NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A Comparative Observational Study Evaluating the Incidence Rate of Endometrial Cancer in Women aged 50 Years and Over Who Use Low-dose Vaginal Estrogen Unopposed by a Progestogen: A Post-authorization Safety Study in the United States and Sweden
Protocol number	B2811020
Protocol version identifier	Final Version (Original Protocol) 7.0
Date	04 January 2022
EU Post Authorization Study (PAS) register number	To be registered after protocol approval
Active substances	1) Conjugated Estrogens Vaginal (Premarin)® 2) Estradiol Vaginal (Estring)® ATC codes: G03CA03, G03CA57.
Medicinal products	1) Premarin® Vaginal Cream (0.625 mg/gram). 2) Estring® 2 mg (vaginal ring).
Research question and objectives	Research Question: What is the incidence rate (IR) of endometrial cancer in postmenopausal women with a uterus who use low-dose vaginal estrogen (LDVE) unopposed by a progestogen compared to non-users and compared to users of estrogen-progestogen combination hormone therapy (E+P HT)? <u>Primary Objectives:</u> 1. To estimate and compare the IR of endometrial cancer in postmenopausal women aged ≥50 years, with a uterus, regardless of prior use of hormone therapy (defined as any estrogen, progestin, E+P HT use or other opposed estrogen hormone therapy), in the following groups:

	a. New users of low-dose vaginal estrogen (LDVE) versus non-users of vaginal estrogen; b. New users of moderate-dose vaginal estrogen (MDVE) versus non-users of vaginal estrogen; c. New users of high-dose Premarin Vaginal Cream (HDVC) versus non-users of vaginal estrogen (HIRD only, as Premarin VC is not marketed in Sweden); 2. To estimate and compare the IR of endometrial cancer separately among the LDVE, MDVE, and HDVC new users (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by prior use of hormone therapy including unopposed estrogen, unopposed progestin, single-entity or combination progestin-opposed estrogen hormone therapy, other opposed estrogen hormone therapy or no prior hormone use. 3. To estimate and compare the IR of endometrial cancer separately among new users of LDVE, MDVE, and HDVC (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by duration of use, formulation, active ingredient, number of dispensings, and number of dispensings per formulation. Secondary Objective: 1. To estimate and compare the IR of endometrial cancer among women aged ≥50 years, with a uterus, and without prior hormone therapy use, in the following groups: a. LDVE new users versus E+P HT new users of hormone therapy; b. MDVE new users versus E+P HT new users of hormone therapy;

	c. HDVC new users versus E+P HT new users of hormone therapy (HIRD only).
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADIN	Action, Decision, Issue, Notification
AE	adverse event
AEM	adverse event monitoring
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CFR	Code of Federal Register
CI	confidence interval
CPT	Current Procedural Terminology
CRF	case report form
E+P HT	Estrogen-progestogen combination hormone therapy
EAC	Endpoint Adjudication Committee
EC	endometrial cancer
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPI	Generic Product Identifier
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCPCS	Healthcare Common Procedure Coding System
HDVC	high-dose Premarin Vaginal Cream
HIPAA	Health Insurance Portability and Accountability Act
HIRD℠	HealthCore Integrated Research Database℠
HR	hazard ratio
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification

Abbreviation	Definition
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-SE	International Classification of Diseases, Tenth Revision, Sweden
IR	incidence rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ITT	intent-to-treat
LDVE	low-dose vaginal estrogen
MAH	Marketing Authorization Holder
MDVE	moderate-dose vaginal estrogen
NIS	non-interventional study
NPR	National Patient Register
OB/GYN	Obstetrics and gynecology
PHI	protected health information
PMR	post-marketing requirement
PS	propensity score
PAS	post-authorization studies
PASS	post-authorization safety studies
PPV	positive predictive value
QC	quality control
SAP	statistical analysis plan
SAS	Statistical Analysis System
SCR	Swedish Cancer Register
SE	Sweden
SOP	standard operating procedure
SPDR	Swedish Prescribed Drug Register
TPR	Total Population Register

Abbreviation	Definition
US	United States
VC	Vaginal Cream
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: A Comparative Observational Study Evaluating the Incidence Rate of Endometrial Cancer in Women Aged 50 Years and Over Who Use Low-dose Vaginal Estrogen Unopposed by a Progestogen: A Post-authorization Safety Study in the United States and Sweden.

Protocol Version: 7.0; **Date of Protocol**: 04 January 2022

Name and Affiliation of Main Authors: Sampada Gandhi, MD, PhD, Pfizer, Inc; Kimberly Daniels, PhD, MS, HealthCore, Inc.

Rationale and Background: The United States (US) Food and Drug Administration (FDA) has issued a post-marketing requirement (PMR) to each Marketing Authorization Holder (MAH) of low-dose vaginal estrogen (LDVE) to conduct an observational study evaluating the rate of endometrial cancer in postmenopausal women with a uterus who use LDVE unopposed by a progestogen. While current clinical guidelines indicate that vaginal estrogen should be administered at the lowest effective doses, they do not include recommendations for use of progestogens to oppose vaginal estrogen use.[1-3] However, the risk of endometrial cancer is higher among women who use unopposed oral estrogen in a wide range of doses and durations,[4] and LDVE use results in systemic absorption, though theoretically at lower levels than oral estrogens.[2] Therefore, it is important to assess the rate of endometrial cancer with LDVE use without concomitant use of progestogen therapy. This protocol describes a non-interventional study (NIS) that will be conducted in the US and Sweden to fulfill the PMR commitment to the FDA (Reference IDs: 4269544; 4269546). Pfizer is the MAH for Estring® 2 mg (vaginal ring, 7.5 mcg/24 hours) and Premarin® Vaginal Cream 0.625 mg/gram (Premarin VC) and received a PMR notification for each product. Premarin Vaginal Cream (VC) is indicated for both low-dose and high-dose treatment regimens. In order to address the safety concerns for Premarin VC set forth in the PMRs, it is included in this study, with high-dose regimens evaluated as a separate exposure group. Analyses including Premarin VC will only be conducted in the HealthCore Integrated Research Database℠ (HIRD) as Premarin VC is not marketed in Sweden

Research Question and Objectives: What is the incidence rate (IR) of endometrial cancer in postmenopausal women with a uterus who use LDVE unopposed by a progestogen compared to non-users and compared to users of estrogen-progestogen combination hormone therapy (E+P HT)?

Primary Objectives:

1. To estimate and compare the IR of endometrial cancer in postmenopausal women aged ≥50 years, with a uterus, regardless of prior use of hormone therapy (defined as any estrogen, progestin, E+P HT use or other opposed estrogen hormone therapy) in the following groups:

a. New users of low-dose vaginal estrogen (LDVE) versus non-users of vaginal estrogen.

b. New users of moderate-dose vaginal estrogen (MDVE) versus non-users of vaginal estrogen.

c. New users of high-dose Premarin Vaginal Cream (HDVC) versus non-users of vaginal estrogen (HIRD only, as Premarin VC is not marketed in Sweden);

2. To estimate and compare the IR of endometrial cancer separately among the LDVE, MDVE, and HDVC new users (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by prior use of hormone therapy including unopposed estrogen, unopposed progestin, single-entity or combination progestin-opposed estrogen hormone therapy, other opposed estrogen hormone therapy, or no prior hormone use.

3. To estimate and compare the IR of endometrial cancer separately among new users of LDVE, MDVE, and HDVC (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by duration of use, formulation, active ingredient, number of dispensings, and number of dispensings per formulation.

Secondary Objective:

1. To estimate and compare the IR of endometrial cancer among women aged ≥50 years, with a uterus, and without prior hormone therapy use, in the following groups:

    a. LDVE new users versus E+P HT new users of hormone therapy;

    b. MDVE new users versus E+P HT new users of hormone therapy;

    c. HDVC new users versus E+P HT new users of hormone therapy (HIRD only).

Study Design: This study is a retrospective cohort study using a longitudinal US healthcare claims data source (HealthCore Integrated Research Database℠ [HIRD]) and longitudinal data collected from five Swedish National Registers. The three exposed treatment groups are new users of LDVE, MDVE, and HDVC (HIRD only), regardless of prior use of hormone therapy. The two comparator groups are as follows: (1) for the purpose of the primary objective, non-users of vaginal estrogen who are women over age 50 with at least one gynecological visit without prior or current use of vaginal estrogen at the time of the gynecological visit, but regardless of their prior use of hormone therapy will be included, and (2) for the purpose of the secondary objective, E+P HT new users with no prior use of hormone therapy will be included.

