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Official Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases - A Postmarketing Requirement for Mirena (APEX IUD)
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Bayer HealthCare

Statistical analysis plan

Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)			
Medicinal product:	Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices		
Study Purpose:	This is a United States postmarketing requirement study assessing outcomes of uterine perforation and intrauterine device (IUD) expulsion in association with breastfeeding, time since delivery, and type of IUD. The study aims to quantify the risk of uterine perforation and IUD expulsion for the following comparisons: • Women who are breastfeeding at the time of IUD insertion versus not breastfeeding at the time of IUD insertion • Women who had a first observed IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) versus women who had their first observed IUD insertion more than 52 weeks postpartum, including women without a recorded delivery within the past 52 weeks This study will also assess the risk of perforation and expulsion (separately) by type of IUD. In addition, this study aims to assess the following interactions: • The extent to which type of IUD (levonorgestrel-releasing vs. copper IUD) modifies the association between perforation and/or expulsion and breastfeeding status and/or postpartum status • The extent to which breastfeeding status modifies the association between perforation and/or expulsion and postpartum status		
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The approval of the Statistical Analysis Plan is documented in a separate signature document.

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Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
EHR	Electronic Health Record
EURAS-IUD	European Active Surveillance Study for Intrauterine Devices
FDA	Food and Drug Administration
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
IRD	Incidence Rate Difference
IRR	Incidence Rate Ratio
IUD	Intrauterine Device
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California
KPWA	Kaiser Permanente Washington
LB	Lower Bound (of the 95% confidence interval)
LNG	Levonorgestrel
LNG-IUD	Levonorgestrel-Releasing Intrauterine System
PMR	Postmarketing Requirement
RI	Regenstrief Institute
RTI-HS	RTI Health Solutions, a unit of RTI International, a nonprofit research organization
SAP	Statistical Analysis Plan
TLF	Tables, Listings and Figures
TM	Trademark
UB	Upper Bound (of the 95% confidence interval)
US	United States

1 Introduction

1.1 Background

Mirena, a levonorgestrel (LNG)-releasing intrauterine system, was approved for use in the United States (US) in December 2000 (Bayer HealthCare Pharmaceuticals Inc., 2015). In August 2015, Bayer received a postmarketing requirement from the US Food and Drug Administration (FDA) to evaluate the incidence of and risk factors for uterine perforation in US women receiving Mirena intrauterine devices (IUDs) at postpartum intervals reflecting US clinical practice (communication from FDA to Bayer, 18 August 2015). Bayer proposed to conduct a retrospective cohort study of women with LNG-IUD or copper IUD in four electronic health record (EHR) databases to assess the risk of uterine perforation and IUD expulsion and potential risk factors, including breastfeeding at the time of IUD insertion, timing of postpartum IUD insertion, and type of IUD (LNG-IUD vs copper). After communication from the FDA in May 2018, Bayer added an assessment of uterine perforation and IUD expulsion by indication for use (as evidenced by diagnosis of heavy menstrual bleeding).

The study aims to quantify the risk of uterine perforation and IUD expulsion for the following comparisons:

- Women who are breastfeeding at the time of IUD insertion versus not breastfeeding at the time of IUD insertion
- Women who had a first observed IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) versus women who had their first observed IUD insertion more than 52 weeks postpartum, including women without a recorded delivery within the past 52 weeks

This study will also assess the risk of perforation and expulsion (separately) by type of IUD. In addition, this study aims to assess the following interactions:

- The extent to which type of IUD (LNG-releasing vs. copper IUD) modifies the association between perforation and/or expulsion and breastfeeding status and/or postpartum status
- The extent to which breastfeeding status modifies the association between perforation and/or expulsion and postpartum status

1.2 Protocol Version and Amendments

Bayer submitted a protocol for the postmarketing requirement (PMR) study to the FDA that was formally accepted for FDA review on 13 December 2017 (PMR #3129-1). On 18 April 2018, the FDA provided comments and recommendations on the protocol that were further clarified in e-mail exchanges between Bayer and the FDA on 23 April and 01 May 2018. The updated protocol (version 2.0) was submitted to the FDA on 29 June 2018 (with this statistical analysis plan) and is aligned to this original version of the statistical analysis plan (version 1.0). The updated protocol (version 2.0) was approved by the FDA (via e-mail) on September 11, 2018.

2 Study Objectives

The overall goal of this study is to assess the impact of breastfeeding and timing of postpartum IUD insertion on uterine perforation and IUD expulsion in a population of US women. The study aims to quantify the risk of perforation and expulsion associated with breastfeeding and early postpartum IUD insertion as well as by IUD type and indication for use (e.g., IUD used with concomitant heavy menstrual bleeding). The study includes the following objectives:

2.1 Primary Objectives

1. To evaluate whether the risk of uterine perforation among women who were breastfeeding at the time of the first observed IUD insertion differs from the risk of uterine perforation among women who were not breastfeeding at the time of the first observed IUD insertion.
2. To evaluate whether the risk of uterine perforation among women who had a first observed IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) differs from the risk of uterine perforation among women who had their first observed IUD insertion more than 52 weeks postpartum, including women without a recorded delivery within the past 52 weeks.

2.2 Secondary Objectives

Rates: uterine perforation

3. To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs
4. To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs for the following categories of timing of IUD insertion:
    - ≤ 6 weeks postpartum
    - > 6 weeks and ≤ 14 weeks postpartum
    - > 14 weeks and ≤ 52 weeks postpartum
    - > 52 weeks postpartum, including women without recorded delivery within the past 52 weeks
    - ≤ 14 weeks postpartum
    - > 14 weeks postpartum, including women without recorded delivery within the past 52 weeks
    - ≤ 36 weeks postpartum
    - > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks
5. To estimate the incidence rate and cumulative incidence of uterine perforation among women who were and were not breastfeeding at the time of IUD insertion
6. To estimate the incidence rate and cumulative incidence of uterine perforation among women with different types of IUD (i.e., LNG-IUD and copper IUD)
7. To estimate the incidence rate and cumulative incidence of uterine perforation among women with and without menorrhagia (heavy menstrual bleeding) in the 12 months before IUD insertion

Rates: IUD expulsion

8. To estimate the incidence rate and cumulative incidence of IUD expulsion among users of IUDs
9. To estimate the incidence rate and cumulative incidence of IUD expulsion among users of IUDs for the following categories:
    - ≤ 6 weeks postpartum
    - > 6 weeks and ≤ 14 weeks postpartum
    - > 14 weeks and ≤ 52 weeks postpartum
    - > 52 weeks postpartum, including women without recorded delivery within the past 52 weeks
    - ≤ 14 weeks postpartum

- > 14 weeks postpartum, including women without recorded delivery within the past 52 weeks
- ≤ 36 weeks postpartum
- > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks

10. To estimate the incidence rate and cumulative incidence of IUD expulsion among women who were and were not breastfeeding at the time of IUD insertion
11. To estimate the incidence rate and cumulative incidence of IUD expulsion among women with different types of IUD (i.e., LNG-IUD and copper IUD)
12. To estimate the incidence rate and cumulative incidence of IUD expulsion among women with and without menorrhagia in the 12 months before IUD insertion

Prevalence of difficult IUD insertion

13. To describe the prevalence of indicators of a difficult IUD insertion (e.g., need for cervical dilation or ultrasound guidance, clinician experience) among all users

Comparative: uterine perforation

14. To estimate the adjusted hazard ratio of uterine perforation among women who had a first observed IUD insertion early in the postpartum period (i.e., ≤ 14 weeks postpartum) versus those who had a first observed IUD insertion late in the postpartum period (i.e., > 14 weeks postpartum, including women without recorded delivery within the past 52 weeks)
15. To estimate the adjusted hazard ratio of uterine perforation among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (this objective will be performed as a sensitivity analysis; same cut point as in EURAS-IUD)
16. To estimate the adjusted hazard ratio of uterine perforation for women whose first observed IUD was a copper IUD versus women whose first observed IUD was an LNG-IUD
17. To estimate the adjusted incidence rate ratio (IRR) and incidence rate difference (IRD) of uterine perforation at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (same analytic approach as EURAS-IUD)
18. To estimate the adjusted hazard ratios of uterine perforation described in objectives 1, 2, and 14-16 across all subsequent insertions (i.e., not the first insertion) observed within the data. (The site-specific analyses will be performed only if there are more than 20,000 subsequent IUD insertions for that site. The pooled analysis will include all sites regardless of the number of subsequent IUD insertions at a site.)
19. To estimate the adjusted hazard ratio of uterine perforation for women using and IUD who have at least one diagnosis code indicating menorrhagia in the 12 months before IUD insertion versus IUD users who do not have this indication (this analysis will be performed

only if more than 20,000 IUD users with an indication of menorrhagia can be included in the analysis)

Comparative: IUD expulsion

20. To estimate the adjusted hazard ratio of IUD expulsion among women who were breastfeeding at the time of the first observed IUD insertion versus those who were not breastfeeding at the time of the first observed IUD insertion
21. To estimate the adjusted hazard ratio of IUD expulsion for women who had a first observed IUD insertion early in the postpartum period (i.e., ≤ 14 weeks postpartum) versus those who had a first observed IUD insertion late in the postpartum period (i.e., > 14 weeks postpartum, including women without recorded delivery within the past 52 weeks)
22. To estimate the adjusted hazard ratio of IUD expulsion for women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery in the past 52 weeks
23. To estimate the adjusted hazard ratios of IUD expulsion for women who had a first observed IUD insertion in early postpartum categories versus women who had a first observed IUD insertion late in the postpartum period, using the following strata:
    - ≤ 6 weeks postpartum
    - > 6 weeks and ≤ 14 weeks postpartum
    - > 14 weeks and ≤ 52 weeks postpartum
    - > 52 weeks postpartum, including women without recorded delivery in the past 52 weeks (referent category)
24. To estimate the adjusted hazard ratio for IUD expulsion for women whose first observed IUD was an LNG-IUD versus women whose first observed IUD was a copper IUD
25. To estimate the adjusted IRR and IRD of IUD expulsion at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks
26. To estimate the adjusted hazard ratios of IUD expulsion described in objectives 20-24 across all subsequent insertions (i.e., not the first insertion) observed within the data. (The site-specific analyses will be performed only if there are more than 20,000 subsequent IUD insertions for that site. The pooled analysis will include all sites regardless of the number of subsequent IUD insertions at a site.)
27. To estimate the adjusted hazard ratio of IUD expulsion for women using an IUD who have at least one diagnosis code indicating menorrhagia in the 12 months before IUD insertion versus IUD users who do not have this indication (this analysis will be done only if more than 20,000 IUD users with an indication of menorrhagia can be included in the analysis)

Interactions (effect modification)

28. To evaluate the extent to which breastfeeding status (yes vs. no) modifies the association of uterine perforation for women with IUD insertion at different time periods postpartum (i.e., IUD insertion ≤ 14 weeks versus IUD insertion > 14 weeks postpartum) among women

with a recorded delivery within the past 52 weeks at the time of the first observed IUD insertion

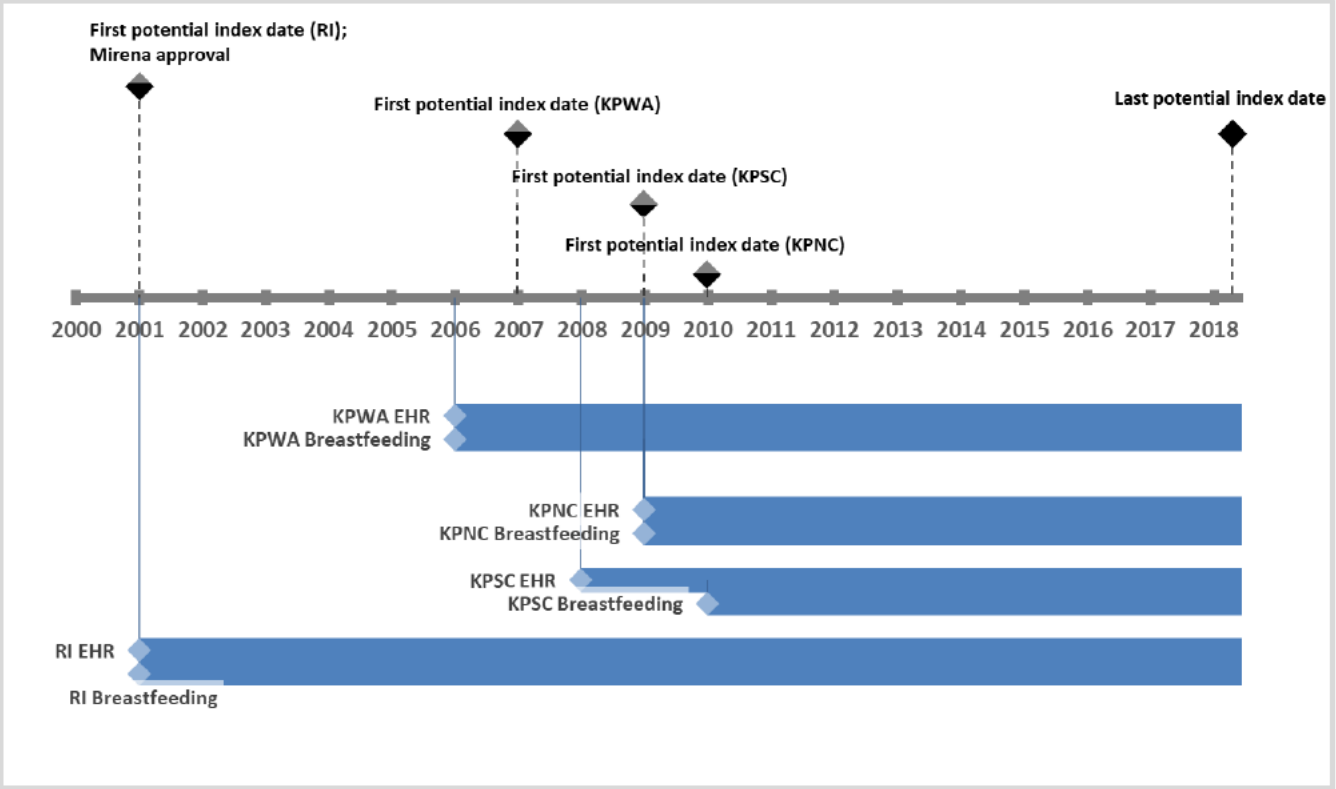
29. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modifies the association between uterine perforation among women who were and were not breastfeeding at the time of the first observed IUD insertion
30. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modifies the association between IUD expulsion among women who were and were not breastfeeding at the time of the first observed IUD insertion
31. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modifies the association of uterine perforation for women with IUD insertion at different time periods postpartum (i.e., ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤ 52 weeks) versus IUD insertion more than 52 weeks postpartum, including no recorded delivery within the past 52 weeks at the time of the first observed IUD insertion
32. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modifies the association of IUD expulsion for women with IUD insertion at different time periods postpartum (i.e., ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤ 52 weeks) versus IUD insertion more than 52 weeks postpartum, including no recorded delivery within the past 52 weeks at the time of the first observed IUD insertion

3 Study Design

A retrospective cohort study design will be used to evaluate uterine perforation and IUD expulsion among women who have an IUD insertion identified within EHR data. The study will consider the impact of breastfeeding status at the time of IUD insertion and timing of IUD insertion during the postpartum period on the outcomes of perforation and expulsion.

