .)

Table B11-1 Complete Cohort

	n	%	95% CI
Local Anesthetic			
Yes			
No			
Miss#			
Implant inserted in the non-dominant arm			
Yes			
No			
Miss#			
Position of implant			
Over biceps muscle			
Over triceps muscle			
In sulcus bicipitalis medialis			
Other			
Miss#			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Additional categories may be added for exploratory reasons

Table B11-2 First time users only (format see Table B11-1)

Table B11-3 Repeat/Consecutive users only (format see Table B11-1)

Section C: Outcomes of interest

Table C1. Duration of Nexplanon use in Years (Date of analysis: . . .)

Table C1-1 Complete Cohort

	NXPL
Duration of use, Mean [SD]	
Duration of use, Minimum	
Duration of use, Percentile 5	
Duration of use, Percentile 25	
Duration of use, Median	
Duration of use, Percentile 75	
Duration of use, Percentile 95	
Duration of use, Maximum	
Duration of use, Miss	

Table C1-2 First time users only (format see Table C1-1)

Table C1-3 Repeat/Consecutive users only (format see Table C1-1)

Table C2. Implant palpability reported by the woman (Date of analysis: . . .)

Table C2-1 Complete Cohort

		Follow-up					
	Insertion	**FU1**	**FU2**	**FU3**	**FU4**	**FU5**	**Localization / Removal FU***
Women who could feel implant (%)							
Women who could not feel implant (%)							
Missing information (%)							

* reported by HCP

Table C2-2 First time users only (format see Table C2-1)
Table C2-3 Repeat/Consecutive users only (format see Table C2-1)

Table C2-4 BMI <20 (format see Table C2-1)
Table C2-5 BMI >=20 - <30 (format see Table 2-1)
Table C2-6BMI >=30 (format see Table C2-1)

Table C3. Validated[1] insertion related complications reported by the woman: Absolute numbers of reports and incidence proportion (per 1,000 insertions) (Date of analysis: . . .)

Table C3-1 Complete Cohort

	n	Incidence Proportion*	95% CI
Severe Pain *reported:* At Baseline At FU At / After Removal			
Injury to blood vessels or blood clots in the arm *reported:* At Baseline At FU At / After Removal			
Pins and needles / numbness in the arm / hand / fingers *reported:* At Baseline At FU At / After Removal			
Altered strength / movement in the arm *reported:* At Baseline At FU At / After Removal			

** per 1,000 insertions*

[1] Validated means that for a self-reported event / complaint by the women further information is collected from the woman and the treating physician or hospital to confirm the validity of the information

Additional categories may be added for complications

Table C3-2 First time users only (format see Table C3-1)
Table C3-3 Repeat/Consecutive users only (format see Table C3-1)

Table C3-4 BMI <20 (format see Table C3-1)
Table C3-5 BMI >=20 - <30 (format see Table 3-1)
Table C3-6 BMI >=30 (format see Table C3-1)

Table C3-7 Age <30 (format see Table C3-1)
Table C3-8 Age >=30 (format see Table C3-1)

Table C3-9 Experience of Physician <10 Implanon insertions in the past year (format see Table C3-1)
Table C3-10 Experience of Physician >=10 Implanon insertions in the past year (format see Table C3-1)

Table C3-11 Experience of Physician <5 Nexplanon insertions in total (format see Table C3-1)
Table C3-12 Experience of Physician >=5 Nexplanon insertions in total (format see Table C3-1)

Table C4. Any significant issues during insertion procedure insertion / insertion attempt (reported by HCP): absolute number and incidence proportion (per 1.000 insertions) (Date of analysis: . . .)

Table C4-1 Complete Cohort

Category	n	Incidence Proportion*	95%CI
Insertion successful			
Yes, first attempt successful			
Yes, but multiple insertion attempts required (i.e. at least 1 unsuccessful insertion)			
No, implant insertion unsuccessful			
Any significant issues during insertion procedure			
of which			
Difficulty removing protection cap			
Difficulty sliding needle to its full length into skin			
Needle stick injury			
Difficulty unlocking purple slider			
Needle inserted too deep			
Difficulty moving purple slider fully to the back			
Needle inserted too superficial			
Implant (partially) sticks out of skin after insertion			
Injury to nerve or blood-vessel			
Needle visible after insertion (not fully retracted)			
Other			
Miss			