Study Population: The study includes women aged ≥50 years with an intact uterus and no prior use of vaginal estrogens. The exposed group of LDVE will include new users who had ≥1 dispensing of LDVE (daily doses ≤10 mcg/day estradiol or ≤0.3 mg/day conjugated estrogen) unopposed by a progestogen, regardless of prior use of other hormone therapy between 01 January 2007 and 31 December 2020 (or most recent available date) in the HIRD, and between

01 July 2007 to 31 December 2019 (or most recent available date) in the Swedish National Registers (the exposure ascertainment period). Similarly, two additional exposure groups will be created for MDVE (daily doses >10 mcg – 25 mcg/day estradiol or >0.3 mg – 0.45 mg/day conjugated estrogen) and, in the HIRD only, HDVC (daily doses >0.45 mg/day conjugated estrogen). These two additional groups will also include women with ≥1 dispensing of MDVE or HDVC, respectively, regardless of prior use of hormone therapy. The difference in study periods between the HIRD and Swedish databases is due to the difference in lag time for data availability between the two data sources. The comparator groups are: (1) women with ⩾1 gynecological visit on or after age 50 with no prior use of vaginal estrogen at the time of their gynecological visit (i.e., non-users) and (2) new users of E+P HT with no prior use of hormone therapy. Women with less than 12 months of continuous health plan enrollment in the HIRD or less than 24 months of medical history in Sweden prior to the index date, without a uterus, or with a history of endometrial cancer will be excluded.

Variables: Vaginal estrogen use will be determined using prescription drug codes from pharmacy claims and dispensings. Diagnosis of endometrial cancer will be identified in the HIRD using codes that have been validated in the HIRD, and in Sweden using records in the Swedish Cancer Register. Covariates will include patient demographics, comorbidities, medications, and healthcare utilization. A listing of study variables is provided in Section 9.3 Variables.

Data Sources: The HIRD is a longitudinally integrated research database comprising automated payment claims for healthcare encounters since 01 January 2006 from included health insurance plans across the US. It is among the largest of its kind in the US, with current enrollment of approximately 70 million members as of 2018. The HIRD has been extensively used for pharmacoepidemiologic research, including many post approval safety studies.[5-7] The HIRD includes enrollment data, medical care, physician specialty, laboratory results (one third of patients), prescription drug use, and healthcare utilization that can be tracked for each individual throughout the course of their enrollment.

The Swedish registry data includes five, large, nationally held registers: the Swedish National Patient Register (NPR), the Swedish Prescribed Drug Register (SPDR), the Swedish Cancer Register (SCR), the Cause of Death Registry, and the Total Population Register (TPR). These registers include data for patients, drugs, cancer, death, and the population linkable by patients' personal identity numbers. Entrance into the registers is upon birth or immigration to Sweden and exit from the registers is upon death or emigration.

Study Size: The study is designed to have sufficient size to detect with 80% power the hazard of endometrial cancer for women using unopposed LDVE that is 1.5 times the hazard of endometrial cancer associated with no use of vaginal estrogen. In the HIRD, assuming a 1:4 exposed:comparator ratio, α=0.05, a median follow-up duration of 2.4 years, and a background endometrial cancer incidence rate of 74.5 events per 100,000 person-years,[8] the study would require 33,377 LDVE users and 133,504 non-users to achieve 80% power to detect a hazard ratio of 1.5. For the comparison between LDVE new users and non-users in the primary analysis, the sample is estimated to include at least 152,941 new users and 611,764 non-users. Given the available sample sizes, the study will have >99% power to detect a hazard ratio (HR) of 1.5 for the LDVE new users cohort.

In Sweden, the LDVE new users cohort is estimated to include 100,800 women. The non-user comparator is estimated to include 1,378,928 women. Assuming a 1:4 exposed:comparator ratio, α=0.05, a median duration of follow-up of 2.4 years, and a background endometrial cancer incidence rate of 70.4 events per 100,000 person-years, the study would have >99% power to detect a hazard ratio equal to 1.5 for the new users of LDVE cohort. For achieving a power of 80% to detect a hazard ratio of 1.5, the total number of endometrial cancer events required is 299. The total number of person-years needed to observe the required number of events is 84,770 person-years in the new users of LDVE cohort and 339,077 person-years in the non-users cohort. Equivalently, the sample size required for achieving 80% power is 35,321 in the new users of LDVE cohort and 141,282 in the non-users cohort.

Data Analysis: Propensity score (PS) matching will be applied to each comparison group with a 1:4 exposed:comparator matching ratio. Propensity scores will be estimated separately for each comparison using logistic regression and a set of baseline covariates. Descriptive statistics and all additional analyses will be performed on the PS-matched cohorts. Descriptive statistics will be presented to characterize each exposed group and each comparator group in terms of demographic information, medical history, and use of medications associated with endometrial cancer during the baseline period. Baseline characteristics will be compared across the study cohorts to assess comparability. The IR of endometrial cancer and 95% confidence intervals (CIs) will be computed for each study cohort.

In the primary analysis, hazard ratios (HRs) will be calculated using Cox proportional hazards models to compare the hazard of endometrial cancer between 1) LDVE new users and non-users of vaginal estrogen, 2) MDVE new users and non-users of vaginal estrogen, and 3) HDVC new users and non-users of vaginal estrogen (HIRD only). Separate stratified estimates of HRs comparing each vaginal estrogen exposure group to non-users will be performed by prior hormone therapy use. Categories of the prior hormone therapy will include estrogen only, progestin only, estrogen and progestin combination or single-entity therapy, other opposed estrogen hormone therapy, and no prior hormone therapy. Additional separate stratified analyses estimating HRs comparing each vaginal estrogen exposure group to non-users will be performed by drug utilization characteristics including duration of use, formulation, active ingredient, and number of dispensings, and number of dispensings per formulation. In the secondary analysis, HRs will also be estimated using Cox proportional hazards models in similar comparisons as the primary analysis except the subset of vaginal estrogen new users without any prior hormone therapy use will be compared to E+P HT new users with no prior use of hormone therapy. The primary and secondary analyses will incorporate an induction period of six months for vaginal estrogen new users and E+P HT new users.

Milestones: The first milestone is final approval of the study protocol by the FDA. Following approval of the study protocol, the statistical analysis plan (SAP) will be submitted to the FDA for approval. Upon approval of the SAP, HealthCore and IQVIA will carry out data management and analytic activities in their respective data sources, including endometrial cancer validation, PS-matching and descriptive and comparative analyses to support the development of a final report. The final study report will be submitted to the FDA with a planned submission date of 31 October 2023.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	TBD
Draft protocol submission to the FDA	31 December 2020[a]
Final protocol submission to the FDA	04 January 2022
Start of data collection (estimated)	01 April 2022^
End of data collection (estimated)	31 March 2023#
Complete validation study	31 March 2023
Final study report submission to the FDA (estimated)	31 October 2023

a. Additional revised protocols were submitted on 30 April 2021, 24 September 2021, and 23 November 2021 following the draft protocol submission on 31 December 2020.

^ Start of data collection is the planned data extraction date for the purposes of the study analysis. This date assumes FDA approval of the January 2022 submitted protocol.

End of data collection is the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the study objective(s).

7. RATIONALE AND BACKGROUND

Decreased estrogen production after menopause is associated with vaginal atrophy and pain.[9] One of the goals of estrogen therapy is to provide sufficient estrogen to reverse atrophic vaginal changes and relieve associated symptoms in postmenopausal women.[1] Low-dose vaginal estrogen (LDVE) is indicated for use in women with a uterus for the treatment of vaginal atrophy and moderate to severe vasomotor symptoms associated with menopause[10,11] and is available in various formulations and strengths (Annex 1: Appendix A and Appendix E).

Observational studies indicate an increased risk of endometrial cancer among postmenopausal women who use oral estrogen products without concomitant use of progestogen.[12] One study found that relative to women who had never used oral estrogen therapy, women who had taken unopposed oral estrogens had a four-fold increase in the risk of endometrial cancer (odds ratio = 4.0, 95% confidence interval [CI] 3.1-5.1).[12] Another study found that women using oral estrogen therapy, with less than 10 days of progestogen therapy for every one month of estrogen therapy, had a 1.76 (95% CI 1.51-2.05) higher odds of endometrial cancer compared to those women using oral estrogen therapy with continuous progestogen therapy.[13] Among women using oral estrogen, concomitant use of progestogen from 10 to 25 days per month has been shown to reduce the risk of endometrial cancer.[13-15]

While current clinical guidelines indicate that vaginal estrogen should be administered at the lowest effective doses, they do not include recommendations for using progestogens to oppose vaginal estrogen use.[1-3] Given that the risk of endometrial cancer is higher among women who use unopposed oral estrogen at a wide range of doses and durations[4] and that vaginal estrogen use does result in systemic absorption (though likely at lower levels than oral estrogen use),[2] it is important to assess the real-world safety of LDVE use without concomitant use of progestogen therapy in the populations for which the product is prescribed.