The earliest possible start for a patient to be eligible for the study population of women with IUD insertion will be 01 January 2001 (after approval of Mirena), and the latest date for a patient to be included in the study population will be 2 months before the end date of the data pull (anticipated to be approximately 30 June 2018 to coincide with anticipated approval of the protocol). The study start date at each study site will be determined by the earlier of (1) the date when Mirena was approved or (2) the date when EHRs were implemented in the four research sites—Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), Regenstrief Institute (RI), and Kaiser Permanente Washington (KPWA). Further, the start date at each site for inclusion in the breastfeeding assessment will be dictated by the date at which breastfeeding data became available (Figure 1).

Figure 1. Start and End Dates of EHR Data and Breastfeeding Data, Including First and Last Potential Index Dates, by Data Source



EHR = electronic health records; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Note: RI EHRs were implemented prior to 2001.

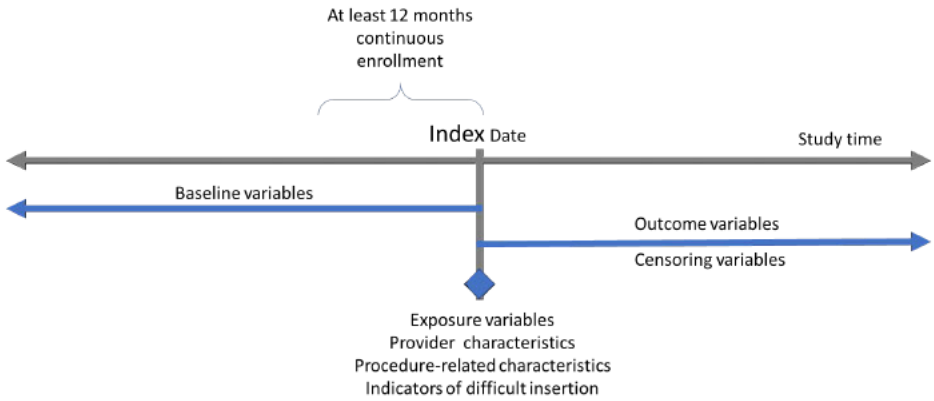
This study will include all women with evidence of an IUD insertion that have at least 12 months of enrollment history preceding IUD insertion (RI, which does not have enrollment dates, will require a clinical visit at least 12 months before IUD insertion). The first observed IUD insertion for each woman that meets study inclusion/exclusion criteria will be included in the primary analyses. All eligible IUD insertions occurring during the study period will be included in the study for a subset of secondary analysis (objectives 18 and 26).

Each IUD insertion is eligible for inclusion in the study if the database has evidence of insertion of an IUD during the study time window and the woman has been continuously enrolled in the database for at least 12 months before the IUD insertion. IUD insertions will be excluded from the study if a woman is aged more than 50 years at the time of the IUD insertion (IUD insertions that occur in eligible patients at younger ages will be included).

Patients will be followed from the time of IUD insertion until the first occurrence of any of the following: uterine perforation, IUD expulsion, IUD removal, indication of IUD reinsertion, indication of new pregnancy, hysterectomy, death, expiration of IUD, disenrollment from the database, or end of the study period. All person-time at risk that meets these criteria will be included, and there will be no requirement for minimum or maximum follow-up time. All IUD insertions occurring with at least 12 months of enrollment before the insertion that are noted within the data sources will be included in the study. The index date will be captured for each insertion, and baseline data will be collected for each index date (Figure 2). The main analyses for the study will

assess only the first observed IUD insertion for each woman in the database. Secondary analyses will be conducted assessing subsequent insertions (i.e., not the first IUD insertion), as recorded in the database. The sequential number of each insertion, as captured in the data for each woman, will be collected and included as a baseline covariate within these secondary analyses.

Figure 2. Covariate data collection around index date



Exposures of postpartum status (based on pregnancy delivery date), breastfeeding status, IUD type, and menorrhagia (as a proxy for indication of use) will be assessed as of the index date of IUD insertion. Outcomes of uterine perforation and IUD expulsion will be assessed beginning on the index date. Baseline data—such as patient demographics, patient characteristics (e.g., personal history of gynecologic conditions such as endometriosis), procedure characteristics, medications, and comorbid conditions (e.g., diabetes)—will be collected from all time in the database before the index date (which will be defined as the day of IUD insertion) and on the index date (Figure 2). Provider characteristics, procedure-related characteristics, and indicators of a difficult insertion will be assessed on the index date (i.e., on the same date or within the same encounter as the index date). The variables to be obtained from each research site are provided in Sections 3.1 through 3.8.

3.1 Exposures

- *Pregnancy delivery date* is the date on which delivery occurred
- *Breastfeeding status* at the time of IUD insertion: breastfeeding status is defined for every insertion based on whether there is any evidence of breastfeeding (including any breastfeeding or pumping across a 24 hour period) at the time of IUD insertion. For postpartum $\leq$ 52 weeks, breastfeeding status is defined as Yes, No, or Undetermined. For postpartum > 52 weeks, including no evidence of a live birth in the past 52 weeks, breastfeeding is not assessed (and will be classified as No when used as a covariate).
- *IUD type*: three-level categorical variable indicating the type of IUD inserted:
  - LNG-IUD: Mirena, Liletta, Skyla, Kyleena
  - Copper IUD: ParaGard, other copper
  - Unknown IUD type

- *Menorrhagia*: diagnosis of menorrhagia assessed in two variables
  - As an exposure: indicator variable (0 = No, 1 = Yes) for whether the patient was diagnosed with menorrhagia in the year (365 days) prior to or on the index date
  - As a covariate within other exposure assessments: four-level categorical variable for whether the patient was diagnosed with menorrhagia
    - Diagnosed in the year prior to or on the index date, but not diagnosed before that time
    - Not diagnosed in the year prior to or on the index date, but was diagnosed before that time
    - Diagnosis recorded within the year prior to or on the index date and also before that time
    - No diagnosis of menorrhagia within the data

3.2 Outcomes

- *Date uterine perforation confirmed* is the date on which uterine perforation is documented. Either partial or complete perforation will be considered as an outcome, and no distinction will be made between partial and complete perforation.
- *Date IUD expulsion confirmed* is the date on which IUD expulsion is documented. Either partial or complete expulsion will be considered as an outcome, and no distinction will be made between partial and complete expulsion.

If both perforation and expulsion occurred on the same date, then the outcome will be classified as both perforation and expulsion, since these outcomes are evaluated separately throughout this study. No analysis will be conducted to assess both perforation and IUD expulsion as a composite outcome or as a subgroup analysis among those with both outcomes.

3.3 Baseline Demographic and Clinical Characteristics

- *Age*: age in years as of the index date
- *Race/ethnicity*: categorical variable with nine categories: non-Hispanic white, Hispanic white, non-Hispanic black, Hispanic black, other Hispanic, Asian/Pacific Islander, multiple races/ethnicities, other race/ethnicity, unknown
- *Smoking status*: indicator variable for smoking status as of the index date (0 = no recent smoking, 1 = recent smoking [active smoker within 365 days prior to or on the index date])
- *Body mass index (BMI)*: continuous variable assessed at the index date or the closest date before or after the index date
- *Dysmenorrhea*: four-level categorical variable for whether the patient was diagnosed with dysmenorrhea
  - Diagnosed in the year prior to or on the index date, but not diagnosed before that time
  - Not diagnosed in the year prior to or on the index date, but was diagnosed before that time
  - Diagnosis recorded within year prior to or on the index date and also before that time
  - No diagnosis of dysmenorrhea within the data
- *Fibroids*: indicator variable (0 = No, 1 = Yes) for whether the patient was ever diagnosed with or reported diagnosis of uterine fibroids prior to or on the index date
- *Parity*: cumulative number of viable pregnancies (i.e., carried to at least 20 weeks gestation) prior to and on the index date
- *Cesarean delivery* will be captured only among women who had at least one delivery prior to the index date and will be captured in two variables:
  - Indicator variable (0 = No, 1 = Yes) for whether the patient *ever had a Cesarean delivery* prior to or on the index date
  - Indicator variable (0 = No, 1 = Yes) for whether the patient had a *Cesarean delivery for the most recent delivery* that is within 52 weeks prior to or on the index date
- *Calendar year of index date*: calendar year of the index date (2001-2018, depending on data source)
- *Month of index date*: calendar month of the index date (1-12 corresponding to January-December, respectively).

3.4 Procedure-Related Characteristics

- The following concomitant gynecological procedures will each be captured as indicator variables (0 = No, 1 = Yes): *abortion*, *aspiration and curettage*, *dilation and curettage*, *excision/biopsy of cervix or uterus*, *ablation*, *colposcopy and other cervical procedures*, *hysteroscopy*, *laminaria*, *laparoscopy*, *lysis adhesions*, *myomectomy*, *nerve procedure*, *salpingectomy/oophorectomy*. If insufficient data are available to assess (RI only), then concomitant gynecological procedures will be missing.

3.5 Indicators of a Difficult IUD Insertion

- *Cervical dilation*: indicator variable (0 = No, 1 = Yes) for whether cervical dilation was used during the IUD insertion procedure
- *Ultrasound guidance:* indicator variable (0 = No, 1 = Yes) for use of ultrasound guidance during placement of the IUD on the day of the IUD insertion
- *Paracervical block*: indicator variable (0 = No, 1 = Yes) for whether the patient received a paracervical block during the IUD insertion procedure
- *Provider note indicating a difficult insertion or complicated procedure*: indicator variable (0 = No, 1 = Yes) for whether the patient record includes a notation from the provider regarding a difficult insertion or complicated procedure
- *Use of misoprostol*: indicator variable (0 = No, 1 = Yes) for whether the patient received misoprostol during the 7 days before or on the date of the IUD insertion procedure

3.6 Provider-Related Characteristics (Not Captured in RI Data)

- *Provider number of IUD insertions in the previous year*: number of IUD insertions the provider performed in the previous year as of the index date
- *Provider length of employment in the previous year*: continuous variable of the number of days employed within the health care system in the past year as of the index date

3.7 Start and Stop Dates[1]

- *IUD insertion date* is the date on which IUD insertion is documented
- *Beginning date of study period*: the first date EHR data are available from the data source for this study (KPNC, KPSC, and KPWA) or the date when Mirena was launched (RI)
- *End date of study period*: the last date on which EHR data are available from the data source for this study
- *Date of start of enrollment* (KPNC, KPSC, and KPWA only) is the earliest date of enrollment in the database for the woman (will be used to calculate look-back period)
- *Date of first clinical encounter* (RI only) is the earliest in-person visit in the database for the woman (will be used to calculate look-back period)
- *Date of disenrollment from the database* (KPNC, KPSC, and KPWA only) is the date, after the index date, on which the woman was no longer enrolled in an eligible insurance plan (one gap of ≤ 31 days per year will be allowed)
- *Date of last clinical encounter in database* (RI only) is the last date on which a woman had an in-person encounter that was recorded in the database

[1] Note that the actual dates will remain at each data source research partner. The dates may be offset for each patient as an additional data protection measure before transfer of data to RTI-HS.

- *Censoring date* is the earliest of the following dates: date of removal of IUD, date of a subsequent IUD reinsertion, date of start of new pregnancy, hysterectomy date, date of bilateral oophorectomy or other type of sterilization, expiration of IUD, death date, date of disenrollment from database (KPNC, KPSC, and KPWA only) or last clinical encounter (RI only), and end date of study period

3.8 Other Parameters

- *Database*: categorical variable of the four data sources included in the study
- *Live birth at most recent delivery*: indicator variable (0 = No, 1 = Yes) for whether the patient had a pregnancy ending in live birth within the 52 weeks before the index date
- *Date of start of most recent (continuous) enrollment* (KPNC, KPSC, and KPWA only) is the date, prior to the index date, on which the woman started enrollment in an eligible insurance plan (one gap of $\leq$ 31 days per year will be allowed)

4 General Statistical Considerations

All issues concerning patient eligibility, data consistency checks, permissible data modifications, and coding of medical terms and medication will be documented and maintained by research partners following the Data Structure Template (a central document including operational definitions developed by RTI Health Solutions (RTI-HS) and the data source research partners) and the Work Practice Document for quality control. All statistical issues including derived variables are to be detailed in this statistical analysis plan. Determination of sample size was detailed in the study protocol.

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA), except when noted otherwise.

The analysis conducted at RTI-HS will follow the relevant RTI-HS standard operating procedures. Programs, logs, and output will be reviewed for accuracy according to the standard operating procedures for programming and quality control. In addition to table creation, some variables will be derived by RTI-HS from the data provided by the research sites; these derived variables are described in Section 4.6. Variables listed in Section 3 will be provided by sites from their databases via use of operational definitions defined by the research team. For data analyses at each site, the standard operating procedures for the site will be used to ensure data quality and security.