** per 1,000 insertions*

Additional categories may be added for complications

Table C4-2 First time users only (format see Table C4-1)
Table C4-3 Repeat/Consecutive users only (format see Table C4-1)

Table C4-4 BMI <20 (format see Table C4-1)

Table C4-5 BMI >=20 - <30 (format see Table 4-1)
Table C4-6 BMI >=30 (format see Table C4-1)

Table C4-7 Age <30 (format see Table C4-1)
Table C4-8 Age >=30 (format see Table C4-1)

Table C4-9 Experience of Physician <10 Implanon insertions in the past year (format see Table C4-1)
Table C4-10 Experience of Physician >=10 Implanon insertions in the past year (format see Table C4-1)

Table C4-11 Experience of Physician <5 Nexplanon insertions in total (format see Table C4-1)
Table C4-12 Experience of Physician >=5 Nexplanon insertions in total (format see Table C4-1)

Table C5. Localization procedures (reported by HCP): Absolute numbers of reports and incidence proportion (per 1,000 insertions) **(Date of analysis: . . .)**

Table C5-1 Complete Cohort

	n	Incidence Proportion*	95% CI
Implant not palpable			
reported:			
At Insertion			
At L/R			
Any Localization procedure			
No			
Yes			
If Yes, reported:			
At Insertion			
At L/R			
X-Ray			
reported:			
At Insertion			
At L/R			
Ultrasound			
reported:			
At Insertion			
At L/R			
CT			
reported:			
At Insertion			
At L/R			
MRI			
reported:			
At Insertion			
At L/R			

Table C5-1 continued

Hormone Assay (ENG)			
reported:			
At Insertion			
At L/R			
ENG detected			
ENG not detected			
ENG Result pending			
Implant migration (at L/R)			
Yes			
No			
Location of Implant (at Insertion)			
Dermal			
Subdermal connective tissue			
Adjacent to the fascial tissue			
Within the muscle			
Not determined			
Miss			
Location of Implant (at L/R)			
Dermal			
Subdermal connective tissue			
Adjacent to the fascial tissue			
Within the muscle			
Not determined			
Miss			
Hospitalization needed for localization procedure (L/R)			
Yes			
No			

Table C5-1 continued

Consequences of localization procedure (at Insertion)			
Implant left in situ			
Implant removed and replaced			
Implant removed			
Other			
Miss			

**per 1,000 insertions*

A woman can have more than one localization procedure during the study period, and also the same localization procedure more than one time

Additional categories may be added

Table C5-2 First time users only (format see Table C5-1)
Table C5-3 Repeat/Consecutive users only (format see Table C5-1)

Table C5-4 BMI <20 (format see Table C5-1)
Table C5-5 BMI >=20 - <30 (format see Table 5-1)
Table C5-6 BMI >=30 (format see Table C5-1)

Table C5-7 Age <30 (format see Table C5-1)
Table C5-8 Age >=30 (format see Table C5-1)

Table C5-9 Experience of Physician <10 Implanon insertions in the past year (format see Table C5-1)
Table C5-10 Experience of Physician >=10 Implanon insertions in the past year (format see Table C5-1)

Table C5-11 Experience of Physician <5 Nexplanon insertions in total (format see Table C5-1)
Table C5-12 Experience of Physician >=5 Nexplanon insertions in total (format see Table C5-1)

Table C6. Number of Women with non-palpable Implant and related Localization Procedures (Date of analysis: . . .)

Table C6-1 Complete Cohort

	n	%	95% CI
Implant inserted			
thereof			
Implant not palpable by HCP			
thereof			
Any Localization procedure			
thereof			
X-Ray			
Thereof Implant localized			
Ultrasound			
Thereof implant localized			
CT			
Thereof implant localized			
MRI			
Thereof implant localized			
Hormone Assay (ENG)			
Thereof ENG positive			

Table C6-2 First time users only (format see Table C6-1)
Table C6-3 Repeat/Consecutive users only (format see Table C6-1)

Table C6-4 BMI <20 (format see Table C6-1)
Table C6-5 BMI >=20 - <30 (format see Table C6-1)
Table C6-6 BMI >=30 (format see Table C6-1)