The United States (US) Food and Drug Administration (FDA) has issued a post-marketing requirement (PMR) to each Marketing Authorizations Holder (MAH) of an LDVE for an observational study to evaluate the rate of endometrial cancer among postmenopausal women with a uterus who use LDVE unopposed by a progestogen. Pfizer is the MAH for Estring® 2 mg (vaginal ring, 7.5 mcg/24 hours) and Premarin® Vaginal Cream 0.625 mg/gram (Premarin VC) and received a PMR notification for each product. Premarin VC has a higher estrogen concentration but is indicated for both low-dose and high-dose treatment regimens. In order to address the safety concerns for Premarin VC set forth in the PMRs, Pfizer includes Premarin VC in this study, with high-dose regimens evaluated as a separate exposure group. Analyses including Premarin VC will only be conducted in the HealthCore Integrated Research Database℠ (HIRD) as Premarin VC is not marketed in Sweden. A comprehensive feasibility assessment (submitted to the FDA on 28 June 2018) was conducted to ensure a scientifically valid observational study could be successfully executed using the HealthCore Integrated Research Database℠ (HIRD). This protocol describes the non-interventional study that will be conducted in the US and Sweden to fulfill the PMR commitment to the FDA to assess endometrial cancer risk among users of LDVE. Sweden was specifically requested by the FDA in order to fulfill this PMR. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the FDA.

8. RESEARCH QUESTION AND OBJECTIVES

What is the incidence rate (IR) of endometrial cancer in postmenopausal women with a uterus who use LDVE unopposed by progestogen compared to non-users and compared to users of estrogen-progestogen combination hormone therapy (E+P HT)?

Primary Objectives:

1. To estimate and compare the IR of endometrial cancer in postmenopausal women aged ≥50 years, with a uterus, regardless of prior use of hormone therapy (defined as any estrogen, progestin, E+P HT use or other opposed estrogen hormone therapy), in the following groups:

    a. New users of low-dose vaginal estrogen (LDVE) versus non-users of vaginal estrogen;

    b. New users of moderate-dose vaginal estrogen (MDVE) versus non-users of vaginal estrogen;

    c. New users of high-dose Premarin Vaginal Cream (HDVC) versus non-users of vaginal estrogen (HIRD only, as Premarin VC is not marketed in Sweden)

2. To estimate and compare the IR of endometrial cancer separately among the LDVE, MDVE, and HDVC new users (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by prior use of hormone therapy including unopposed estrogen, unopposed progestin, single-entity or combination progestin-opposed estrogen therapies, other opposed estrogen hormone therapies, or no prior hormone use.

3. To estimate and compare the IR of endometrial cancer separately among new users of LDVE, MDVE, and HDVC (HIRD only) aged ≥50 years, with a uterus, and regardless of prior use of hormone therapy relative to non-users of vaginal estrogen stratified by duration of use, formulation, active ingredient, number of dispensings and number of dispensings per formulation.

Secondary Objective:

1. To estimate and compare the IR of endometrial cancer among women aged ≥50 years with a uterus and without prior hormone therapy use, in the following groups:

    a. LDVE new users versus E+P HT new users of hormone therapy.

    b. MDVE new users versus E+P HT new users of hormone therapy.

    c. HDVC new users versus E+P HT new users of hormone therapy (HIRD only).

9. RESEARCH METHODS

9.1. Study Design

This is a non-interventional, retrospective cohort study among women aged ≥50 years using a US healthcare claims data source (the HIRD) and longitudinal data collected from five Swedish National Registers. The three exposed groups are new users of vaginal estrogen grouped into 3 dose categories: LDVE, MDVE, and HDVC (HIRD only) regardless of prior use of hormone therapy (full study population). The comparator groups are non-users with no prior vaginal estrogen use, regardless of other prior use of hormone therapy and E+P HT new users with no prior use of hormone therapy. Incidence rates of endometrial cancer will be presented and adjusted hazard ratios will be estimated for each exposure group as compared to both non-users of vaginal estrogen and E+P HT new users.

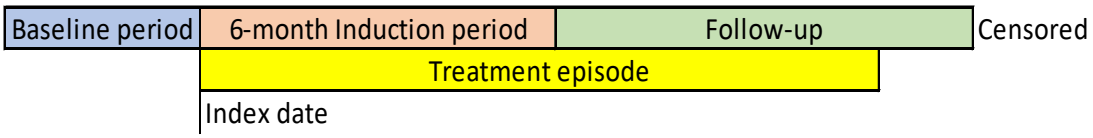
9.1.1. Time Periods

The study period, i.e., the beginning of the baseline period to the end of the follow-up period, is 01 January 2006 (earliest available date) through 31 December 2020 (or most recent available date) in the HIRD, and 01 January 1997 (earliest available date for medical record history) through 31 December 2019 (or most recent available date) in the Swedish registers. The difference between the two data sources in end of study dates is due to the difference in the lag time for populating the HIRD and the Swedish registers.

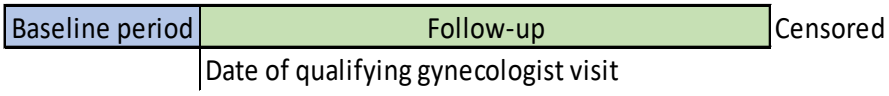
Ascertainment of exposure and follow-up will be 01 January 2007 – 31 December 2020 (or most recent available date) in the HIRD, and 01 July 2007 – 31 December 2019 (or most recent available date) in the Swedish Registers to allow for a 12- or 24-month baseline period in the HIRD and Swedish data bases, respectively. The index date is the day of initiating a study drug or, for non-users, the date of a gynecological visit that meets all inclusion and exclusion criteria. For new users of vaginal estrogens and E+P HT, a 6-month induction period is allowed following initiation of exposure and prior to beginning follow-up to allow for induction and diagnosis of endometrial cancer (Figure 1). For non-users, follow-up and accrual of person-time starts the day after the index date. The unexposed period before a woman starts any vaginal estrogen will be included as time at risk for a non-user until they begin using one of these drugs. The unexposed time at risk (non-users) will be censored if and when they start using vaginal estrogen, E+P HT or other non-study estrogen or progestogen medications. A sensitivity analysis is included that varies the length of the induction period and includes an induction period for the non-user cohort. Table 1 summarizes the different time periods for the two data sources. Patients may differ in their follow-up dates depending on when they meet the study inclusion, exclusion, and censoring criteria.

Figure 1. Study Time Periods Between Treatment and Comparator Groups

A. New user of vaginal estrogen or E+P HT



B. Non-users



Abbreviations: E+P HT, estrogen-progestogen combination hormone therapy.

Table 1. Study Time Periods Between the HIRD and Swedish National Registers

Time Period	HIRD	Swedish National Registers
Study period	01 January 2006 (earliest available date) – 31 December 2020 (or most recently available date)	01 Jan 1997 (earliest available date for medical record history) – 31 December 2019 (or most recently available date)
Baseline period	At least 12 months prior to and including index date	At least 24 months prior to and including index date
Exposure ascertainment period	01 January 2007 – 31 December 2020	01 July 2007 – 31 December 2019
Induction period (vaginal estrogen and E+P HT users)	(Index date + 1 day) + 6 months	(Index date + 1 day) + 6 months
Follow-up period (vaginal estrogen and E+P HT users)	Last day of induction period + 1 day – censored date	Last day of induction period + 1 day – censored date
Follow-up period (non-users)	Index date + 1 day – censored date	Index date + 1 day – censored date

Abbreviations: E+P HT, estrogen-progestogen combination hormone therapy; HIRD, HealthCore Integrated Research Database.[SM]