4.1.1 Descriptive Analyses

Descriptive analysis of the data will be performed using summary statistics for categorical and quantitative (continuous) data. Continuous data will be described by the number of nonmissing values, median, mean, standard deviation, minimum, and maximum, as well as lower and upper quartiles. Frequency tables will be generated for categorical data. Selected continuous variables will be categorized in a clinically meaningful way or by tertiles of the distribution.

4.1.2 Crude Incidence Rates

Crude incidence rates (I) will be calculated as the number of incident outcomes (E) occurring during the person-time at risk divided by the total person-years at risk (Y).

$$I = \frac{E}{Y}$$

The exact confidence intervals (CIs) will be calculated using the relationship between the Poisson distribution and chi-square distribution as described in Dobson et al. (1991). The lower and upper bounds (LB and UB) of the 95% CI will be calculated as follows:

$$I_{LB} = max\left(0, \left(\frac{X^2_{2E,0.025}}{2}\right) / Y\right), I_{UB} = \left(\frac{X^2_{2(E+1),0.975}}{2}\right) / Y$$

where $X^2_{d,a}$ represents the ath percentile of the chi-square distribution with d degree of freedom.

Crude incidence rates will be reported as point estimates (number of cases per 1,000 person-years) and 95% CIs.

4.1.3 Crude Cumulative Incidence

Crude estimates of the cumulative incidence, defined as the number of incident outcomes occurring up to a time point out of the number of IUD insertions, will be estimated using the Kaplan-Meier method.

4.1.4 Crude Hazard Ratios

Crude hazard ratios will be estimated using Cox regression models. These crude hazard ratios will be calculated for each outcome without adjustment for covariates. All crude hazard ratios will be reported as point estimates with 95% CIs.

The proportional hazards assumption between each exposure-outcome pairing will be assessed using visual examination of hazard functions, log-log survival curves, and goodness-of-fit testing using Schoenfeld residuals (Kleinbaum and Klein, 2012). Parallel hazard function and log-log survival curves for exposure groups (i.e., the vertical distance between exposure groups is constant) would indicate that the assumption of proportional hazards is met. The hazard function and log-log plot will be generated using the PLOTS=(H LLS) option in the PROC LIFETEST procedure in SAS. The goodness-of-fit global correlation test based on Schoenfeld residuals will be conducted using the ZPH(GLOBAL) option in the PROC PHREG procedure in SAS. A test with $P < 0.05$ will indicate that the proportional hazards assumption does not hold. If both visual examination and the global correlation test suggest nonproportional hazards, the time-dependent exposure covariate will be included in crude and adjusted hazard ratio models by fitting interaction terms with continuous or categorical time (Paul, 1995). The form of the interaction terms will be determined after reviewing the plots of hazard functions and log-log survival curves. An example SAS program code follows, where *brstime* is the time-dependent exposure covariate created with the programming statement in the PHREG procedure as an exposure-by-time interaction:

```
PROC PHREG DATA=start;
        CLASS brstfeed;
        MODEL personyr * outcome (0) = brstfeed brstime / TIES=EFRON;
        brstime = brstfeed * (personyr > 0.5); /* use 0.5 as an example*/
RUN;
```

For any models including time-dependent exposure covariates, separate hazard ratios will be reported for estimates of the effect of the exposure over time.

4.1.5 Confounder or Bias Adjusted Analyses

Confounding will be controlled through the use of propensity scores, based on the values of covariates at the time of IUD insertion. The propensity score estimates the probability that a given patient will be exposed conditional on measured covariates and can serve as a summary confounder variable. Propensity scores can perform better than conventional regression methods when the number of events relative to the number of potential confounders is small, because rather than having to model the events with many variables, which may lead to overfitting of the outcome model, one can instead model the exposure, for which the larger number of exposed people provides sufficient data to accommodate a rich model (Cepeda et al., 2003). This advantage may be important in this study, given the low number of expected events, particularly for uterine perforation, within this study.

The steps in estimating adjusted exposure effects are listed as follows:

1. Derive variables that will be considered for inclusion in the propensity score models.
2. Assess balance between exposure groups in the sample.
3. Identify key variables to be included in the propensity score model.
4. Estimate propensity scores and assess the overlapping area among all exposure groups.
5. Calculate weights, normalize the weights, and examine the normalized weights.
6. Assess balance between exposure groups in the weighted sample.
7. Add to the propensity score model additional terms (e.g., interaction or higher order terms) of the covariates that do not balance.
8. Fit the new propensity score model and estimate the propensity scores.
9. Repeat steps 5-8 until all the key covariates are balanced.
10. Estimate the exposure effect that accounted for the confounders via weighting.

Propensity scores for exposure variables will be estimated by fitting a logistic regression model (for dichotomous exposure variables) or a multinomial logistic regression model (for exposure variables with more than two categories). The dependent variable in the propensity score model is exposure status (e.g., women breastfeeding at the time of IUD insertion vs. not breastfeeding at the time of IUD insertion).

Breastfeeding status, postpartum timing, and IUD type will be included within the propensity score model (as independent variables when not the dependent variable). Other covariates will be assessed

for inclusion in propensity score models based on association with the study outcome (Brookhart et al., 2006); thus, analysts will not be blinded to the outcome. Baseline covariates to be considered for inclusion are listed in Sections 3 and 4.6. Categorical variables will be assessed for inclusion based on indicator coding of the categories. Continuous variables (including integer count variables) will be assessed for inclusion as continuous, dichotomous, and categorical (i.e., indicator coded) variables, as appropriate. Covariates will be included in the propensity score model if the crude hazard ratio is greater than 1.11 or less than 0.90. Additional confounders will be selected for inclusion within propensity score models if at least a 10% change in the hazard ratio of the exposure-outcome relationship occurs when adjusting for that variable, including at least a 10% change in any level of a categorical exposure variable relative to the referent group (> 52 weeks postpartum for postpartum period).

From the fitted logistic regression models, propensity scores and the overlap weights (Li et al., 2018) will be estimated for each IUD insertion. Overlap weighting is a relatively new weighting scheme to adjust for confounding effects. Overlap weights belong to a class of balancing weights, including commonly used weights for inverse probability weighting. Li et al. (2018) mathematically proved and verified in simulations that the overlap weights minimize asymptotic variance among balancing weights. Other advantages of overlap weights over inverse probability weighting include perfect balance for means and bounded weights avoiding explosive weights or the need for arbitrary truncation. In addition, the overlap weights focus on the naturally comparable "overlap" population, and therefore propensity score 'trimming' for a common support area is not necessary. The overlap weights have been applied in observational studies, for example, Schneider et al. (2001), although the term "overlap weights" was not established at that time.

For dichotomous exposure variables, the propensity score is the probability of being exposed. The propensity score for patient (insertion) i is denoted as $e_i = \Pr(Z_i = 1|X_i)$, where Z_i denotes the exposure (1= exposed, 0 = unexposed), and X_i denotes a vector of baseline covariates. The overlap weight for patient i is defined as follows:

$$w_i = \begin{cases} 1 - e_i, Z_i = 1 \\ e_i, \quad Z_i = 0 \end{cases}$$

For categorical exposure variables with more than two levels, the propensity scores will be estimated for each patient and exposure level. Consider an exposure variable with K exposure groups ($K > 2$). The propensity score for patient i and exposure k, k=1,…K, denoted as e_{ik}, is the probability that a patient will be exposed to exposure k conditional on measured covariates X_i:

$$e_{ik} = \Pr(Z_i{=}k|X_i), \text{ with } \sum_{k=1}^{K} e_{ik} = 1$$

The overlap weight for patient i given exposure k is defined as follows:

$$w_{ik} = \frac{1}{e_{ik} \sum_{k=1}^{K} \frac{1}{e_{ik}}}$$

The overlap weights will be normalized by multiplying the weights by $\frac{n}{\sum_{i=1}^{n} w_i}$, where n is the total sample size. The extreme weights (min, max), mean, and standard deviation of the normalized weights will be assessed, although extreme weights are not expected to be an issue with overlap weights because the overlap weights are bounded.

The distribution of propensity scores among exposed (e.g., breastfeeding at the time of IUD insertion) and unexposed (e.g., not breastfeeding at time of IUD insertion) patients will be examined using histograms with kernel smoothing to identify the overlapping area. However, all patients will be included in the analysis when applying overlap weights. The overlap weights put the strong focus on those patients with the highest overlap in their propensity scores and therefore avoid the need for trimming the population.

The balance across exposure groups will be assessed before and after weighting. The distribution of each variable will be compared between categories of the exposure variable, and balance parameters (i.e., standardized differences) (Austin and Stuart, 2015) will be calculated. Pairwise balance parameters (e.g., pairwise standardized differences) will be used for the categorical exposure variable in which each category will be compared to the referent group (> 52 weeks postpartum for postpartum period). The maximum of the pairwise standardized differences will also be reported. The balance between exposure groups will be assessed overall and within each data source. If the groups are unbalanced on key covariates after application of overlap weighting, then the logistic regression model will be revised by including interaction terms (e.g., with data source), higher order terms, or transformation of variables, and the covariate balance between the groups overall and within each data source will be re-evaluated based on the revised model. When satisfactory balance between the exposed and unexposed groups is achieved, the weighting will be incorporated in modeling for confounder-adjusted outcome assessments (Section 4.1.5). The exposure groups are considered balanced if the standardized difference is less than 0.20 (generally considered small) (McCaffrey et al., 2013). If satisfactory balance is difficult to achieve, which is not expected for overlap weighting, matching of patients between groups may be considered.

Separate propensity score models will be developed for exposure-outcome pairings related to breastfeeding status, postpartum period, IUD type, and menorrhagia for uterine perforation and IUD expulsion. The list of propensity score models is provided in Section 9.3. Sections 6.2 and 6.3 includes additional information for specific objectives. In general, the selection of covariates for inclusion in propensity score models will be conducted only using first insertions. The association between baseline covariates and outcomes (crude hazard ratio) will be assessed only using the complete study population, which includes only the first IUD insertion for each woman. No covariate selection will be conducted for *subsequent* insertion models. Instead, for each specific pairing, covariates and terms included in the final propensity score model for first insertions will be included in the propensity score model for subsequent insertions. Additionally, IUD insertion count (the sequential number) may be included in the propensity score model if it is not balanced across exposure groups for *subsequent* insertions. Propensity scores and weights will be estimated from the corresponding propensity score models.

4.1.6 Adjusted Hazard Ratios

The adjusted hazard ratios and 95% CIs will be estimated using weighted Cox regression models. Hazard ratios will be adjusted for possible confounding effects using overlap weighting (Section 4.1.5). This will be conducted in SAS using PROC PHREG with the WEIGHT statement. Normalized weights will be used for the weighted Cox models. The normalized weights add up to the sample size, so that the estimated covariance matrix of the parameter estimators is invariant to the scale of the weights. To account for the fact that the weights are estimated, a robust, sandwich-type variance estimator will be used to calculate 95% CIs. This will be conducted by using the COVSANDWICH option in the PROC PHREG procedure in SAS. Adjusted hazard ratios will be reported as point estimates with 95% CIs.

Time-dependent exposure covariates will be included if violation of the proportional hazards assumption is identified in the unweighted Cox model (described in Section 4.1.4.).

4.1.7 Crude IRR

The crude IRR will be calculated as the crude incidence rate in the exposed divided by the crude incidence rate in the unexposed.

$$IRR = \frac{Incidence\ rate\ in\ the\ exposed}{Incidence\ rate\ in\ the\ unexposed} = \frac{E_1/Y_1}{E_2/Y_2}$$

where E_1 is the number of incident outcomes occurring during person-years at risk in the exposed group, Y_1 is the total person-years at risk in the exposed group, E_2 is the number of incident outcomes occurring during the person-years at risk in the unexposed group, and Y_2 is the total person-years at risk in the unexposed group.

The 95% CI of the crude IRR will be calculated using a Poisson distribution and test-based methods defined in Sahai and Khurshid (1996). The lower and upper bounds of the 95% CI will be calculated as follows:

$$IRR_{LB} = \left(\frac{Y_2}{Y_1}\right)\left(\frac{E_1}{E_2+1}\right)\frac{1}{F_{0.025,2(E_2+1),2E_1}}, IRR_{UB} = \left(\frac{Y_2}{Y_1}\right)\left(\frac{E_1+1}{E_2}\right)F_{0.025,2(E_1+1),2E_2}$$

where $F_{0.025,\,v1,\,v2}$ represents the 2.5th percentile of the F distribution with $v1$ and $v2$ degrees of freedom.

All crude IRRs will be reported as point estimates with 95% CIs.

4.1.8 Adjusted IRR Via Weighting

The IRR will be adjusted for possible confounding effects via weighted estimation of the rates using overlap weights (Section 4.1.5) derived from the same propensity score models as those developed for adjustment of the hazard ratios. The adjusted IRR will be calculated as the weighted incidence rate in the exposed divided by the weighted incidence rate in the unexposed.

$$IRR_w = \frac{Weighted\ incidence\ rate\ in\ the\ exposed}{Weighted\ incidence\ rate\ in\ the\ unexposed} = \frac{E_{w1}/Y_{w1}}{E_{w2}/Y_{w2}}$$

where E_{w1} is the number of weighted incident outcomes occurring during person-years at risk in the exposed group, Y_{w1} is the total weighted person-years at risk in the exposed group, E_{w2} is the number of weighted incident outcomes occurring during the person-years at risk in the unexposed group, and Y_{w2} is the total weighted person-years at risk in the unexposed group.

The 95% CI of IRR_w will be calculated as described in Section 4.1.7 using a Poisson distribution and the number of weighted incident outcomes and weighted person-years.