Table C6-7 Age <30 (format see Table C6-1)
Table C6-8 Age >=30 (format see Table C6-1)

Table C6-9 Experience of Physician <10 Implanon insertions in the past year (format see Table C6-1)
Table C6-10 Experience of Physician >=10 Implanon insertions in the past year (format see Table C6-1)

Table C6-11 Experience of Physician <5 Nexplanon insertions in total (format see Table C6-1)
Table C6-12 Experience of Physician >=5 Nexplanon insertions in total (format see Table C6-1)

Table C7. Complications during removal: Absolute numbers of reports and Incidence Proportion (per 1,000 insertions) (Date of analysis: . . .)

Table C7-1 Complete Cohort

	n	Prop*	95% CI
Implant removed			
Yes			
No			
Any Complications during removal (attempt)			
No			
Yes			
thereof			
Injury to nerve/blood vessel			
Implant located near nerve and/or blood vessel			
Implant encased in fibrotic tissue making removal difficult			
Implant located too deep			
Implant migrated			
Implant not found			
Multiple attempts required			
Others			
Additional surgical procedure required			
Yes			
No			
Local anesthesia used			
General anesthesia used			
Hospitalization for removal			
Yes			
No			

**per 1,000 insertions*

Additional categories may be added for complications

Table C7-2 First time users only (format see Table C7-1)
Table C7-3 Repeat/Consecutive users only (format see Table C7-1)

Table C7-4 BMI <20 (format see Table C7-1)
Table C7-5 BMI >=20 - <30 (format see Table C7-1)
Table C7-6 BMI >=30 (format see Table C7-1)

Table C7-7 Age <30 (format see Table C7-1)
Table C7-8 Age >=30 (format see Table C7-1)

Table C7-9 Experience of Physician <10 Implanon insertions in the past year (format see Table C7-1)
Table C7-10 Experience of Physician >=10 Implanon insertions in the past year (format see Table C7-1)

Table C7-11 Experience of Physician <5 Nexplanon insertions in total (format see Table C7-1)
Table C6-12 Experience of Physician >=5 Nexplanon insertions in total (format see Table C7-1)

Table C8: Pregnancies: Absolute numbers of reports and Pearl Index (per 100 WY) (Date of analysis: . . .)

Table C8-1 Complete Cohort

Category	n	PI*	95%CI
Total Pregnancies			
thereof			
Pre-Treatment Pregnancies			
In-Treatment Pregnancies			
thereof			
Taking concurrent medication with potential interaction			
Post-Treatment Pregnancies[2]			
Thereof			
With an estimated date of conception 1-7 days after removal			
With an estimated date of conception 8-14 days after removal			
With an estimated date of conception more than 14 days after removal			
Non-insertion Pregnancies			

* pregnancies per 100 WYs of exposure[3]

Table C8-2 First time users only (format see Table C8-1)
Table C8-3 Repeat/Consecutive users only (format see Table C8-1)

Table C8-4 BMI <20 (format see Table C8-1)
Table C8-5 BMI >=20 - <30 (format see Table C8-1)
Table C8-6 BMI >=30 (format see Table C8-1)

Table C8-7 Body weight <155lb only (format see Table C8-1)
Table C8-8 Body weight >=155lb only (format see Table C8-1)

Table C8-9 Age <30 only (format see Table C8-1)
Table C8-10 Age >=30 only (format see Table C8-1)

[2] For Post-Treatment Pregnancies the PI calculation does always include the In-treatment pregnancies and (if applicable) pregnancies from the previous Post-treatment Period

[3] Nexplanon exposure: time from insertion day to estimated conception day or, in case of post-removal pregnancies, the day of Nexplanon removal

Table C9: Outcomes of Pre-, In- and Post-Treatment Pregnancies (Date of analysis: . . .)