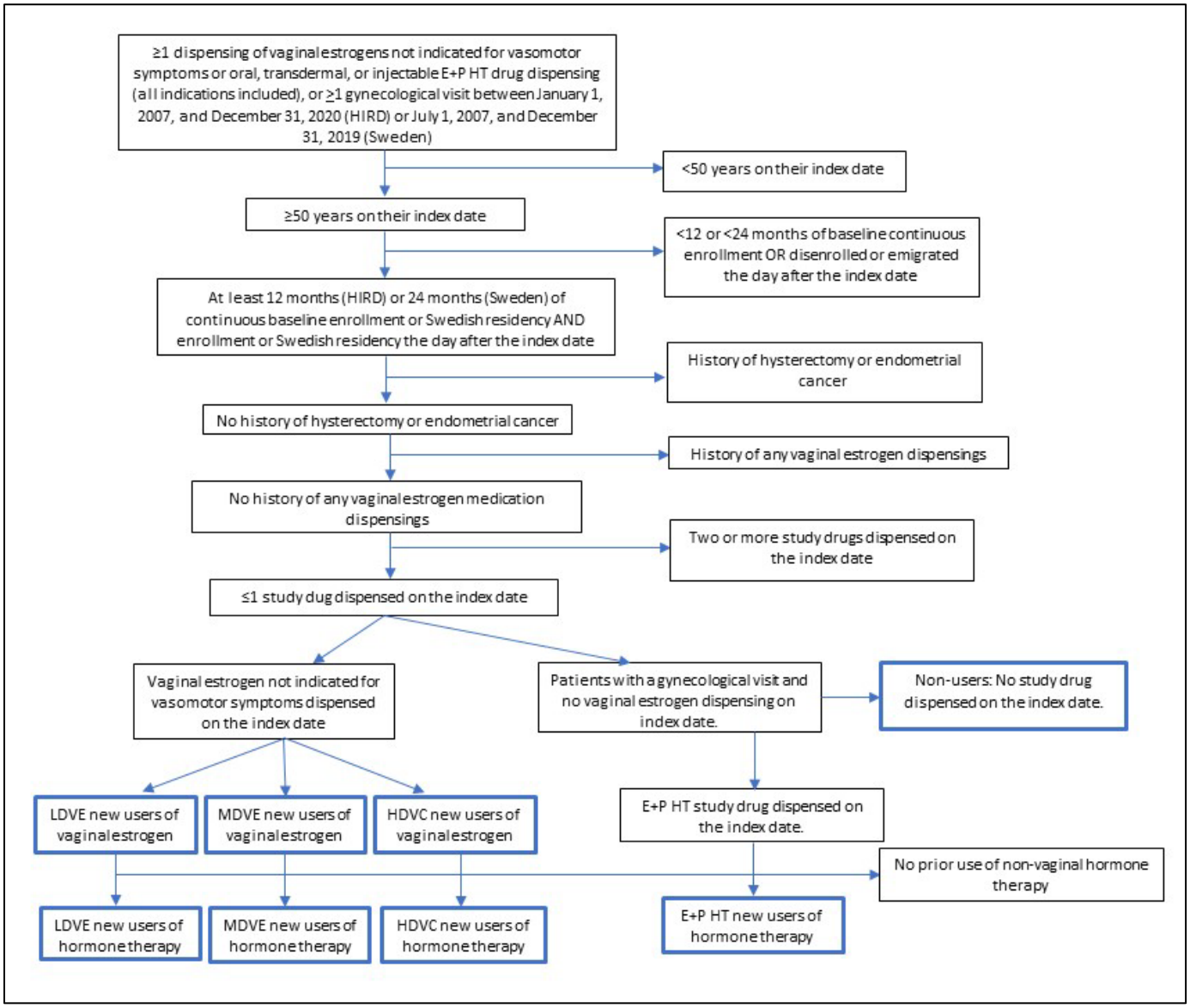
9.1.2. Exposure and Comparator Groups

The study will include three vaginal estrogen new user exposure groups: LDVE, MDVE, and HDVC (HIRD only). The two comparator groups are non-users of vaginal estrogens regardless of prior use of hormone therapy and new users of E+P HT without any prior hormone therapy use.

The study population and characterization of the exposure and comparator groups are illustrated as a flowchart in Figure 2.

Due to the higher estrogen concentration for Premarin VC than non-Premarin LDVEs, higher daily doses of Premarin VC of >0.45 mg/day conjugated estrogen will be analyzed as a separate exposure group (HIRD only, as Premarin VC is not marketed in Sweden). This exposure group is referred to throughout as the HDVC group. Low-dose regimens ≤0.3 mg/day conjugated estrogen are also indicated for Premarin VC (i.e., 0.5 grams applied daily for 21 days or 0.5 grams applied twice weekly). These low-dose regimens will be evaluated as part of the LDVE exposure group.

Figure 2: Study Population



Abbreviations: E+P HT, estrogen-progestogen combination hormone therapy; HDVC, high-dose Premarin VC (HIRD only); HIRD, HealthCore Integrated Research Database; LDVE, low-dose vaginal estrogen; MDVE, moderate-dose vaginal estrogen.

Note: Bolded boxes outlined in **blue** indicate an exposure or comparator group.

The three vaginal estrogen exposure groups and the two comparator groups are described below and summarized in Figure 2 (for definitions of study drugs and gynecological visits, see Section 9.2 Setting and Section 9.3 Variables):

- Exposure 1: New Users of LDVE.
    - Women who had ≥1 dispensing of an LDVE during the exposure ascertainment period with prescription daily doses[1] ≤10 mcg estradiol or ≤0.3 mg conjugated estrogen at cohort entry and no prior dispensings of vaginal estrogen.[1] Low-dose Premarin VC (HIRD only) is defined as 0.5 g/day dose (equal to daily average strength 0.3 mg or less conjugated estrogens. It should be noted that these women may or may not have used hormone therapy prior to the index date and will be included regardless of such prior use.
- Exposure 2: New Users of MDVE.
    - Women who had ≥1 dispensing of a MDVE during the exposure ascertainment period with prescription daily doses >10 mcg – 25 mcg estradiol or >0.3 mg – 0.45 mg conjugated estrogen at cohort entry and no prior dispensings of vaginal estrogen. It should be noted that these women may or may not have used hormone therapy prior to the index date and will be included regardless of such prior use. The Swedish cohort will only include subjects with ⩾ 1 dispensing of 25mcg estradiol (Vagifem).
- Exposure 3: New Users of HDVC (HIRD Only).
    - Women who had ≥1 dispensing of Premarin VC during the exposure ascertainment period with prescription daily doses >0.45 mg conjugated estrogen at cohort entry and no prior dispensings of vaginal estrogen. It should be noted that these women may or may not have used hormone therapy prior to the index date and will be included regardless of such prior use.
- Primary Comparator: Non-users of vaginal estrogen.
    - Women who had ≥1 gynecological visit during the exposure ascertainment period, and no dispensings of vaginal estrogen prior to or on the gynecological visit. It should be noted that these women may or may not have used hormone therapy prior to the index date and will be included regardless of such prior use.
    - The unexposed period before a woman starts any vaginal estrogen will be included as time at risk for a non-user until they begin using one of these drugs. The unexposed time at risk (non-users) will be censored when they start using vaginal estrogen, E+P HT or other non-study progestin or estrogen medications.
- Secondary Comparator: New Users of E+P HT.
    - Women who had ≥1 dispensing of E+P HT during the exposure ascertainment period, and no prior dispensings of any hormone therapy (excluding contraceptives).

9.2. Setting

The study population consists of women in the HIRD and Sweden who are at least 50 years of age. For subjects using a vaginal estrogen or E+P HT, cohort qualification status will be assessed for the first study drug dispensing (index date) during the exposure ascertainment period (see Table 1) based on the inclusion and exclusion criteria described below. For the purpose of the primary objective, non-users of vaginal estrogen, subjects with at least one gynecological visit after age 50 and without any prior or current use of vaginal estrogens at the time of their gynecological visit (index date for non-users) will be included in this population regardless of their prior use of hormone therapy. Subjects may have multiple qualifying gynecological visits. For the purpose of the secondary objective, E+P HT new users with no prior use of hormone therapy will be included.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Women must have ≥1 study drug dispensing, or ≥1 gynecological visit, that meets each of the following criteria to be eligible for inclusion in a study cohort (Figure 3; for additional details on study drugs and gynecological visits, see Section 9.3 Variables):

- ≥1 dispensing of vaginal estrogen not indicated for severe vasomotor symptoms or any E+P HT, or a gynecological visit for non-users, from 01 January 2007 through 31 December 2020 (or most recent available date) in the HIRD, and 01 July 2007 – 31 December 2019 (or most recent available date) in Sweden (see Annex 1: Appendix B and Appendix F for vaginal estrogen and E+P HT medications)

Vaginal estrogen: Vaginal estrogen drugs include products which are approved only for one or more symptoms of vulvar and vaginal atrophy due to menopause.[1] Thus, Femring (estradiol acetate vaginal) and Ogen (estropipate vaginal) which are also indicated for moderate to severe vasomotor symptoms, are not included as study drugs. Estrace (estradiol cream) is also excluded due to its indication for vasomotor symptoms and its high concentration of estradiol resulting in greater systemic absorption.[2] Vaginal estrogen study drugs include the following products:

HIRD: Estring, Vagifem, Yuvafem, Imvexxy, generic estradiol (tablet), and Premarin VC;

Sweden: Oestring and Vagifem.

E+P HT: oral, transdermal, or injectable estrogen-progestogen combination hormone therapy products.

Gynecological visit: outpatient office visit with provider specialty of gynecology, or diagnosis/procedural codes for gynecological exam or Pap smear.

2. Female aged ≥50 years on the first study drug dispensing date or on the gynecological visit date for non-users (the index date).