4.1.9 Crude IRD

The crude IRD will be calculated as the crude incidence rate in the exposed minus the crude incidence rate in the unexposed:

$$IRD = \frac{E_1}{Y_1} - \frac{E_2}{Y_2}$$

with an approximate 95% CI as outlined in Rothman et al. (2008):

$$IRD \pm Z_{0.025}\sqrt{\frac{E_1}{Y_1^2}+\frac{E_2}{Y_2^2}}$$

Where $Z_{0.025}$ is the 2.5th percentile of the standard normal distribution.

All crude IRDs will be reported as point estimates with 95% CIs.

4.1.10 Adjusted IRD Via Weighting

The IRD will be adjusted for possible confounding effects via weighted estimation of the rates using overlap weights (Section 4.1.5) derived from the same propensity score models as those developed for adjustment of the hazard ratios. The adjusted IRD will be calculated as the weighted incidence rate in the exposed minus the weighted incidence rate in the unexposed.

$$IRD_w = \frac{E_{w1}}{Y_{w1}} - \frac{E_{w2}}{Y_{w2}}$$

The 95% CI of IRD_w will be calculated as described in Section 4.1.9 using the number of weighted incident outcomes and weighted person-years.

4.2 Handling of Loss to Follow-Up and Premature Discontinuation

This is a retrospective study. To minimize use of records with incomplete data for baseline covariates, women will be required to have 12 months of continuous enrollment within the data source prior to the index date. Additionally, at the Kaiser Permanente sites, censoring will occur if more than 31 days passes without insurance coverage sufficient to maintain enrollment.

This study will be conducted using data from four health care systems with EHRs: KPNC, KPSC, KPWA, and RI. Date of disenrollment from the database, that is, the date on which a woman is no longer enrolled in an eligible insurance plan, will be captured by KPNC, KPSC, and KPWA. For RI, date of last clinical encounter—the last date on which a woman has an in-person encounter that is recorded in the database—will be captured. The dates of disenrollment and last clinical encounter will be used as stopping dates for person-time at risk.

4.3 Handling of Missing Data

Missing data will be treated as missing, unless specified otherwise, and no imputations will be performed. In database analyses of previously collected data, if information on a particular binary variable, such as a disease diagnosis or a medication, is available in the database, patients are assumed to have the factor only if there is evidence for its presence (i.e., absence of information will be taken to mean absence of the condition or medication).

Where appropriate, variables will include a "missing" category for analyses. Consequently, data analyses will be conducted using all women and insertions to the extent possible with respect to their observed available data (i.e., the IUD insertion will not be included in an analysis if missing data for any variable in that analysis, except where "missing" is a separate category for the analysis).

Counts of missingness will be reported in descriptive analysis of categorical variables, and percentages for the nonmissing categories will be based on the number of nonmissing values. For continuous variables, the number of nonmissing values will be reported, and descriptive summaries

will be based on the number of nonmissing values. In addition, the percentage of patients or insertions with missing data will be provided for breastfeeding and IUD type.

4.4 Interim Analyses and Data Monitoring

No interim analyses are planned. Data monitoring is not applicable in this retrospective cohort study based on secondary use of EHR data.

4.5 Data Rules

The index date will be the date of the IUD insertion. In the primary analyses, only the first eligible IUD insertion will be considered; all subsequent IUD insertions will be included in secondary analyses (objectives 18 and 26). Baseline characteristics will be assessed for each eligible insertion. The look-back time will consist of all available data on or before the index date, unless otherwise specified for a particular variable in Section 4.6. Because all insertions included in the study are required to have at least 12 months of data before the index date, a minimum of 12 months of data from which to evaluate baseline characteristic values will be available. For some insertions, more information will be available, and all information within the database on or prior to the index date will be considered to reduce misclassification of baseline information.

4.6 Definition of Derived Variables and Subgroups

The variables described in Table 1 will be derived by RTI-HS using the data provided by the four research sites. Since the unit of observation in the data provided by the research partners will be an IUD insertion, these variables will be calculated for each insertion and included in the final dataset. If a woman has more than one eligible insertion in the dataset, the variables will be derived for each insertion using data relevant to that insertion.

Table 1. Definition of Derived Variables

Variable	Definition[a]
Baseline covariates	
IUD insertion count	The number of eligible IUD insertions for the woman as of the index date (including the index insertion). *IUD insertion count* increases by 1 each time a new *index date* is identified for the woman
Initial IUD insertion	Indicator variable: If IUD insertion count = 1 then initial IUD insertion = 1 If IUD insertion count > 1 then initial IUD insertion = 0
Difficult insertion	Indicator variable: 1 = Yes if any of the following occur on the index date (or in 7 days before index date for misoprostol): *cervical dilation, ultrasound guidance*, *paracervical block*, *provider note*, *use of misoprostol* 0 = No if none of the above indicators of difficult insertion are found on the index date
Age tertile	Categorical variable for age based on tertiles (or closest integer cut point [i.e., in years]) for all ages at all first index dates observed within the data
Duration of look-back period	Derived number of days, starting on the *date of start of enrollment or first clinical encounter* in the EHR database and ending on the index date *Duration of look-back period* is calculated for each index date
Categorical indicator for provider number of insertions in previous year	Indicator variable: 0 = fewer than 50 *provider number of IUD insertions* in the 365 days prior to and on the index date, 1 = 50 or more *provider number of IUD insertions* in the 365 days prior to and on the index date
Provider annualized number of insertions in previous year	*Provider number of IUD insertions in previous year divided by provider length of employment in previous year, multiplied by 365*
Concomitant gynecological procedure	Indicator variable: 1 = Yes if any of the following procedures occurred on the index date: abortion, aspiration and curettage, dilation and curettage, excision/biopsy of cervix or uterus, ablation, colposcopy and other cervical procedures, hysteroscopy, laminaria, laparoscopy, lysis adhesions, myomectomy, nerve procedure, salpingectomy/oophorectomy 0 = No if none of the above procedures occurred on the index date
Exposures	
Postpartum number of days	Number of person-days, starting on the most recent *pregnancy delivery date* prior to or on the index date and ending on the *index date*. There will be a derived *postpartum number of days* associated with each insertion for each woman. This variable will range from 0 to 365 days and will be missing if the most recent *pregnancy delivery date* is not recorded or is more than 365 days before the *index date*.
Postpartum—14-week, dichotomous	Indicator variable: * If postpartum number of days ≤ 98, then postpartum—14-week, dichotomous = 1 * If postpartum number of days > 98 or missing, then postpartum—14-week, dichotomous = 0

Variable	Definition[a]
Postpartum—36-week, dichotomous	Indicator variable: * If postpartum number of days ≤ 252, then postpartum—36-week, dichotomous = 1 * If postpartum number of days > 252 or missing, then postpartum—36-week, dichotomous = 0
Postpartum—categorical	Categorical variable: * If postpartum number of days ≤ 42, then postpartum—categorical = 1 (6 weeks or less) * If postpartum number of days > 42 and ≤ 98, then postpartum—categorical = 2 (> 6 to ≤ 14 weeks) * If postpartum number of days > 98 and ≤ 365, then postpartum—categorical = 3 (> 14 to ≤ 52 weeks) * If postpartum number of days > 365 or missing, then postpartum—categorical = 0 (> 52 weeks or no delivery)
Outcomes	
Person-time at risk (days, i.e., time to event/censor)	Number of person-days, starting on the *index date* of IUD insertion and ending on the earliest of *date uterine perforation confirmed*, *date IUD expulsion confirmed*, or *censoring date*. A derived number for *person-time at risk* will be associated with **each** *IUD insertion* for each woman.
Uterine perforation event indicator	Indicator variable: 0 = No *date of uterine perforation confirmed* during the *person-time at risk* 1 = Yes, *date of uterine perforation confirmed* during the *person-time at risk*
IUD expulsion event indicator	Indicator variable: 0 = No *date of IUD expulsion confirmed* during the *person-time at risk* 1 = Yes, *date of IUD expulsion confirmed* during the *person-time at risk*
Other parameter	
Continuous enrollment	For KPNC, KPSC, and KPWA: Number of days from the latest of *beginning date of the study period* or *date of start of most recent enrollment* before the index date to the earliest of *end date of study period* or *date of most recent disenrollment* following the index date. See illustration in Section 9.6. For RI: Number of days from the latest of *beginning date of the study period* or *date* of *first clinical encounter* to the earliest of *end date of study period* or *date of last clinical encounter* following the index date.

EHR = electronic health record; IUD = intrauterine device.
[a] Variables in *Italic*, if not defined in this table, are defined in Sections 3.1-3.8.

5 Analysis Sets

5.1 Assignment of Analysis Sets

The complete study population will be defined by the study inclusion and exclusion criteria. However, subsets of the complete study population will be used to address certain study objectives. The analysis sets for the *first eligible IUD insertions* are outlined in Table 2. The analysis sets for subsequent IUD insertions will be defined in the same way for the corresponding IUD insertions.

Table 2. Women Included in Analysis Sets 1 and/or 2

Event in Electronic Health Record	Postpartum Status	Breastfeeding Status[a]		
		Yes	No	Undetermined
Delivery in the past year (52 weeks)	≤ 6 weeks	1, 2	1, 2	1
	> 6 weeks and ≤ 14 weeks	1, 2	1, 2	1
	> 14 and ≤ 52 weeks	1, 2	1, 2	1
No evidence of delivery in the past year	No delivery in the past 52 weeks	NA	1	NA

NA = not applicable.

[a] The numbers indicate the analysis set numbers.

5.1.1 Analysis Set 1: Complete Study Population

This analysis set will include women with eligible insertions based on study inclusion and exclusion criteria outlined in Section 3 and in the study protocol. This analysis set will include women with missing data for breastfeeding status and/or IUD type for the insertion. The missing data within breastfeeding status and IUD type may be considered a separate group in the analyses (e.g., when developing the propensity score model for postpartum period).

5.1.2 Analysis Set 2: Breastfeeding Status Available

Women who were less than 52 weeks postpartum at the time of IUD insertion and have either "yes" or "no" breastfeeding status at the time of IUD insertion will be included in this analysis set. Women who have undetermined breastfeeding status for the insertion will not be included.

5.1.3 Analysis Set 3: IUD Type Available

Women with a known type of IUD (either LNG-IUD or copper IUD) for the insertion will be included in this analysis set. Women who have an undetermined IUD type for the insertion will not be included.

6 Statistical Methodology

All analyses will be conducted and/or presented using the pooled data and by data source, as appropriate. However, due to the expected sparse outcomes and the data source restriction on reporting IUD type, some analyses will be conducted using only the pooled data, not by data source. In addition, if sparse cells (i.e., count < 10 for exposures, covariates, or outcomes) are identified during the analysis, the sparse cells may be combined into other meaningful categories, excluded from analysis, or left as they are. Decisions will be made by the study team at the time sparse cells are identified.

Objectives and the corresponding exposures, outcomes, analysis sets, and insertions (e.g., first insertions or subsequent insertions) are summarized in Sections 9.1 and 9.2. Propensity score models and the corresponding objectives are summarized in Section 9.3. A list of tables and figures is included in Section 9.4. Table shells are provided as a separate document and are embedded in Section 9.5.

6.1 Population Characteristics

Descriptive analyses will be conducted to describe baseline demographics and clinical characteristics at the time of the IUD insertion among the three analysis sets (Analysis Tables 0.1.1 through 0.6.5). Separate tables will be generated for the pooled study population and for each of the

four databases. Characteristics will be presented overall and for each outcome category of the two study endpoints, perforation and expulsion.

Important characteristics that will be summarized are as follows:

- Demographics (age at index date, race/ethnicity)
- Clinical characteristics (BMI, dysmenorrhea, parity, previous cesarean delivery)
- Procedure-related characteristics (indicator for concomitant procedure and indicators for a difficult IUD insertion [cervical dilation, ultrasound guidance])
- Provider-related characteristics (number of IUD insertions performed)

All variables to be included in the descriptive analyses are described in Sections 3 and 4.6 and listed in the table shells in Section 9.5. Categorical variables will be summarized using frequencies and percentages, and continuous variables will be summarized using means, standard deviations, medians, lower quartiles, upper quartiles, and minimum and maximum values, as described in Section 4.1.1.

Analysis Tables 0.1.1 through 0.3.5 will present demographic summaries for the primary analysis population, which includes only the first observed IUD insertion. Because a woman can have only one eligible insertion in the primary analyses, Analysis Tables 0.1.1 through 0.3.5 will be at the patient level. Analysis Tables 0.4.1 through 0.6.5 will present demographic summaries at the insertion level for the secondary analysis population, which includes all subsequent IUD insertions. Because the unit of observation in the secondary analyses is an IUD insertion, if a woman has more than one eligible insertion during the study period, she will be included more than once in the columns of Analysis Tables 0.4.1 through 0.6.5, with baseline demographic characteristics summarized at each index date. These tables will include number of patients or insertions, as well as number of person-years at risk.

6.2 Analysis of Primary Variable(s)

The primary endpoint in the study is time to diagnosis of uterine perforation (defined in Table 1). Study objectives related to uterine perforation and the corresponding exposures and analysis sets are summarized in Section 9.1. A list of planned analysis tables and figures is included in Section 9.4.

6.2.1 Analysis for Primary Objectives

In the following groups of women, the adjusted hazard ratios for uterine perforation will be evaluated:

- Objective 1. Women who were breastfeeding at the time of the first observed IUD insertion versus those who were not breastfeeding at the time of the first observed IUD insertion.
- Objective 2. Women who had a first observed IUD insertion within different time periods postpartum (i.e., $\leq$ 6 weeks, > 6 weeks and $\leq$ 14 weeks, > 14 weeks and $\leq$ 52 weeks) versus those who had a first observed IUD insertion late in the postpartum period (more than 52 weeks postpartum, including those without recorded delivery in the past 52 weeks).

For objective 1, analyses will be conducted using Analysis Set 2 (breastfeeding status is available). For objective 2, analyses will be conducted using Analysis Set 1 (complete study population). Both analyses will use only the first observed IUD insertion.

Cox regression models will be used to obtain crude hazard ratios overall and by data source with assessment of the proportional hazards assumption (Section 4.1.4).