Table C9-1 Complete Cohort

Category	n	%	95%CI
Outcome of Pre-Treatment Pregnancy			
Healthy child			
Induced abortion			
Spontaneous abortion			
Ectopic Pregnancy			
Malformation			
Outcome of In-Treatment Pregnancy			
Healthy child			
Induced abortion			
Spontaneous abortion			
Ectopic Pregnancy			
Malformation			
Outcome of Post-Treatment Pregnancy			
With an estimated date of conception1-7 days after removal			
Healthy child			
Induced abortion			
Spontaneous abortion			
Ectopic Pregnancy			
Malformation			
With an estimated date of conception 8-14 days after removal			
Healthy child			
Induced abortion			
Spontaneous abortion			
Ectopic Pregnancy			
Malformation			

Table C9-2 First time users only (format see Table C9-1)
Table C9-3 Repeat/Consecutive users only (format see Table C9-1)

Table C9-4 BMI <20 (format see Table C9-1)
Table C9-5 BMI >=20 - <30 (format see Table C9-1)
Table C9-6 BMI >=30 (format see Table C9-1)

Table C9-7 Body weight <155lb only (format see Table C9-1)
Table C9-8 Body weight >=155lb only (format see Table C9-1)

Table C9-9 Age <30 only (format see Table C9-1)
Table C9-10 Age >=30 only (format see Table C9-1)

Table C10-Reasons for removing the Implant (Date of analysis: . . .)

Table **C10**-1 Complete Cohort

Event category	n	%	95% CI
The implant had been in place for at least 3 years			
Planning pregnancy and/or contraception no longer needed			
Became pregnant despite Nexplanon use			
Problem with implant			
Menstrual/bleeding problems			
Miss#			

number of missing answers are presented, percentages and confidence intervals based only on the total number of non-missing answers

Additional categories may be added for reasons

Table **C10**-2 First time users only (format see Table **C10**-1)
Table **C10**-3 Repeat/Consecutive users only (format see Table **C10**-1)

Table **C10**-4 BMI <20 (format see Table **C10**-1)
Table **C10**-5 BMI >=20 - <30 (format see Table **C10**-1)
Table **C10**-6 BMI >=30 (format see Table **C10**-1)

Table **C10**-7 Age <30 (format see Table **C10**-1)
Table **C10**-8 Age >=30 (format see Table **C10**-1)

Table C11- Validated SAEs not related to insertion-, localization- or removal-procedure of Nexplanon: Absolute numbers of reports and incidence rate (per *10,000 WY of exposure*) (Date of analysis: . . .)

Table **C11**-1 Complete Cohort

Event category	n	Incidence Rate*	95% CI
Cardiovascular Events			
Gastro-intestinal Events			
Genito-urinary Events			
Cancer			
Hospitalization			

**per 10,000 WY of exposure*

Additional categories / subcategories may be added for SAEs

Table **C11**-2 First time users only (format see Table **C11**-1)
Table **C11**-3 Repeat/Consecutive users only (format see Table **C11**-1)

Table **C11**-4 BMI <20 (format see Table **C11**-1)
Table **C11**-5 BMI >=20 - <30 (format see Table **C11**-1)
Table **C11**-6 BMI >=30 (format see Table **C11**-1)

Table **C11**-7 Age <30 (format see Table **C11**-1)
Table **C11**-8 Age >=30 (format see Table **C11**-1)

Table **C11**-9ff by History of respective disease (format see Table **C11**-1)

Table C12- Effect of Prognostic Factors on Outcomes of Interest **(Date of analysis: . . .)**

The quantitative impact (relative risks) of potential prognostic factors on the outcomes of interest (e.g., implant palpability reported by physician, more frequent SAEs) presented in Tables C1 – C11 will be analyzed using multivariate regression models if there are at least 5 events per cell. The choice of the regression model will depend on the data: logistic regression will be used for data where the outcome is a proportion, Cox for data where the outcome is a rate.
Predefined covariates are .age (< 30 vs. ≥30yrs), BMI (<30 vs. ≥30), user status (first time users vs. repeat users), experience of healthcare professional with Implanon insertions in the past year (<10/y vs. >=10/y) and Nexplanon insertions in total (<5 NXPL vs. >=5 NXPL). Additional prognostic factors and classification categories might be added on request of regulatory authorities or the Safety Monitoring and Advisory Board. The relative risks will be presented in the following format.

Outcome of interest	**Prognostic Factor**	**RR**	**95% CI**
Outcome of interest 1			
	Age		
	BMI		
	User status		
	Experience with Implanon		
	Experience with Nexplanon		
Outcome of interest 2			
	Age		
	BMI		
	User status		
	Experience with Implanon		
	Experience with Nexplanon		
Outcome of interest …			