3. Minimum required baseline observation period:

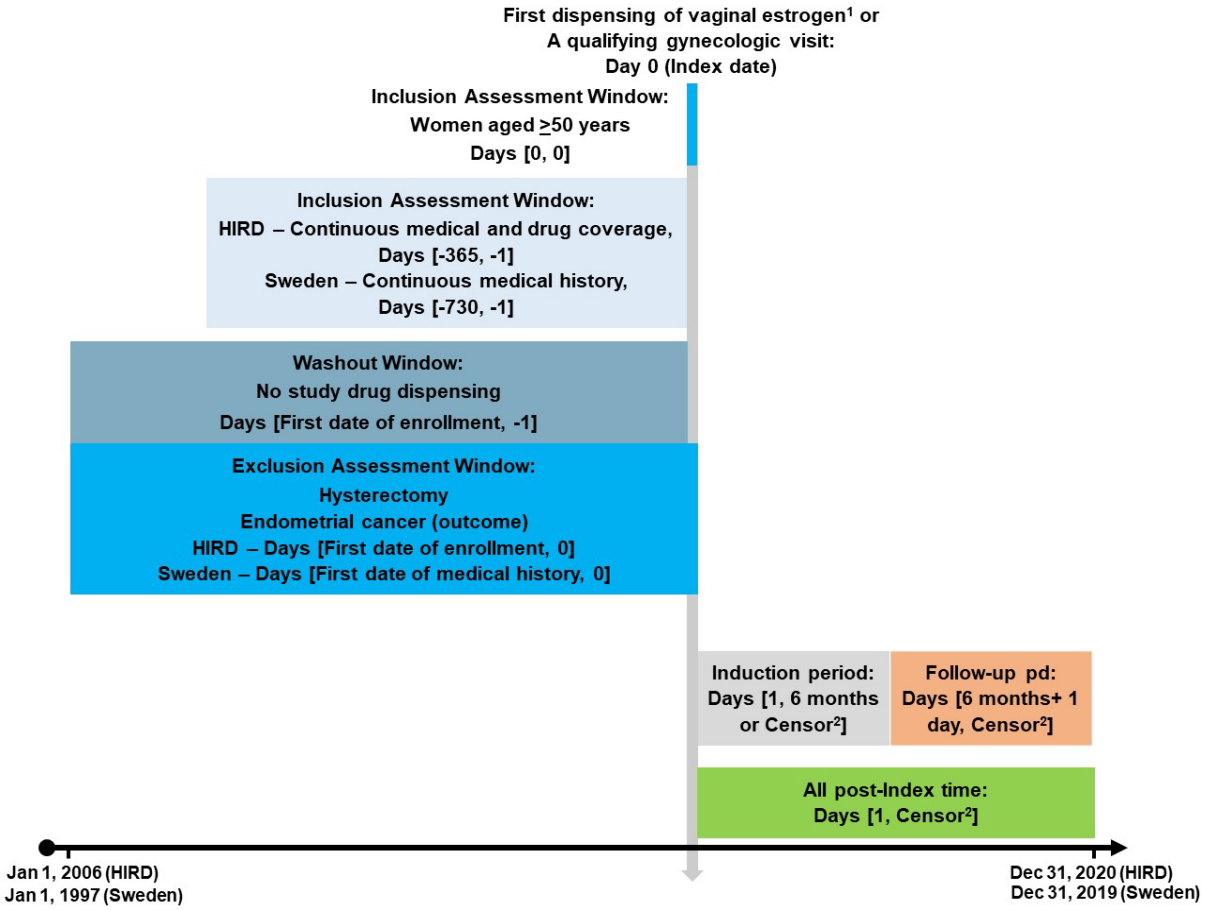
HIRD: A minimum of 12 months of continuous eligibility in the HIRD prior to and including the study drug dispensing date, or the gynecological visit date for non-users.

Sweden: A minimum of 24 months of medical history (i.e., 24 months of continuous residence in Sweden with no migration observed) prior to and including the study drug dispensing date, or the gynecological visit date for non-users.

The reason for using different baseline requirements is that greater turnover in the HIRD reduces the duration of enrollment, and one wishes to preserve available enrollment for follow-up. The baseline period includes all available enrollment data (HIRD) and medical history (HIRD, Sweden) on and prior to the index date (date of first dispensing of a study drug or gynecological visit).

4. Must be enrolled (HIRD) or residing in Sweden (Swedish registers) on the day after the index date.

Figure 3. Cohort Selection for Primary Study Population: Vaginal Estrogen Treatment Groups and Non-Users



Abbreviations: HIRD, HealthCore Integrated Research Database

[1]Vaginal estrogens include vaginal estradiol estrogen (excluding Estrace), and vaginal conjugated estrogen (Premarin Vaginal Cream, HIRD only) in low, moderate, and high doses.

[2]Censoring date for new users is earliest of: hysterectomy, endometrial cancer, switching of treatment group study drug, dispensing of an estrogen-containing product (vaginal or non-vaginal) that does not belong to a treatment group, dispensing of a progestogen-containing product (vaginal or non-vaginal), death, disenrollment (HIRD), emigration from Sweden (Sweden), end of the study period. Censoring date for non-users is earliest of: hysterectomy, endometrial cancer, dispensing of any study drug, dispensing of an estrogen-containing product (single-entity or combination, vaginal or non-vaginal) that does not belong to a treatment group, dispensing of a progestogen-containing product (single-entity or combination, vaginal or non-vaginal), death, disenrollment (HIRD), emigration from Sweden (Sweden), end of the study period.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

Exclusion criteria are applied to all treatment and comparator groups unless otherwise noted. Information during the baseline period is used to assess whether a subject meets the criteria unless otherwise noted (see definitions in Section 9.3 Variables). The exclusion criteria will include the following (summarized in Figure 3 above):

- Hysterectomy;
- Endometrial cancer;
- ≥1 prior dispensing of any vaginal estrogen (including study drugs and non-study drugs) prior to the index date for new users of vaginal estrogen. For non-users and E+P HT new users, this criterion will be assessed during the entire baseline period, including the potential index dates.
- ≥2 dispensings of vaginal estrogen drugs on the index date that differ by strength, formulation, or active ingredient.
- Secondary analyses only:
    - ≥1 prior dispensing of E+P HT prior to the index date for new users of E+P HT. For vaginal estrogen users, this criterion will be assessed during the entire baseline period, including the index date;
    - ≥1 prior dispensing of vaginal or non-vaginal progestogen hormone therapy product (single-entity or combination, except contraceptives) not included as E+P HT study drugs.
    - ≥1 dispensing of oral, transdermal, or injectable estrogen hormone therapy product (single-entity or combination, except contraceptives) not included as E+P HT study drugs.

9.2.3. Post-Index Period

For new users of vaginal estrogen and E+P HT, the post-index period includes the induction period and the follow-up period. The induction period starts the day after the index date and lasts for six months or until the one of the censoring criteria (below) is met. If a censoring criterion has been met during the induction period, that subject is censored and contributes no follow-up time in the main analysis but may be included in a sensitivity analysis (see Section 9.7.4 Sensitivity Analyses). If no censoring criteria has been met during the six-month induction period, the follow-up period begins on the day after the end of the induction period. Person-time for new users of vaginal estrogen and E+P HT will only be counted during follow-up and only endometrial cancer cases occurring during follow-up will be included in the analysis as cases.

The endometrial cancer incidence rate in non-users is unrelated to treatment so the induction period does not apply to this group. Therefore, follow-up and person-time accrual for non-users begins the

day after their index date (i.e., the date of a gynecological visit that meets all inclusion and exclusion criteria). Follow-up for all subjects will extend through the earliest of the following censoring events:

- Hysterectomy;
- Endometrial cancer;
- Dispensing of an estrogen hormone therapy product not included as a study drug (single-entity or combination, vaginal or non-vaginal formulation)
- Dispensing of a progestogen hormone therapy product not included as E+P HT (single-entity or combination, vaginal or non-vaginal formulation);
- End of continuous health plan eligibility (HIRD only);
- Emigration from Sweden (Sweden only);
- Death;
- End of the study period.
- Dispensing of a study drug that is in a different treatment group than the index treatment group, i.e., switching between LDVE, MDVE, HDVC, or E+P HT treatment groups;

Additional censoring criteria for non-users only:

- Dispensing of any study drug, which are defined in Section 9.2.1 Inclusion Criteria.

9.3. Variables

In the HIRD, diagnoses and procedures for both outpatient and inpatient visits are identified by International Classification of Diseases, Nineth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnostic and procedure codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes. Outpatient pharmacy claims are captured by National Drug Codes, which can then be translated to broader categories of coding such as Generic Product Identifier (GPI) codes that correspond to the generic drug subclass level of resolution. Specific codes used to generate the variables of interest are provided in Annex 1: Appendices B-D.

In the Swedish National Patient Register (NPR), inpatient and outpatient hospital diagnoses will be identified using ICD-10-Sweden (SE) codes and procedures will be identified using Swedish procedure codes (Klassifikation av vårdåtgärder) (Swedish for “Classification of Healthcare Measures”), and Nordic Medico-Statistical Committee procedure codes. Exposure to drugs will be identified from the Swedish SPDR using Anatomical Therapeutic Chemical (ATC) codes and information on dispensing date, package size, product name, dispensed amount of drug, drug strength, defined daily dose, and drug formulation. Endometrial cancer will be ascertained from the Swedish Cancer Register using information on tumor location coded to ICD-O-2/3.