Confounding effects will be adjusted using the propensity score weighting method (Section 4.1.5). After developing the propensity score model, calculating the weights, and assessing the balance between exposure groups in the weighted sample, adjusted hazard ratios will be estimated using the weighted Cox regression model as described in Section 4.1.6. Additionally, the interaction effect between the data source and the exposure will be assessed after adjustment for confounding. The interaction will be assessed by including terms for exposure, database, and the interaction between the database and the exposure in the weighted Cox models. A type 3 group test for the interaction terms will be conducted. If the test is statistically significant ($P < 0.05$), then the interaction terms will be retained in the final model, and the adjusted hazard ratios will be reported for each data source. If the interaction terms are not statistically significant, then the interaction terms will be removed, and the overall adjusted hazard ratios (the main effect) will be reported as the results of the primary analyses.

Two-sided 95% CIs of the adjusted hazard ratios for uterine perforation will be presented overall or by data source, as appropriate. If the exposure-by-data source interaction is not significant, then the corresponding two-sided test of the null hypothesis that the natural logarithm of the overall adjusted hazard ratio equals 0 will be performed. The significance level of 0.05 will be applied. There will be no adjustment for multiplicity.

As a sensitivity analysis, confounding effects will be accounted for by including selected key covariates in the unweighted Cox models. The Cox models will include exposure, site, exposure-by-site interaction, and baseline covariates. Due to the sparse outcomes, limited covariates will be selected for inclusion based on their association with the study outcome. The sensitivity analysis will be conducted only for the primary objectives.

Planned Analysis Tables 1.1 (for breastfeeding status) and 2.1 (for postpartum status) will present crude hazard ratio and hazard ratio adjusted via overlap weighting. Analysis Tables 1.2.1 through 1.3.5 and 2.2.1 through 2.3.5 will present baseline characteristics by exposure and standardized differences (described in Section 4.1.5) prior to and after overlap weighting. Analysis Tables 1.4 and 2.4 will present hazard ratios adjusted by including baseline covariates in the model. Results related to the development of propensity score models will be presented in Analysis Tables 33.1.1, 33.2.1, 33.2.2, 33.3.1, 33.3.2 and Analysis Figures 33.1.1 and 33.1.2.

6.2.2 Analysis for Secondary Objectives

6.2.2.1 Crude Incidence Rates and Cumulative Incidence

Crude incidence rates during follow-up and crude cumulative incidence at year 1 and year 5 for the first observed IUD insertions will be calculated overall and by exposure groups (objectives 3-7, as described in Sections 4.1.2 and 4.1.3). Analyses will be conducted using the pooled data and by data source (Analysis Tables 3.1 through 5). Due to data source restrictions, any results on type of IUD by data source will not be reported.

Additionally, the cumulative incidence curve over time, also known as the failure function (i.e., 1 - survival function), will be estimated using the Kaplan-Meier method and plotted overall for each analysis set (Analysis Figures 3.1 through 7.1).

6.2.2.2 Comparing Adjusted Hazard Ratios Among First Observed IUD Insertions

Adjusted hazard ratios associated with the first observed IUD insertions will be estimated for secondary objectives 14-16, and 19 using the same analysis approach (i.e., overlap weighting) as described in Section 6.2.1, with the following exceptions.

1. For type of IUD, analyses may be conducted by data source. However, due to data source restrictions, any results on type of IUD by data source will not be reported.
2. For secondary objectives that include dichotomization of "early" and "late" postpartum categories, separate propensity score models will not be developed. Rather, the propensity score model developed for the four-category variable will be used. The propensity score for dichotomous exposed group will be calculated by collapsing multiple categories (e.g., propensity score for ≤ 14 weeks = propensity score for ≤ 6 weeks + propensity score for > 6 to ≤ 14 weeks).
3. The analyses for objective 19 (menorrhagia) will be performed only if more than 20,000 IUD insertions with an indication of menorrhagia can be included in the analysis.

Balance will be assessed between exposure groups prior to and after weighting. Crude hazard ratios will also be reported.

The same set of analysis tables and figures as those created for objective 1 will be generated, except that no sensitivity analyses will be conducted for these secondary objectives.

6.2.2.3 Comparing Adjusted IRR and Adjusted IRD

To compare results from this study to those obtained in EURAS-IUD, we will estimate the adjusted IRR and IRD of uterine perforation at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (objective 17). Adjusted IRRs and IRDs will be calculated via weighted estimation of the rates using overlap weights as described in Sections 4.1.8 and 4.1.10, respectively.

Using the final analysis datasets after propensity score development and weighting, we will calculate adjusted IRRs and IRDs for the study outcomes. Tables will display the weighted number of outcomes, total weighted person-years, and weighted incidence rates for women who had a first observed IUD insertion ≤ 36 weeks postpartum and for women who had a first observed IUD insertion > 36 weeks postpartum. The adjusted IRRs and IRDs along with 95% CIs will be displayed. Analysis Tables 17.1 will be created for uterine perforation.

6.2.2.4 Comparing Adjusted Hazard Ratios for Subsequent IUD Insertions

Adjusted hazard ratios associated with subsequent IUD insertions will be estimated for secondary objectives 18. These analyses will be conducted using the same analysis approach (i.e., Cox models with overlap weights) described previously for first insertions except using subsequent IUD insertions.

Propensity score models will be developed using subsequent IUD insertions. IUD insertion count (the sequential number) may be included in the propensity score model, as needed. To account for the correlation within women with multiple IUD insertions, a robust, sandwich-type variance estimator will be used to calculate 95% CIs. This will be conducted by using the COVSANDWICH

option in the PROC PHREG procedure in SAS. This is the same variance estimator to account for the fact that the weights are estimated.

The site-specific analyses will be performed only if there are more than 20,000 subsequent IUD insertions for that site. The pooled analysis will include all sites regardless of the number of subsequent IUD insertions at individual sites. The crude and adjusted hazard ratios and 95% CIs will be reported.

6.2.2.5 Assessing Effect Modification

Estimation of effect modification of the adjusted hazard ratios will be conducted for secondary objectives 28, 29, 31. The crude and adjusted hazard ratios will be estimated as described in Sections 4.1.4 and 4.1.6 within each level of the potential effect modifier. Due to the expected sparse outcomes and the data source restriction on IUD type, these analysis will be conducted only using the pooled data, not by data source.

For objective 28, the Cox model will include breastfeeding status, early (≤ 14 weeks) versus late (> 14 weeks) postpartum status, and their interaction. The *P* value of the type 3 group test for interaction will be reported. The hazard ratio for breastfeeding status (yes vs. no) will be reported within each level of early (≤ 14 weeks) and late (> 14 weeks) postpartum status. The hazard ratio for postpartum status (≤ 14 weeks vs. > 14 weeks) will be reported within each level of breastfeeding status. In addition, for reporting purposes, the group of no breastfeeding and > 14 weeks postpartum will be considered the referent, and hazard ratios will be reported for postpartum period ≤ 14 weeks and breastfeeding, ≤ 14 weeks and no breastfeeding, and > 14 weeks and breastfeeding. The adjusted hazard ratio will be obtained using the weighted Cox model. One propensity score model using these four (2 x 2) categories as the dependent variable will be developed. Balance on baseline covariates among the four categories in the weighted sample will be assessed.

For objectives 29 and 31, the Cox models will include the exposure of interest (breastfeeding status or postpartum categories), IUD type, and the interaction between exposure and IUD type. The *P* value of the type 3 group test for interaction will be reported. The hazard ratio for the exposure of interest will be reported within each level of IUD type. The adjusted hazard ratio will be obtained using the weighted Cox model. The weights will be estimated using the same propensity score models developed for the exposure-outcome pairing (Section 9.3).

6.3 Analysis of Secondary Variable(s)

6.3.1 Analysis of IUD Expulsion

The secondary endpoint in the study is time to diagnosis of IUD expulsion (defined in Table 1). In the following groups of women, the adjusted hazard ratios for IUD expulsion will be evaluated:

- Objective 20. Women who were breastfeeding at the time of the first observed IUD insertion versus those who were not breastfeeding at the time of the first observed IUD insertion.
- Objective 23. Women who had a first observed IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) versus those who had a first observed IUD insertion late in the postpartum period (more than 52 weeks postpartum, including those without recorded delivery in the previous 52 weeks).

Study objectives related to IUD expulsion and the corresponding exposures and analysis sets are summarized in Section 9.2 Analyses will be the same as those for uterine preformation, as described

in Section 6.2, except (1) no sensitivity analyses will be conducted and (2) assessment of effect modification using a Cox model including breastfeeding status, early (≤ 14 weeks) versus late (> 14 weeks) postpartum status, and their interaction will not be conducted.

6.3.2 Analysis of Difficult Insertion

The prevalence of indicators of a difficult insertion (objective 13) will be presented via contingency tables including frequencies and percentages of each level of each exposure and outcome variable for five individual indicators of difficult IUD insertion—cervical dilation, ultrasound guidance, paracervical block, provider note, use of misoprostol—plus an indicator for *any* difficult insertion. Analyses will be conducted for the first observed IUD insertion using the pooled data and by data source (Analysis Tables 13.1-13.5). In addition, difficult insertion indicators will be included in summary tables of baseline characteristics.

6.3.3 Impact of Transition From ICD-9-CM to ICD-10-CM[2]

The results of this study are dependent on accurate capture of data from source files based on definitions of variables in this study. Since variables will be determined from diagnosis codes (ICD-9-CM, ICD-10-CM), Current Procedural Terminology codes, medication codes (National Drug Codes), and clinical notes (e.g., via natural language processing software) there is a possibility of misclassification. Algorithms for the outcome variables (uterine perforation and IUD expulsion) have been validated in these four databases prior to use of ICD-10-CM coding. No formal validation of the algorithms with ICD-10-CM codes to identify uterine perforation or IUD expulsion will be performed. However, the rate of these outcomes will be reviewed before and after implementation of ICD-10-CM coding to ensure consistency over time. Specifically, 01 October 2015 is the date of transition from ICD-9-CM to ICD-10-CM. The "before" time period will be defined as 01 October 2014 through 30 September 2015, and the "after" time period will be defined as 01 October 2015 through 30 September 2016. The number of patients with an outcome in each time period and the number of patients enrolled in each time period will be reported by data source research partners. The percentage of patients with an outcome among enrolled patients in each time period will be calculated. This analysis will be conducted using the "complete study population" defined in Section 5.1. The count and percentage will be reported for each outcome before and after the transition in the pooled data and by data source (planned Analysis Table 34.1).

6.4 Safety Analysis

No additional safety analysis is planned.

6.5 Analysis of Representativeness

The study will include all eligible patients identified from KPNC, KPSC, KPWA, and RI. This will cover the following geographic regions in the United States: northern California, southern California, Washington, and Indiana. Summary statistics for demographics and other baseline characteristics of the study cohorts will be provided as described in Section 6.1.

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[2] ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification;*
ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification.*

6.6 Additional Analyses Planned to be Reported Outside the Study Report

No additional analyses are planned.

7 Document History and Changes in the Planned Statistical Analysis

- Final statistical analysis plan (SAP) v1.0, dated 29 June 2018 – initial version, submitted to FDA.
- SAP v2.0, dated 24 October 2018
    - The methods for confounder- or bias-adjusted analyses (previously Section 6.5) was moved to Section 4.1.5 as requested by FDA.
    - Section 4.1.5 (previously Section 6.5) was updated to state that a covariate will be included in the propensity score model if there is "at least a 10% change" rather than "a 10% change."
    - Section 4.1.5 (previously Section 6.5) was revised to include key potential confounders (breastfeeding status, postpartum timing, and IUD type) within the propensity score model (as independent variables when not the dependent variable). Changes were also made to Section 4.1.6 (previously Section 4.1.5) and 6.2.2.3 to incorporate this change. Section 4.1.8 and 4.1.11 were removed as they were no longer needed.
    - The name of the baseline covariate "colposcopy" was changed to "colposcopy and other cervical procedures."

8 References

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9 Appendix

9.1 Study Objectives With Corresponding Exposures, Analysis Sets, and Effect Estimates for Uterine Perforation

Exposure (Analysis Set)	Objectives (Identified by Number) and Effect Estimates Related to Uterine Perforation				
	Crude IR, cum. incidence (first insertion)	**Adj. HR via weighting, crude HR (first insertion)**	**Adj. HR via weighting, crude HR (subsequent insertions)**	**Weighted IRR and IRD (at 1 year and 5 years), crude IRR and IRD (first insertion)**	**Adj. and crude HR within each level of the modifier (first insertion)**
Breastfeeding (AS2)	5	1[a]	18		28, interaction with ≤ 14 vs > 14 weeks postpartum
					29, modified by IUD type
4-level postpartum (AS1)	4	2[a]	18		31, modified by IUD type
≤ 14 wks vs. > 14 weeks postpartum (AS1)	4	14	18		
≤ 36 wks vs. > 36 weeks postpartum (AS1)	4	15	18	17	
IUD type[b] (AS3)	6	16	18		
Menorrhagia (AS1)	7	19			
Overall (AS1, AS2, AS3)	3				

AS1 = Analysis Set 1: complete study population; AS2 = Analysis Set 2: breastfeeding status available; AS3 = Analysis Set 3: IUD type available; HR = hazard ratio; IR = incidence rate; IRD = incidence rate difference; IRR = incidence rate ratio; IUD = intrauterine device.

[a] Also, regression adjustment will be conducted as a sensitivity analysis.

[b] Aggregated analysis only, not by site.