9.3.1. Exposures, Comparators, and Treatment Episodes

GPI codes will be used to identify vaginal estrogen and E+P HT products in the HIRD, (Annex 1: Appendix B) and ATC codes, formulation, brand name, and strength will be used to identify vaginal estrogen and E+P HT Swedish products (Annex 1: Appendix F). Gynecological visits for non-users will be identified in the HIRD using ICD-9-CM and ICD-10-CM diagnostic codes, HCPCS codes for annual exams, CPT codes for pap smear procedures, and physician's specialty code (Annex 1: Appendix C). Gynecological visits will be captured as non-primary outpatient care in the Swedish NPR. Proxies for gynecological visits (i.e., related procedure codes, specialist encounters, and/or reimbursement) will be considered, as appropriate.

Treatment episodes (Annex 1: Appendix I) will be created based on segments of continuous use among the study drug treatment groups, i.e., LDVE, MDVE, HDVC, and E+P HT. Continuous use is defined as consecutive drug dispensings for a treatment group, with no more than 90 days between the end of the days' supply of the earlier prescription and the dispensing date of the next prescription. In order to determine exposure status for vaginal estrogen users during the treatment episode, daily dose must first be computed for each prescription starting with the index dispensing. In the HIRD, daily dose for vaginal estrogen dispensings will be calculated as the drug strength dispensed multiplied by the drug quantity and divided by the days' supply. In Sweden, days' supply is not directly available from the SPDR. Thus, days' supply and daily dose will be estimated for each dispensed vaginal estrogen prescription based on assumptions such as defined daily dose and duration for use. For the E+P HT comparator group, dispensed amount of drug, drug strength and defined daily dose will be used to construct treatment episodes of continuous use. Exposure definitions will be further detailed in the statistical analysis plan (SAP).

The prescription daily doses of the vaginal estrogen dispensings will then be categorized as follows:[16,17]

- LDVE: ≤10 mcg/day estradiol or ≤0.3 mg/day conjugated estrogen;
- MDVE: >10 – 25 mcg/day estradiol or >0.3 – 0.45 mg/day conjugated estrogen;
- HDVC: >0.45 mg/day conjugated estrogen.

Vaginal estrogen users will enter the exposure group corresponding to the dose of their first study drug dispensing. Women whose first dispensing was E+P HT will enter the E+P HT comparator group. If a vaginal estrogen user changes dose categories or switches to E+P HT, she will be censored on the dispensing date of the new prescription. Similarly, if an E+P HT user switches to vaginal estrogen use, she will be censored on the vaginal estrogen dispensing date.

Patients may use different products and strengths for study drugs within their treatment group. If there are overlapping prescriptions for different products within the same treatment group, then it will be assumed that the patient stopped taking the first prescription drug and started the second prescription drug on the day it was dispensed (no stockpiling). If the patient has overlapping prescriptions for the same drug and dose, the prescriptions will be stockpiled, i.e., the overlapping days from the second prescription will be added to the end of the days' supply of the first

prescription. Multiple dispensings for the same drug on the same day should also be treated as overlapping prescriptions.

The first treatment episode for each of the treatment groups and the E+P HT group will start on the day after the index date and continue for the number of days' supply plus 90 days. If there is no consecutive prescription within the allowable 90-day gap, the treatment episode end date will be considered the 90th day after the date on which the days' supply of the patient's last dispensing ended. Follow-up will continue after the end of the first treatment episode and include subsequent treatment episodes until the subject meets a censoring criterion.

9.3.2. Endpoint

The endpoint is the occurrence of endometrial cancer. An algorithm for endometrial cancer will be developed and validated as part of the current study to identify the outcome in administrative claims data. The performance of endometrial cancer algorithms will be assessed for the HIRD database through medical record review and adjudication. The protocol for the validation study is included in Annex 2.

This validation component will begin after building the analytic files for the current study, identifying the cohort of patients who meet the inclusion/exclusion criteria (as described in Section 9.2 Setting), and constructing the exposure and comparator groups.

The final algorithm for endometrial cancer will be determined prior to conducting analyses to estimate and compare incidence rates of endometrial cancer for the exposure and comparator groups. The validated algorithm for endometrial cancer will be used in the HIRD. In Sweden, endometrial cancer will be identified using ICD-O-2/3-SE diagnosis codes in the Swedish Cancer Registry (Annex 1: Appendix G).

9.3.3. Vaginal Estrogen Use

The following drug utilization characteristics will be described during the post-index period for the vaginal estrogen exposure groups:

- Active ingredient at date of first dispensing:
    - Estradiol vaginal
    - Conjugated estrogen vaginal
- Formulation at date of first dispensing (vaginal cream, ring, tablet, or insert).
- Duration of use (i.e., duration of all treatment episodes combined).
- Computed for each treatment group as the sum of days in all treatment episodes.

Categorized in the HIRD and Sweden as:

- <0.5 years.
- 0.5 to <1 year.
- ≥1 to <2 years.
- ≥2 to <3 years.
- ≥3 years.

- Number of dispensings.
- Number of dispensings per formulation.

9.3.4. Baseline Covariates

The study will identify and describe baseline covariates and prior use of estrogen and progestogen use using all available data prior to and including the index date (see Section 9.1.1 Time Periods). A continuous variable measuring the duration of use will be created for each of the following drug categories:

- Single-entity progestogen contraceptives (oral, transdermal, or injectable);
- E+P contraceptives (oral, transdermal, or injectable).
- Unopposed estrogen hormone therapy: These include oral, transdermal, and injectable single-entity estrogen medications without a progestin dispensed during the baseline period.
- Unopposed progestin hormone therapy: These include oral, transdermal, injectable, and vaginal medications without an estrogen dispensing during the baseline period.
- Progestin opposed estrogen hormone therapy: These include prior use of E+P HT study drugs and subjects who used single-entity estrogen AND single-entity progestin medications during the baseline period (the two medications' usage does not need to overlap).
- Other opposed estrogen hormone therapy: These include prior use of estrogen-testosterone combination medications, conjugated estrogen-bazedoxifene, or the use of single-entity estrogen and single-entity testosterone medications during the baseline period (the two medications' usage does not need to overlap).
- No prior estrogen or progestin hormone therapy use (not including contraceptives). This will be a binary variable indicating no prior hormone therapy use.

Prior contraceptive use may be further divided into categories for time since last dispensing:

- <6 months;

- 1-2 years;
- 2+ years.

The following variables will also be assessed using all available data during the baseline period, unless otherwise noted:

Demographic characteristics:

- Age, continuous, in years, on the date of the cohort-qualifying event;
- Region of residence in the US on the date of the cohort-qualifying date event. Categories of the region of residence will be as follows: Northeast, South, Midwest, or West. Region of residence will not be used as a covariate in Swedish analyses.
- Urbanicity (urban, suburban, rural)
- Calendar year of the index date.
- Duration of baseline period (in months).

Medical comorbidities (Annex 1: Appendix C and Appendix G):

- All-cause cancer (other than endometrial cancer and basal cell carcinoma);
- Breast cancer;
- Ovarian cancer;
- Thyroid cancer;
- Renal cancer;
- Colorectal cancer;
- Endometrial hyperplasia;
- Benign breast lumps (fibrocystic nodule);
- Polycystic ovary syndrome;
- Osteoporosis;
- Osteoarthritis;
- Vasomotor symptoms;

- Stroke/transient ischemic attack;
- Myocardial infarction;
- Congestive heart failure;
- Coronary heart disease;
- Hyperlipidemia;
- Hypertension;
- Venous thromboembolism;
- Diabetes;
- Major depression;
- Charlson Comorbidity Index;

Prescription medications (Annex 1: Appendix D and Appendix H):

- Selective estrogen receptor modulators;
- Androgens;
- Corticosteroids;
- Lipid lowering agents;
- Antihypertensives;
- Antidiabetics;
- Antidepressants;
- Sedatives/hypnotics;
- Anticonvulsants;
- Antifungals;
- Antivirals;
- Macrolides;

- Immunosuppressants.

Healthcare utilization within the 12 months prior to and including the index date:

- Count of distinct hospitalizations;
- Count of office visits;
- Count of gynecological office visits;
- Count of unique medication classes dispensed;

Other variables within the 12 months prior to and including the index date:

- Pelvic radiation therapy.
- Top 25 most frequently occurring procedures;
- Top 25 most frequently occurring medications
- Top 25 most frequently occurring comorbidities

In the HIRD, the 25 most frequently occurring diagnoses, procedures, and medications among all women in each pre-matched cohort (e.g., LDVE vs. non-users, MDVE vs, non-users, LDVE vs. E+P HT, etc.) within the 12 months prior to and including the index date will be identified using ICD-9-CM diagnosis codes (first four digits), ICD-10-CM diagnosis codes (first four characters), CPT procedure codes (excluding codes for evaluation and management), and medication GPI code (first four digits).

In Sweden, the 25 most frequently occurring diagnoses, procedures, and medications within the past 12 months prior to and including the index date will be identified using International Classification of Diseases, Tenth Revision, Sweden (ICD-10-SE) diagnosis codes (first four characters), procedure codes, and ATC codes. These diagnoses, procedures, and medications are included in the analysis because they may be associated with endometrial cancer and will be considered for inclusion in the propensity score (PS) analysis.

9.4. Data Sources

9.4.1. HIRD, US

The HIRD is a longitudinally integrated research database comprising automated payment claims for healthcare encounters since 01 January 2006 from included health insurance plans across the US. It is among the largest of its kind in the US, with current enrollment of approximately 70 million members as of 2018. The HIRD has been extensively used for pharmacoepidemiologic research, including many post approval safety studies.[5-7] The HIRD includes enrollment data, medical care, physician specialty, laboratory results (one third of patients), prescription drug use, and healthcare utilization that can be tracked for each individual throughout the course of their enrollment.

9.4.2. Swedish Registers, Sweden

The Swedish registry data include five large, nationally held registers: the Swedish NPR, the Swedish Prescribed Drug Register (SPDR), the Swedish Cancer Register (SCR), the Cause of Death Registry, and the Total Population Register (TPR). These registers include data for patients, drugs, cancer, death, and the population linkable by patients' personal identity numbers. Entrance into the registers is upon birth or immigration to Sweden and exit from the registers is upon death or emigration.

Healthcare in Sweden is primarily government-funded and managed at the national, regional, and local level. Only a small proportion of the population (6%) also have some type of supplementary private health insurance.[18] In most regions, there is no formal gatekeeping and patients may contact specialists directly.[18] Applications for data access are sent to the National Board of Health and Welfare and Statistics Sweden and processed by a pre-defined data permit process. The data permit process is preceded by a separate ethical review process by the Swedish Ethical Review Agency. The five Swedish registers are detailed below.

- The Swedish NPR includes information regarding inpatient and outpatient non-primary (i.e., specialist) encounters across Sweden; outpatient general practice encounters are not captured in the NPR. Beginning in 1987, coverage for inpatient admissions became nationwide and is near 100%.[19] Coverage for outpatient non-primary care began nationwide in 2001 and is around 87% (although it may be higher for somatic care such as rheumatology).[19] Key variables include diagnosis, surgery, external causes of injury (E codes), age, sex, hometown, hospital, specialty, and information related to hospital admissions and discharges (e.g., dates, main and contributory diagnoses, mode of discharge). Information on patient anthropometric data (e.g., height, weight, body mass index [BMI]) is not available nor are laboratory test results (e.g., absolute lymphocyte count, blood lipid levels) or clinical measurements (e.g., blood pressure). A number of diagnoses have been reported to have high positive predictive values in the inpatient register.[19] The NPR is updated annually.

- The SPDR, maintained by the National Board of Health and Welfare, contains information on all prescribed and dispensed medication for patients in Sweden. The SPDR was started in July 2005. The register contains data recorded using personal identification numbers and can thus be linked with other Swedish registers. Coverage of prescriptions is close to 100%, however, inpatient administrations and hospital administered drugs in specialized outpatient care are not captured. Information recorded in the SPDR includes basic demographic characteristics such as age, sex, and residency, as well as medication-specific information such as the prescribed/dispensed drug (e.g., ATC code, International Non-proprietary Names), prescription dispensing date, pack size, dispensed amount, formulation, dosage, prescribing healthcare practitioner, and costs. The SPDR is updated monthly.

- The Swedish Cancer Register was started in 1958 and is managed by the National Board of Health and Welfare. The registry records every cancer case diagnosed by clinical, morphological or other laboratory examinations as well as cases diagnosed at autopsy. Since the mid-1980s[20] there are six regional registries associated with the oncological centers in each medical region of Sweden where the registration, coding and major check-up and

correction work is performed. The register includes information on patient characteristics, tumor characteristics, diagnosis, and date and cause of death. Data is updated on an annual basis with a lag time of approximately 13 months.

- The Swedish Cause of Death Registry has been maintained by the National Board of Health and Welfare since 1994 and uses the International Classification of Diseases (ICD) coding, but the rules of the World Health Organization.[21] Variables include, date of birth, country of birth, nationality, sex, marital status, date of death, underlying cause of death, and contributing causes of death. Data are updated annually.

- Patient demographics are available from the national TPR, maintained by Statistics Sweden since 1968. The TPR is produced by the Swedish Tax Agency and the data are transferred to Statistics Sweden. The TPR covers all registered individuals in Sweden and their personal identity numbers with 100% coverage. The register includes demographic information related to population size and composition, such as age, sex, marital status, nationality, place of birth, place of residency in Sweden, migrations within Sweden and to/from abroad, births and deaths.[22] The TPR will be used to ascertain length of medical history available for women eligible for the study (i.e., an enrollment file).

Unless specified otherwise, the Swedish registries are updated yearly, and it can take six to nine months to receive a data extraction. As a result, there is a lag in data availability of approximately 12-18 months.

9.5. Study Size

9.5.1. HIRD, US

For the purposes of calculating sample size, the study is designed to have sufficient size to detect a risk of endometrial cancer for women using LDVE that is 1.5 times the risk of endometrial cancer associated with no use of LDVE. For the HIRD, assuming a 1:4 exposed:comparator ratio, α=0.05, a median follow-up duration of 2.4 years, and a background endometrial cancer incidence rate of 74.5 events per 100,000 person-years,[8] the study would require 33,377 LDVE users and 133,504 non-users to achieve 80% power to detect a hazard ratio of 1.5. To detect a hazard ratio of 1.5, the number of endometrial cancer events required is 60 events in the exposed and 239 events in the comparator. Based on a median duration of 2.4 years, the total number of person-years needed to observe the required number of events is 80,105 person-years in the LDVE cohort and 320,410 person-years in the non-user cohort.

Preliminary patient counts for the study period in the HIRD show that the cohort of LDVE new users (exposed) in the primary analysis will include approximately 152,941 women. Based on a 1:4 exposed:comparator ratio, the potential non-users comparator cohort in the primary analysis will include 611,764 women. Given the available sample sizes, the study will have >99% power to detect a hazard ratio of 1.5 for the LDVE new users cohort.

9.5.2. Swedish Registers, Sweden

Any data extraction from the Swedish national registries requires a full data application, with an estimated timeline of six to nine months. Thus, applying for raw data for the purpose of estimating study size was not feasible due to the strict timelines of this protocol. Therefore, the size of the Swedish study population was estimated based on officially available information.

The publicly available data does not allow to accurately consider the interactions between the various exclusion criteria of this study. When estimating the study size, several assumptions were made to compensate for this, which should be kept in mind when interpreting the resulting estimates. For details about the assumptions used to estimate study size in Sweden, see Annex 3.

In Sweden, the LDVE new users cohort is estimated to include 100,800 women. The non-users cohort is estimated to include 1,378,928 women.

Assuming a 1:4 exposed:comparator matching ratio, α=0.05, a median duration of follow-up of 2.4 years, and a background endometrial cancer incidence rate of 70.4 events per 100,000 person-years,[20] the study would have >99% power to detect a hazard ratio equal to 1.5 for the new users of LDVE cohort. For achieving a power of 80% to detect a hazard ratio of 1.5, the total number of endometrial cancer events required is 299. The total number of person-years needed to observe the required number of events is 84,770 person-years in the LDVE new users cohort and 339,077 person-years in the non-users cohort. Equivalently, the sample size (after matching) required for achieving 80% power is 35,321 in the LDVE new users cohort and 141,282 in the non-users cohort.

Additional details about the estimated study population size are described in Annex 3.

9.6. Data Management

9.6.1. HIRD, US

All analyses will be conducted using Statistical Analysis System ([SAS®]; SAS Institute Inc., Cary, North Carolina, US) software version 9.2 or higher and R version 3.0 or higher.

9.6.2. Swedish Registers, Sweden

In Sweden, raw data are stored at the different National Registers and linkage is performed centrally by government agencies (the National Board of Health and Welfare and Statistics Sweden). Due to legislation prohibiting Swedish patient-level data from leaving the country, the linked and de-identified dataset will be provided to IQVIA in Sweden. The IQVIA investigators in Sweden will use SAS® software or other appropriate analytical software to access the raw data, manage the analytic datasets, and conduct data analysis locally. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation guidelines for data management. In addition, the data will be checked for consistency in terms of the range of values, units of measurement, and relevance of clinical information (e.g., a prostate cancer diagnosis for a female patient).

9.6.3. Case Report Forms (CRFs)/Electronic data record

As referred to in the Validation Study located in Annex 2 of this protocol, the term "Clinical Review Form" (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient in the Validation Study. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The third party responsible for performing medical record review has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the third party responsible for performing medical record review or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.4. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, HealthCore and IQVIA agree to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the third party responsible for performing medical record review, according to local regulations or as specified in the vendor contract or research agreement, whichever is longer. The third party responsible for performing medical record review, must ensure that the records continue to be stored securely for so long as they are retained.