9.2 Study Objectives With Corresponding Exposures, Analysis Sets and Effect Estimates for IUD Expulsion

Exposure (Analysis Set)	Objectives (Identified by Number) and Effect Estimates Related to IUD Expulsion				
	Crude IR, cum. incidence (first insertion)	Adj. HR via weighting, crude HR (first insertion)	Adj. HR via weighting, crude HR (subsequent insertions)	Weighted IRR and IRD (at 1 year and 5 years), crude IRR and IRD (first insertion)	Adj. and crude HR within each level of the modifier (first insertion)
Breastfeeding (AS2)	10	20	26		30, modified by IUD type
4-level postpartum (AS1)	9	23	26		32, modified by IUD type
≤ 14 wks vs. > 14 weeks postpartum (AS1)	9	21	26		
≤ 36 wks vs. > 36 weeks postpartum (AS1)	9	22	26	25	
IUD type[a] (AS3)	11	24	26		
Menorrhagia (AS1)	12	27			
Overall (AS1, AS2, AS3)	8				

AS1 = Analysis Set 1: complete study population; AS2 = Analysis Set 2: breastfeeding status available; AS3 = Analysis Set 3: IUD type available; HR = hazard ratio; IR = incidence rate; IRD = incidence rate difference; IRR = incidence rate ratio; IUD = intrauterine device.

[a] Aggregated analysis only, not by site.

9.3 Propensity Score Models Defined by Exposure and Outcomes of Interest

Model Number	Exposure (Dependent Variable of Propensity Score Model)	Outcome (Not Included in Propensity Score Model)	IUD Insertion	Covariate Selection	Objective Number
1	Breastfeeding status (yes vs. no)	Uterine perforation	First insertion	Yes	1 (primary objective) 29
2	Postpartum insertion (4 categories)	Uterine perforation	First insertion	Yes	2 (primary objective) 14[a] 15[a] 17[a] 31
3	IUD type (LNG vs. copper)	Uterine perforation	First insertion	Yes	16
4	Menorrhagia (yes vs. no)	Uterine perforation	First insertion	Yes	19
5	Breastfeeding status (yes vs. no)	IUD expulsion	First insertion	Yes	20 30
6	Postpartum insertion (4 categories)	IUD expulsion	First insertion	Yes	23 21[a] 22[a] 25[a] 32
7	IUD type (LNG vs. copper)	IUD expulsion	First insertion	Yes	24
8	Menorrhagia (yes vs. no)	IUD expulsion	First insertion	Yes	27
9	Interaction of breastfeeding and early vs. late postpartum (breastfeeding/≤ 14 weeks; breastfeeding/> 14 weeks; no breastfeeding/≤ 14 weeks; no breastfeeding/> 14 weeks [referent])	Uterine perforation	First insertion	Yes	28
10	Breastfeeding status (yes vs. no)	Uterine perforation	Subsequent insertions	No[b]	18
11	Postpartum insertion (4 categories)	Uterine perforation	Subsequent insertions	No[b]	18[a]
12	IUD type (LNG vs. copper)	Uterine perforation	Subsequent insertions	No[b]	18
13	Breastfeeding status	IUD expulsion	Subsequent insertions	No[b]	26
14	Postpartum insertion (4 categories)	IUD expulsion	Subsequent insertions	No[b]	26[a]
15	IUD type (LNG vs. copper)	IUD expulsion	Subsequent insertions	No[b]	26

IUD = intrauterine device; LNG = levonorgestrel.

[a] Secondary objectives include dichotomization of "early" and "late" postpartum categories. Separate propensity score models will not be *developed* for these objectives. Rather, the propensity scores calculated with the four-category variable will be used. The propensity scores for dichotomous exposure groups will be calculated by collapsing multiple categories (e.g., propensity score for ≤ 14 weeks = propensity score for ≤ 6 weeks + propensity score for > 6 to ≤ 14 weeks).

[b] Covariates and terms included in the final propensity score model for first insertions will be included in the propensity score model for subsequent insertions. Additionally, IUD insertion count (the sequential number) may be included in the propensity score model if it is not balanced across exposure groups for subsequent insertions.

9.4 List of Planned Analysis Tables and Figures

Table/Figure Number	Content	Table Layout[a]	Note
Population Characteristics			
Tables 0.1.1 through 0.1.5	Baseline characteristics overall, by uterine perforation and by IUD expulsion; complete patient population, first insertions	Layout 1	Pooled and by site (5 tables)
Tables 0.2.1 through 0.2.5	Baseline characteristics overall, by uterine perforation and by IUD expulsion; breastfeeding status available, first insertions	Layout 1	Pooled and by site (5 tables)
Tables 0.3.1 through 0.3.5	Baseline characteristics overall, by uterine perforation and by IUD expulsion; IUD type available, first insertions	Layout 1	Pooled and by site (5 tables)
Tables 0.4.1 through 0.4.5	Baseline characteristics overall, by uterine perforation and by IUD expulsion; complete patient population, subsequent insertions	Layout 1	Pooled and by site (5 tables)
Tables 0.5.1 through 0.5.5	Baseline characteristics overall, by uterine perforation and by IUD expulsion; breastfeeding status available, subsequent insertions	Layout 1	Pooled and by site (5 tables)
Tables 0.6.1 through 0.6.5	Baseline characteristics overall, by uterine perforation and by IUD expulsion; IUD type available, subsequent insertions	Layout 1	Pooled and by site (5 tables)
Objective 1	Breastfeeding and uterine perforation		
Table 1.1	Crude and adjusted HR for breast feeding status	Layout 2.1	Pooled and by site (1 table)
Tables 1.2.1 through 1.2.5	Baseline characteristics by exposure and absolute standardized difference	Layout 3.1	Pooled and by site (5 tables)
Tables 1.3.1 through 1.3.5	Baseline characteristics and absolute standardized differences after overlap weighting	Layout 3.1	Pooled and by site (5 tables)
Figure 1.1.1 through 1.1.5	Standardized differences in the unweighted and weighted samples		Pooled and by site (5 figures)
Table 1.4	Adjusted HR from Cox model with baseline covariates (sensitivity analysis)	Layout 7	Pooled, including interaction with site (1 table[b])
Objective 2	Postpartum period and uterine perforation		
Tables 2.1	Crude and adjusted HR for postpartum status	Layout 2.2	Pooled and by site (1 table)
Tables 2.2.1 through 2.2.5	Baseline characteristics by exposure and absolute standardized difference	Layout 3.2	Pooled and by site (5 tables)
Tables 2.3.1 through 2.3.5	Baseline characteristics and absolute standardized differences after overlap weighting	Layout 3.2	Pooled and by site (5 tables)

Table/Figure Number	Content	Table Layout[a]	Note
Figure 2.1.1 through 2.1.5	Standardized differences in the unweighted and weighted samples		Pooled and by site (5 figures)
Table 2.4	Adjusted HR from Cox model with baseline covariates (sensitivity analysis)	Layout 7	Pooled, including interaction with site (1 table[b])
Objectives 3 through 12	Crude incidence rate and cumulative incidence by analysis set, postpartum status, breastfeeding status, IUD type, menorrhagia		
Tables 3.1 through 3.5	Crude incidence rate and cumulative incidence	Layout 8	Pooled and by site (5 tables)
Figure 3.1	Kaplan-Meier cumulative incidence plot by analysis set		Pooled (1 figure)
Figure 4.1	Kaplan-Meier cumulative incidence plot by postpartum status		Pooled (1 figure)
Figure 5.1	Kaplan-Meier cumulative incidence plot by breastfeeding status		Pooled (1 figure)
Figure 6.1	Kaplan-Meier cumulative incidence plot by IUD type		Pooled (1 figure)
Figure 7.1	Kaplan-Meier cumulative incidence plot by menorrhagia		Pooled (1 figure)
Objectives 8 through 12	Crude incidence rates and cumulative incidence for IUD expulsion		Same set of tables and figures as objectives 3-7 (5 tables + 5 figures)
Objective 13			
Table 13.1 through 13.5	Prevalence of difficult IUD insertion by exposure and outcome	Layout 9	Pooled and by site (5 tables)
Objective 14	Postpartum period (≤ 14 vs. > 14 weeks) and uterine perforation		Same set of tables and figures as objective 1 excluding Table 1.4 (11 tables + 5 figures)
Objective 15	Postpartum period (≤ 36 vs. > 36 weeks) and uterine perforation		Same set of tables and figures as objective 1 excluding Table 1.4 (11 tables + 5 figures)
Objective 16	IUD type and uterine perforation		Same set of tables and figures as objective 1 excluding Table 1.4 Only pooled results will be reported (3 tables + 1 figures)
Objective 17	Postpartum period (≤ 36 vs. > 36 weeks) and uterine perforation		
Table 17.1	Crude and adjusted incidence rate ratios and differences for uterine perforation at 1 year and 5 years of follow-up	Layout 10	Pooled and by site (1 table)
Objective 18[c]	Subsequent insertions for uterine perforation (subsequent insertions)		Same set of tables and figures as objectives 1, 2, 14, 15, 16 excluding Tables 1.4 and 2.4 (47tables + 21 figures)
Objective 19[d]	Menorrhagia and uterine perforation		Same set of tables and figures as objective 1 excluding Table 1.4 (11 tables + 5 figures)

Table/Figure Number	Content	Table Layout[a]	Note
Objectives 20 through 27[c,d]	Comparative analysis for IUD expulsion		Same set of tables and figures as objectives 1, 2, 14-19, excluding Tables 1.4 and 2.4 (106 tables + 47 figures)
Objective 28	Effect modification		
Table 28.1	Effect modification of breastfeeding status and postpartum status on uterine perforation	Layout 11	Pooled (1 table)
Objective 29	Effect modification		
Table 29.1	Effect modification of IUD type on breast feeding status and uterine perforation	Layout 12.1	Pooled (1 table)
Objective 30	Effect modification		
Table 30.1	Effect modification of IUD type on breast feeding status and IUD expulsion	Layout 12.1	Pooled (1 table)
Objective 31	Effect modification		
Table 31.1	Effect modification of IUD type on postpartum status and uterine perforation	Layout 12.2	Pooled (1 table)
Objective 32	Effect modification		
Table 32.1	Effect modification of IUD type on postpartum status and IUD expulsion	Layout 12.2	Pooled (1 table)
Development of propensity score models			
Tables 33.1.1 through 33.1.2	Assessing relationship with outcome: crude HR for baseline covariates	Layout 4	Pooled (2 tables)
Tables 33.2.1 through 33.2.9	Assessing confounding effect: HR adjusted for one covariate	Layout 5	Pooled (9 tables)
Tables 33.3.1 through 33.3.15	Propensity score model	Layout 6	Pooled (15 tables)
Figure 33.1.1 through 33.1.15	Histograms with kernel smoothing of propensity scores by exposure		Pooled (15 figures)
Impact of transition from ICD-9-CM to ICD-10-CM			
Tables 34.1	Percentage of uterine perforation or IUD expulsion prior to and after implementation of ICD-10-CM coding	Layout 13	Pooled and by site (1 table)

HR = hazard ratio; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ICD-10,CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; IUD = intrauterine device.

Note: In the report, analysis tables related to IUD type will report only the results across all sites, not by site. However, by-site analyses may be conducted for internal purposes and will not be shared with Bayer.

[a] Table layouts are included in Section 9.5.

[b] If breastfeeding status, postpartum timing, or IUD type are not included within a propensity score (as independent variables when not the dependent variable), then a separate Cox model also including these variables as covariates will be developed. If this occurs additional tables will be added using Table Layout 7.

[c] The analyses by site for objectives 18, and 26 will be done only for sites with more than 20,000 subsequent IUD insertions.

[d] The analyses for objectives 19 and 27 will be done only if more than 20,000 IUD users with an indication of menorrhagia can be included in the analysis.

9.5 Analysis Table Layouts

This section includes planned table layouts for the analysis. In the title section of the table layouts, words in yellow highlight are subject to change depending on specific analysis.

List of Analysis Table Layouts

Table Layout 13. Percentage of Uterine Perforation or IUD Expulsion Before and After Implementation of ICD-10-CM Coding; Analysis Set: Complete Study Population, First IUD Insertion; Database: Pooled and by Site

Table Layout 1. Baseline Characteristics Overall, by Uterine Perforation, and by IUD Expulsion;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

Characteristic	Overall	Uterine Perforation			IUD Expulsion		
	(N = XXX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Person-years at risk	XXX,XXX.X	XXX,XXX.X	XXX,XXX.X	XXX,XXX.X	XXX,XXX.X	XXX,XXX.X	XXX,XXX.X
Demographic characteristics							
Age, in years							
Category[a], n (%)							
Category 1	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Category 2	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Category 3	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Race/ethnicity, n (%)							
Asian/Pacific Islander	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Hispanic black	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Hispanic other	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Hispanic white	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Multiple	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Non-Hispanic white	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Non-Hispanic black	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Other	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Unknown	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Recent smoker[c], n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)

Characteristic	Overall (N = XXX,XXX)	Uterine Perforation			IUD Expulsion		
		Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Duration of look-back period, in months							
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Calendar year of index date, n (%)							
2001 - 20XX	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
…	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
20XX - 2018	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Calendar month of index date, n (%)							
January	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
…	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
December	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Clinical characteristics							
BMI, in kg/m^2							
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Dysmenorrhea diagnosis, n (%)							
Recent, on or within1 year before the index date only	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Past, more than 1 year before the index date only	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Records in recent and past periods	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
No record of diagnosis	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)

Characteristic	Overall (N = XXX,XXX)	Uterine Perforation			IUD Expulsion		
		Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Fibroids, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Parity							
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Cesarean delivery before the index date[d], n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Cesarean delivery for most recent delivery before the index date[d], n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Procedure-related characteristics							
Concomitant gynecological procedure, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Abortion procedure, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Aspiration and curettage, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Dilation and curettage, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Excision/biopsy of cervix or uterus, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Ablation, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Colposcopy and other cervical procedures, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Hysteroscopy procedure, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Laminaria procedure, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Laparoscopy, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Lysis adhesions, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Myomectomy, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Nerve procedure, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Salpingectomy/ oophorectomy, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)

Characteristic	Overall (N = XXX,XXX)	Uterine Perforation			IUD Expulsion		
		Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Insertion-related characteristics							
IUD insertion count							
1	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
2	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
3	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
continue to other categories	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Any difficult insertion, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Cervical dilation, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Ultrasound guidance, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Paracervical block, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Difficult insertion noted, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Use of misoprostol, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Provider-related characteristics[e]							
Number of IUD insertions performed							
< 50 insertions, n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Annualized number of insertions in previous year							
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Characteristic	Overall (N = XXX,XXX)	Uterine Perforation			IUD Expulsion		
		Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Length of employment in previous year, in days							
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Other parameters							
Live birth within the past 52 weeks (most recent delivery), n (%)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Continuous enrollment [f] (months)							
N	xxx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx	xx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Continuous enrollment on or before index date [f] (months)							
N	xxx,xxx	xx,xxx	xx,xxx	xxx,xxx	xx,xxx	xx,xxx	xxx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Continuous enrollment on or after index date [f] (months)							
N	xxx,xxx	xx,xxx	xx,xxx	xxx,xxx	xx,xxx	xx,xxx	xxx,xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
Min, max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Characteristic	Overall (N = XXX,XXX)	Uterine Perforation			IUD Expulsion		
		Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Site (data source)							
KPNC	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
KPSC	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
KPWA	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
RI	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Study exposure groups							
Breastfeeding status							
Yes	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
No	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Undetermined	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Postpartum status							
6 weeks or less	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
> 6 to ≤ 14 weeks	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
> 14 to ≤ 52 weeks	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
> 52 weeks or no delivery	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
≤ 14 weeks	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
> 14 weeks or no delivery	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
≤ 36 weeks	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
> 36 weeks or no delivery	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
IUD type							
LNG-IUD	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Copper IUD	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Unknown	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)

Characteristic	Overall (N = XXX,XXX)	Uterine Perforation			IUD Expulsion		
		Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)	Yes (N = XX,XXX)	No (N = XX,XXX)	Undetermined (N = XX,XXX)
Menorrhagia in the past year	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Diagnosis recorded only within 1 year	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Diagnosis recorded only before 1 year	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Diagnosis recorded both within and before 1 year	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
No diagnosis	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)

BMI = body mass index; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system; Q1 = lower quartile (i.e., 25th percentile); Q3 = upper quartile (i.e., 75th percentile); SD = standard deviation.

[a] Age categories were based on tertiles of the distribution.

[b] Available only in the KPSC database.

[c] Available in the KPSC database; partially available in the KPWA and RI databases.

[d] Cesarean delivery summarized only among women who had at least one delivery before the index date.

[e] Available in the KPNC, KPSC, and KPWA databases.

[f] Continuous enrollment is not a baseline covariate. It is included only for summary purposes.

Generated using xxxx.sas on xxxxxxx.

Programming note 1: For tables of first insertions, N is number of patients. For tables of subsequent insertions, N is number of insertions.
Programming note 2: For variables with missing data, number of missing data will be reported.
Programming note 3: IUD insertion count will not be shown for tables using only first insertions because it will be 1 for every patient.
Programming note 4: Site (data source) will be shown only for the pooled table, not for the site tables.
Programming note 5: Results by IUD type will be presented only for the pooled table, not by site.

Table Layout 2.1. Hazard Ratios of Uterine Perforation for Breastfeeding Status;
Analysis Set: Breastfeeding Status Available, First IUD Insertion;
Database: Pooled and by Site

Site	Breastfeeding Status	Events	Insertions	Person-years	Crude HR (95% CI)	Adjusted	
						HR (95% CI)	*P* Value
Pooled	Yes	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	No	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
KPNC	Yes	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	No	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
KPSC	Yes	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	No	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
KPWA	Yes	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	No	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
RI	Yes	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	No	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Note: Crude HRs were estimated from five Cox models using pooled data or within each site. Adjusted HRs were estimated from two Cox models weighted using overlap weights. The adjusted HRs by site were estimated from the Cox model including exposure, site, and site-by-exposure interaction (type 3 group test for interaction: *P* = 0.xxxx); the overall adjusted HR (reported only if the interaction is not significant) was estimated from the Cox model including exposure and site.

Note: The *P* value is from the Cox model for the test of the null hypothesis that the adjusted HR equals one.

Note: The proportional hazards assumption was tested using the global correlation test based on Schoenfeld residuals with the pooled data (*P* = 0.xxxx).

Generated using xxxx.sas on xxxxxxx.

Programming note 1: The pooled adjusted HR and related footnote will be shown only if the interaction term is not statistically significant (*P* > 0.05).

Programming note 2: If the proportional hazards assumption is violated, time-dependent exposure covariates will be included in Cox models. The table above will be expanded to include separate hazard ratios for the effect of exposure over time.

Programming note 3: For tables that include results by IUD type, only pooled results will be presented, not by site.

Programming note 4: For all tables and notes with *P* values, note that the P in "*P* value" is capitalized and in italics, and a space (not a hyphen) follows the *P*.

Table Layout 2.2. Hazard Ratios of Uterine Perforation for Postpartum Status;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled and by Site

Site	Postpartum Status	Events	Insertions	Person-years	Crude HR (95% CI)	Adjusted[a]	
						HR (95% CI)	*P* Value
Pooled	6 weeks or less	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 6 to ≤ 14 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 14 to ≤ 52 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 52 weeks or no delivery	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
KPNC	6 weeks or less	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 6 to ≤ 14 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 14 to ≤ 52 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 52 weeks or no delivery	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
KPSC	6 weeks or less	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 6 to ≤ 14 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 14 to ≤ 52 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 52 weeks or no delivery	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-
KPWA	6 weeks or less	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 6 to ≤ 14 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 14 to ≤ 52 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 52 weeks or no delivery	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-

Site	Postpartum Status	Events	Insertions	Person-years	Crude HR (95% CI)	Adjusted[a]	
						HR (95% CI)	*P* Value
RI	6 or less weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 6 to ≤ 14 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 14 to ≤ 52 weeks	xx	xx	xxx,xxx.x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	0.XXXX
	> 52 weeks or no delivery	xx	xx	xxx,xxx.x	1.00 (Reference)	1.00 (Reference)	-

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Note: Crude HRs were estimated from five Cox models using pooled data or within each site. Adjusted HRs were estimated from two Cox models weighted using overlap weights: The adjusted HRs by site were estimated from the Cox model including exposure, site, and site-by-exposure interaction (type 3 group test for interaction: *P* = 0.xxxx); the pooled adjusted HR (reported only if the interaction is not significant) was estimated from the Cox model including exposure and site.

Note: The *P* value is from the Cox model for the test of the null hypothesis that the adjusted HR equals one.

Note: The proportional hazards assumption was tested using the global correlation test based on Schoenfeld residuals with the pooled data (*P* = 0.xxxx).

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Programming note 1: The pooled adjusted HR and related footnote will be shown only if the interaction term is not significant (*P* > 0.05).

Programming note 2: For tables that include results by IUD type, only pooled results will be presented, not by site.

Table Layout 3.1. Baseline Characteristics and Absolute Standardized Differences of Baseline Characteristics for Breastfeeding Status;
Analysis Set: Breastfeeding Status Available, First IUD Insertion;
Database: Pooled

	Breastfeeding Status		
Characteristic	**Yes (N = XX,XXX)**	**No (N = XX,XXX)**	**Absolute Standardized Difference**
Age, in years			
Category, n (%)			
Category 1	xx (x.x)	xx (x.x)	xx.x
Category 2	xx (x.x)	xx (x.x)	xx.x
Category 3	xx (x.x)	xx (x.x)	xx.x
N	xx	xx	
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	
Min, max	xx, xx	xx, xx	
Continue for other variables under consideration			

IUD = intrauterine device; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

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Programming note 1: For tables that include results by IUD type, only pooled results will be presented, not by site.

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Table Layout 3.2. Baseline Characteristics and Absolute Standardized Differences of Baseline Characteristics for Postpartum Status;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

	Postpartum Status				Absolute Standardized Difference (vs. > 52 Weeks or No Delivery)			
Characteristic	**6 Weeks or less (N = XX)**	**> 6 to ≤ 14 Weeks (N = XX)**	**> 14 to ≤ 52 Weeks (N = XX)**	**> 52 Weeks or No Delivery (N = XX)**	**6 Weeks or Less**	**> 6 to ≤ 14 Weeks**	**> 14 to ≤ 52 Weeks**	**Maximum Difference**
Age, in years								
Category, n (%)								
Category 1	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx.x	xx.x	xx.x	xx.x
Category 2	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx.x	xx.x	xx.x	xx.x
Category 3	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx.x	xx.x	xx.x	xx.x
N	xx	xx	xx	xx				
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x	xx.x	xx.x	xx.x
Median [Q1, Q3]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]				
Min, max	xx, xx	xx, xx	xx, xx	xx, xx				
Continue for other variables under consideration								

IUD = intrauterine device; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

[a] Age categories were based on tertiles of the distribution.

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Table Layout 4. Crude Hazard Ratio of Uterine Perforation for Baseline Characteristics;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

Characteristic	Crude HR (95% CI)
Age, in years	
Category 1	x.xx (x.xx, x.xx)
Category 2	x.xx (x.xx, x.xx)
Category 3	1.00 (Reference)
Continuous age (scale)	x.xx (x.xx, x.xx)
Continue for other variables under consideration	

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Note: HRs were estimated from separate Cox models, each of which included only one baseline covariate in the model.

Generated using xxxx.sas on xxxxxxx.

Programming note 1: The list of variables maybe adjusted after reviewing the data. This may include rescaling, collapsing levels, or categorizing variables.

Table Layout 5. Hazard Ratio of Uterine Perforation for Postpartum Status and Percent Change After Adjustment for a Single Covariate;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

Adjustment Covariate	Postpartum Status	HR (95% CI)	HR % Change After Adjustment	Covariate Included in Final Propensity Score Model
No adjustment	6 weeks or less	x.xx (x.xx, x.xx)	-	
	> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)	-	
	> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)	-	
	> 52 weeks or no delivery	1.00 (Reference)		
Categorical age	6 weeks or less	x.xx (x.xx, x.xx)	xx.x	*Yes or No*
	> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)	xx.x	
	> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)	xx.x	
	> 52 weeks or no delivery	1.00 (Reference)		
Continuous age	6 weeks or less	x.xx (x.xx, x.xx)	xx.x	*Yes or No*
	> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)	xx.x	
	> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)	xx.x	
	> 52 weeks or no delivery	1.00 (Reference)		
Continue for other variables under consideration				

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Generated using xxxx.sas on xxxxxxx.

Programming note 1: The list of variables maybe adjusted after reviewing the data. This may include rescaling, collapsing levels, or categorizing variables.

Table Layout 6. Propensity Score Model for Breastfeeding With Outcome Model for Uterine Perforation;
Analysis Set: Breastfeeding Status Available, First IUD Insertion;
Database: Pooled

Parameter	Coefficient (SE)	*P* Value
Intercept	xx	0.xxxx
Covariate 1		0.xxxx
Category 1	xx	-
Category 2	xx	-
….	xx	-
Category reference	Reference	
Covariate 2 (scale)	xx	0.xxxx
…		

IUD = intrauterine device; SE = standard error.

Note: Postpartum timing and IUD type were included in the propensity score model. Other covariates were included in the propensity score model if the crude hazard ratio was greater than 1.11 or less than 0.90. Additional confounders were selected for inclusion within propensity score models if at least a 10% change in the hazard ratio of the exposure-outcome relationship occurs when adjusting for that variable.

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Table Layout 7. Adjusted Hazard Ratio of Uterine Perforation for Postpartum Status From Cox Model With Baseline Covariates (Sensitivity Analysis);
Analysis Set: Complete Study Population, First IUD Insertion

	Adjusted HR (95% CI)
KPNC	
6 weeks or less	x.xx (x.xx, x.xx)
> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)
> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)
> 52 weeks or no delivery	1.00 (Reference)
KPSC	
6 weeks or less	x.xx (x.xx, x.xx)
> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)
> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)
> 52 weeks or no delivery	1.00 (Reference)
KPWA	
6 weeks or less	x.xx (x.xx, x.xx)
> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)
> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)
> 52 weeks or no delivery	1.00 (Reference)
RI	
6 weeks or less	x.xx (x.xx, x.xx)
> 6 to ≤ 14 weeks	x.xx (x.xx, x.xx)
> 14 to ≤ 52 weeks	x.xx (x.xx, x.xx)
> 52 weeks or no delivery	1.00 (Reference)
Covariate 1	
Category 1	x.xx (x.xx, x.xx)
Category 2	1.00 (Reference)
Covariate 2 (scale)	x.xx (x.xx, x.xx)
Covariate 3	
Category 1	x.xx (x.xx, x.xx)
Category 2	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Note: The adjusted HR was estimated from the Cox model including exposure, site, site-by-exposure interaction (type 3 group test for interaction: *P* = 0.xxxx), and listed baseline covariates.

Generated using xxxx.sas on xxxxxxx.

Programming note 1: The list of variables will be adjusted after reviewing the data.

Table Layout 8. Crude Incidence Rates and Cumulative Incidence for Uterine Perforation;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

Groups	Insertions	Person-years	Events	Crude Incidence Rate[a] (95% CI)	1-Year Crude Cumulative Incidence[b] (95% CI)	5-Year Crude Cumulative Incidence[b] (95% CI)
Analysis set						
Complete study population	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
Breastfeeding status available	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
IUD type available	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
Postpartum status						
6 weeks or less	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
> 6 to ≤ 14 weeks	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
> 14 to ≤ 52 weeks	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
> 52 weeks or no delivery	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
≤ 14 weeks	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
> 14 weeks or no delivery	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
≤ 36 weeks	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
> 36 weeks or no delivery	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
Breastfeeding status						
Yes	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
No	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
Undetermined	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
IUD type						
LNG-IUD	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
Copper IUD	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
Unknown	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)

Groups	Insertions	Person-years	Events	Crude Incidence Rate[a] (95% CI)	1-Year Crude Cumulative Incidence[b] (95% CI)	5-Year Crude Cumulative Incidence[b] (95% CI)
Menorrhagia						
Yes	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)
No	xxx	xxx.x	xx	x.xx (x.xx, x.xx)	xx.x% (xx.x%, xx.x%)	xx.x% (xx.x%, xx.x%)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

[a] Incidence rates are expressed per 1,000 person-years.

[b] Crude estimate of cumulative incidence, defined as the number of incident outcomes occurring during a specific time period out of the number of IUD insertions during the same time period, were estimated using the Kaplan-Meier method.

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Programming note 1: Summary for IUD type available set and ty IUD type will only be presented in the pooled table, not by site.

Table Layout 9. Prevalence of Difficult IUD Insertion by Exposure Group and Outcome;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

Exposure or Outcome Group		N	Cervical Dilation n (%)	Ultrasound Guidance n (%)	Paracervical Block n (%)	Provider Note n (%)	Use of Misoprostol n (%)	Any n (%)
All patients		xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Breastfeeding	Yes	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Undetermined	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Postpartum status	6 weeks or less	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 6 to ≤ 14 weeks	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 14 to ≤ 52 weeks	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 52 weeks or no delivery	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IUD type	LNG-IUD	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Copper IUD	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Undetermined	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Menorrhagia	Yes	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IUD expulsion	Yes	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Uterine perforation	Yes	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

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Programming note 1: Results by IUD type will be presented only for the pooled table, not by site.

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Table Layout 10. Crude and Adjusted[a] Incidence Rate Ratios and Incidence Rate Differences[b] for Uterine Perforation at 1 Year and 5 Years of Follow-up, Comparing Women With a First Observed IUD Insertion ≤ 36 Weeks Postpartum Versus > 36 Weeks Postpartum;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled and by Site

Site		1 Year of Follow-Up		5 Years of Follow-Up	
		≤ 36 Weeks	> 36 Weeks or No Delivery	≤ 36 Weeks	> 36 Weeks or No Delivery
Pooled	Events	xx	xx	xx	xx
	Person-years	xx.x	xx.x	xx.x	xx.x
	Incidence rate	x.xx	x.xx	x.xx	x.xx
	Crude IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Crude IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
KPNC	Events	xx	xx	xx	xx
	Person-years	xx.x	xx.x	xx.x	xx.x
	Incidence rate	x.xx	x.xx	x.xx	x.xx
	Crude IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Crude IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
KPSC	Events	xx	xx	xx	xx
	Person-years	xx.x	xx.x	xx.x	xx.x
	Incidence rate	x.xx	x.xx	x.xx	x.xx
	Crude IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Crude IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference

Site		1 Year of Follow-Up		5 Years of Follow-Up	
		≤ 36 Weeks	> 36 Weeks or No Delivery	≤ 36 Weeks	> 36 Weeks or No Delivery
KPWA	Events	xx	xx	xx	xx
	Person-years	xx.x	xx.x	xx.x	xx.x
	Incidence rate	x.xx	x.xx	x.xx	x.xx
	Crude IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Crude IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
RI	Events	xx	xx	xx	xx
	Person-years	xx.x	xx.x	xx.x	xx.x
	Incidence rate	x.xx	x.xx	x.xx	x.xx
	Crude IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRR (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Crude IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference
	Adjusted IRD (95% CI)	x.xx (x.xx, x.xx)	Reference	x.xx (x.xx, x.xx)	Reference

CI = confidence interval; IRD = incidence rate difference; IRR = incidence rate ratio; IUD = intrauterine device.

[a] Adjusted via weighted estimation of the rates using overlap weights derived from the same propensity score models as those developed for adjustment of the hazard ratios.

[b] Incidence rates and incidence rate differences are expressed per 1,000 person-years.

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Programming note 1: Generate tables x.1 for uterine perforation and x.2 for IUD expulsion.

Table Layout 11. Effect Modification of Breastfeeding Status and Postpartum Status on Uterine Perforation;
Analysis Set: Breastfeeding Status Available, First IUD Insertion;
Database: Pooled

	Postpartum Status	Breastfeeding Status		HR (95% CI) Breastfeeding (Yes vs. No)
		Yes	No	
Number of events/ insertions	14 weeks or less	xx/xx	xx/xx	
	> 14 weeks or no delivery	xx/xx	xx/xx	
Crude HR	14 weeks or less	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 14 weeks or no delivery	x.xx (x.xx, x.xx)	1.00 (Reference)	x.xx (x.xx, x.xx)
	HR (95% CI) 14 weeks or less vs. > 14 weeks or no delivery	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Adjusted HR	14 weeks or less	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 14 weeks or no delivery	x.xx (x.xx, x.xx)	1.00 (Reference)	x.xx (x.xx, x.xx)
	HR (95% CI) 14 weeks or less vs. > 14 weeks or no delivery	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
	Type 3 group test for interaction of breastfeeding status and postpartum status			*P* = 0.xxxx

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Note: Crude HRs were estimated from the Cox model including breastfeeding status, postpartum status, and their interaction. Adjusted HRs were estimated from the Cox models including breastfeeding status, postpartum status, and their interaction, weighted using overlap weights.

Generated using xxxx.sas on xxxxxxx.

Table Layout 12.1. Effect Modification of IUD Type on Breastfeeding Status and Uterine Perforation;
Analysis Set: Breastfeeding Status Available, First IUD Insertion;
Database: Pooled

Modifier IUD Type	Exposure Breastfeeding Status	Number of Events	Number of Insertions	Crude HR (95% CI)	Adjusted HR (95% CI)
LNG-IUD	Yes	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	No	xx	xx	1.00 (Reference)	1.00 (Reference)
Copper IUD	Yes	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	No	xx	xx	1.00 (Reference)	1.00 (Reference)
Type 3 group test for interaction with breastfeeding status					*P* = 0.xxxx

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

Note: Crude HRs were estimated from the Cox model including breastfeeding status, IUD type, and their interaction. Adjusted HRs were estimated from the Cox models including breastfeeding status, IDU type, and their interaction, weighted using overlap weights.

Generated using xxxx.sas on xxxxxxx.

Table Layout 12.2. Effect Modification of IUD Type on Postpartum Status and Uterine Perforation;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled

Modifier IUD Type	Exposure Postpartum Status	Number of Events	Number of Insertions	Crude HR (95% CI)	Adjusted HR (95% CI)
LNG-IUD	6 weeks or less	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 6 to ≤ 14 weeks	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 14 to ≤ 52 weeks	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 52 weeks or no delivery	xx	xx	1.00 (Reference)	1.00 (Reference)
Copper IUD	6 weeks or less	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 6 to ≤ 14 weeks	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 14 to ≤ 52 weeks	xx	xx	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	> 52 weeks or no delivery	xx	xx	1.00 (Reference)	1.00 (Reference)
Type 3 group test for interaction with postpartum status					*P* = 0.xxxx

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

Note: Crude HRs were estimated from the Cox model including postpartum status, IUD type, and their interaction. Adjusted HRs were estimated from the Cox models including postpartum status, IDU type, and their interaction, weighted using overlap weights.

Generated using xxxx.sas on xxxxxxx.

Table Layout 13. Percentage of Uterine Perforation or IUD Expulsion Before and After Implementation of ICD-10-CM Coding;
Analysis Set: Complete Study Population, First IUD Insertion;
Database: Pooled and by Site

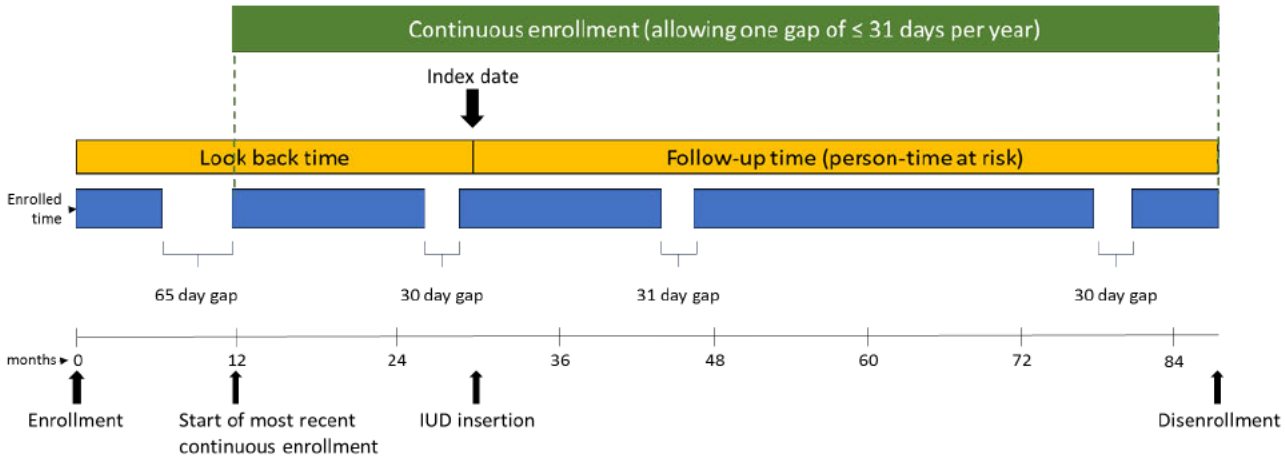
	1-Year Before			1-Year After		
Site	**Patients N**	**Uterine Perforation n (%)**	**IUD Expulsion n (%)**	**Patients N**	**Uterine Perforation n (%)**	**IUD Expulsion n (%)**
Pooled	xx	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)
KPNC	xx	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)
KPSC	xx	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)
KPWA	xx	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)
RI	xx	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)

IUD = intrauterine device.
Generated using xxxx.sas on xxxxxxx.

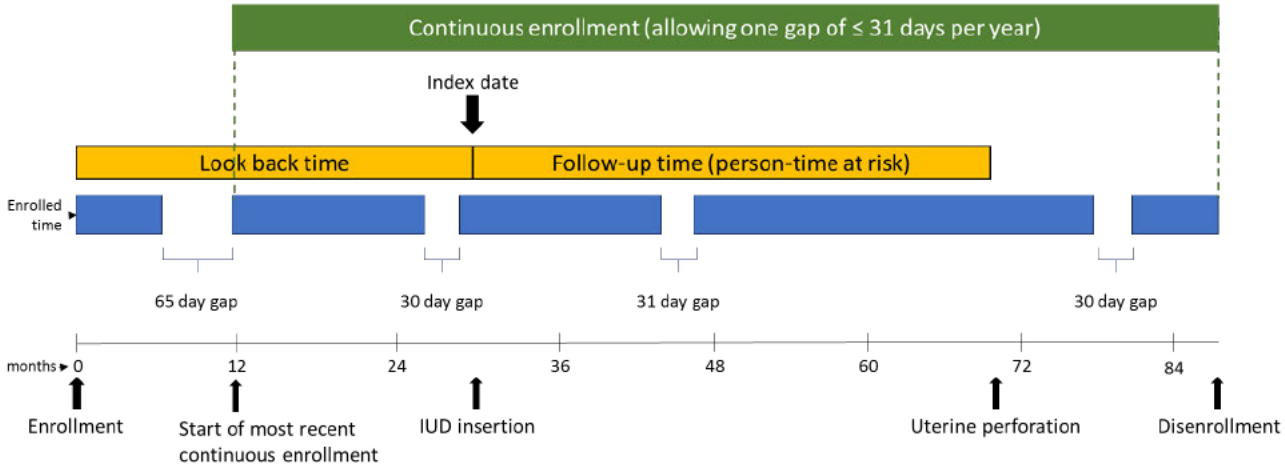
Programming note 1: Research partners will provide counts for this table.

9.6 Illustration of Continuous Enrollment and Look-Back Time for Kaiser Permanente Sites (KPNC, KPSC, and KPWA)

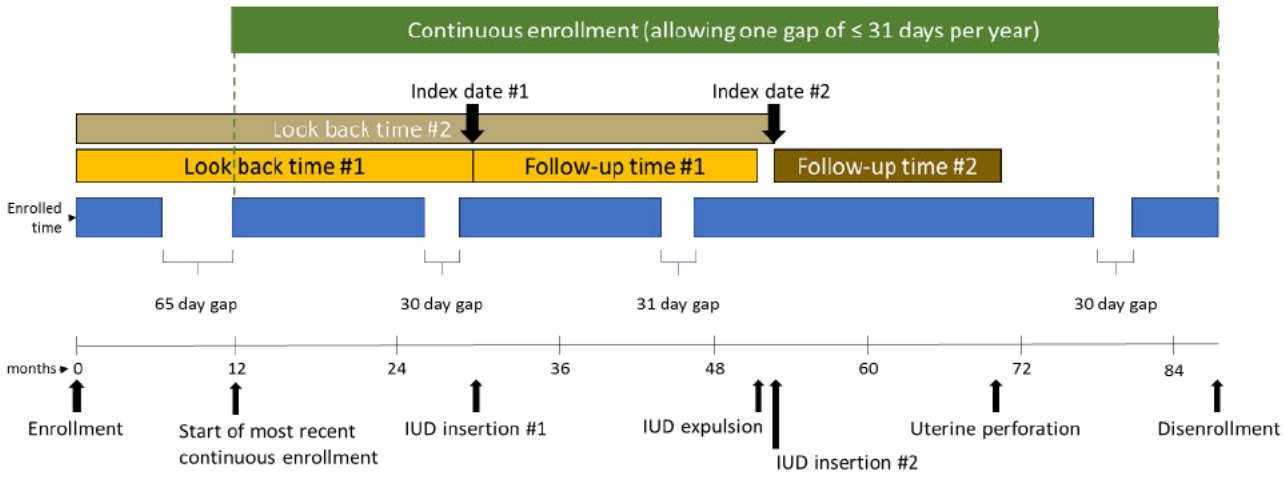
Scenario 1. One IUD Insertion With No Uterine Perforation or IUD Expulsion



Scenario 2. One IUD Insertion With One Uterine Perforation



Scenario 3. Two IUD Insertions, With One IUD Expulsion and One Perforation



Note: if the beginning date of the study period is within the continuous enrollment period (illustrated in the above figures), the beginning date of the study period will be used as the beginning of continuous enrollment. Similarly, if the end date of the study period is within the continuous enrollment period, the end date of the study period will be used as the end of the continuous enrollment.