If the third party responsible for performing medical record review becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless third party responsible for performing medical record review and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The third party responsible for performing medical record review must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All data analyses will be performed separately for each data source, and an analysis to pool data at the aggregate level between Swedish and HIRD data sources will be conducted (see Section 9.7.5 Pooled Analyses).

9.7.1. Propensity Score Matching

Details of the statistical methods for PS estimation and matching will be described in the statistical analysis plan. To control for confounding factors, PS will be constructed from baseline covariates for all cohort comparisons. The PS is the estimated probability of receiving a study drug dispensing (i.e., LDVE, MDVE, HDVC), conditional on a set of observed covariates. Propensity scores will be estimated with covariate information collected during the baseline period for each group and each comparison using logistic regression models. Covariates selected will be variables that are related to the outcome, based on literature and clinical judgment as well as sufficiently prevalent in the population to bias the associations under study.[23] Baseline variables to be considered in the model for computing PSs will include demographics, clinical comorbidities, medication use, duration of prior use of hormone therapy, and healthcare utilization (see Section 9.3.4 Baseline Covariates). Propensity score models will also consider for inclusion the 25 most frequently occurring diagnoses, procedures, and medications within the past 12 months among exposed women in the study population that will be ascertained separately in each database. Inclusion of these diagnoses, procedures, and medications in the PS analysis will be based on evidence of association with endometrial cancer in the literature and prevalence.

Comparison groups will be individually matched to exposure groups according to PS to balance the exposure and comparator group on baseline risk factors for outcome at cohort entry.[24,25] Based on sample size estimates, a matching ratio of 1:4 exposed (e.g., LDVE) to comparator patients (e.g., non-users) is planned. If a 1:4 matching ratio is not possible, 1:3 will be tried, and so on.

The PS matched groups will be evaluated for balance and any patient restrictions done as a result of this matching will be described. For each patient characteristic, the prevalence (categorical variables) or mean (continuous variables) will be calculated in each cohort. Absolute standardized differences, the difference in means or proportions divided by the pooled standard deviation, will be computed for each covariate to check its distribution balance within exposure groups (Annex 1: Table 3).[25] For covariates with an absolute standardized difference greater than 0.10, residual differences will be further controlled in the analysis by including the specific variables in the Cox proportional hazards regression model.

9.7.2. Descriptive Analyses

Duration of baseline period (Annex 1: Table 2), duration of follow-up and reason for censoring will be described for each cohort (Annex 1: Table 4). Descriptive statistics will be presented to characterize the PS-matched exposed and comparator groups in terms of demographic information and medical history during the baseline period (Annex 1: Supplemental Tables 1 and 2; Tables 2-1 and 2-2). Specific characteristics of interest are described in Section 9.3 Variables. Counts and percentages for categorical data, and statistics such as mean, median, standard deviation, interquartile range, and range for continuous variables will be reported. Prior use and the duration of prior use of hormone therapy will be characterized for each cohort (Annex 1: Tables 2-1 and 2-2). Characteristics of LDVE use, including active ingredient, index formulation, duration of use, number of dispensings, number of dispensings per formulation (Annex 1: Table 3).

Incidence rates (IRs) and 95% confidence intervals (CIs) of endometrial cancer will be presented for each of the matched study cohorts, along with the number of events, total number of individuals, and accrued person-time. Incidence rates will be calculated as the number of incident events of endometrial cancer within the follow-up period divided by the total person-time at-risk (Annex 1: Table 5).

9.7.3. Comparative Analyses

Cox proportional hazards regression will be used to estimate hazard ratios (HRs) and 95% CIs.

9.7.3.1. Primary Analysis

The primary analyses will estimate and compare the IR of endometrial cancer in postmenopausal women aged ≥ 50 years with a uterus regardless of prior use of hormone therapy in the following PS matched cohorts: (Annex 1: Table 5).

a. New users of LDVE versus non-users of vaginal estrogen.

b. New users of MDVE versus non-users of vaginal estrogen.

c. New users of HDVC versus non-users of vaginal estrogen (HIRD only).

Person-time for treatment groups will begin after a six-month induction period and include any subsequent follow-up time until a censoring event occurs. Person-time for non-users will begin the day after their index date and continue until a censoring event.

Subgroup Analyses

A subgroup analysis will be conducted by prior use of estrogen and/or progestin hormone therapy (Annex 1: Table 5). In this subgroup analysis, assuming there is a sufficient sample size, the incidence of endometrial cancer will be compared in LDVE vs non-users, MDVE vs non-users, and HDVC vs non-users by the following types of prior hormone therapy:

- Unopposed estrogen

- Unopposed progestin
- Progestin opposed estrogen hormone therapy
- Other opposed estrogen hormone therapy
- No prior hormone therapy

Prior use of these medications will be measured using the entire baseline period.

The following subgroup analyses will be conducted separately among the PS-matched cohorts of new users of LDVE, MDVE, and HDVC and non-users of vaginal estrogens to determine if the HR of endometrial cancer varies by the following covariates (Annex 1: Tables 3 and 6):

- Active ingredient at the cohort entry date:
  - Estradiol vaginal;
  - Conjugated estrogen vaginal.
- Formulation at the cohort entry date:
  - Vaginal cream;
  - Vaginal ring;
  - Vaginal tablet;
  - Vaginal insert.
- Duration of use.
- Number of dispensings.
- Number of dispensings per formulation

9.7.3.2. Secondary Analyses

Like the primary analysis, Cox proportional hazards models will be used to estimate the HRs and 95% CIs for the following PS-matched cohorts of subjects with no prior use of hormone therapy (Annex 1: Table 5):

a. LDVE new users versus E+P HT new users of hormone therapy.

b. MDVE new users versus E+P HT new users of hormone therapy.

c. HDVC new users versus E+P HT new users of hormone therapy (HIRD only).

9.7.4. Sensitivity Analyses

Several sensitivity analyses will be conducted. Results from analyses conducted in the HIRD and Sweden will be pooled.

1. HIRD and Sweden: The impact of various induction periods on the HR estimates will be assessed by calculating IRs and HRs for LDVE users and nonusers using no induction period, and an induction period of 3 months (lagging the start of follow-up for the LDVE group) , and 12 months (Annex 1: Table 7 and 12).[26] Additionally, the impact of lagging the start of follow-up for the non-user group will be assessed. LDVE users will be compared to non-users with a six-month induction period for both groups.

2. HIRD and Sweden: To evaluate the possibility of informed censoring and selection in the main analysis resulting from the inclusion of multiple treatment episodes, a sensitivity analysis restricting follow-up to the first treatment episode will be conducted (Annex 1: Table 8 and 12). The HR of endometrial cancer will be calculated implementing censoring upon restart of index drug. The rationale is that the decision about whether or not to restart treatment could be influenced by past treatment experience. The comparison will be done for the following cohorts:

    a. LDVE users versus non-users.

    b. MDVE users versus non-users.

    c. HDVC users versus non-users (HIRD only).

    d. LDVE new users versus E+P HT new users.

    e. MDVE new users versus E+P HT new users.

    f. HDVC new users versus E+P HT new users (HIRD only).

3. HIRD and Sweden: An intent-to-treat (ITT) analysis will be conducted for the possibility of informed censoring and selection in the main analysis resulting from censoring on switching treatment. The ITT analysis will consider patients at risk during the entirety of their follow-up, regardless of discontinuing, or switching treatment, until the earliest of a diagnosis of endometrial cancer, a hysterectomy procedure, health plan disenrollment (HIRD only), emigration (Sweden only), death, or end of study. The HRs will be calculated comparing LDVE users to non-users, and, if sample sizes allow, stratified by prior use of hormone therapy. (Annex 1: Table 8 and 12).

4. HIRD and Sweden: The HR of endometrial cancer will be calculated without censoring on dispensing of a non-study progestogen (except contraceptives) to inform magnitude of changes on effect estimates should censoring be informative. The comparison will be done for the PS-matched LDVE users cohort versus non-users (Annex 1: Table 8 and 12).

5. HIRD only: To evaluate possible impact of missing information on medical history, we will consider extending the baseline period to 18 months. To assess if there are important differences between the populations with at least 12 months and 18 months of continuous HIRD enrollment, the HR of endometrial cancer will be calculated for LDVE users versus non-users among women who have a baseline period of at least 18 months of continuous HIRD enrollment. Comparing results using different baseline durations will assess the effect of potential misclassification of covariates and the balance with increased random error due to decreased study size (Annex 1: Table 8).

6. HIRD and Sweden: To determine if associations between vaginal estrogen, non-users, and E+P HT and endometrial cancer differ according to a patient's history of cancer, a sensitivity analysis will be conducted. to estimate and compare the IRs of endometrial cancer among women by history of cancer other than endometrial cancer and basal cell carcinoma (if case counts are sufficient to support estimation) in the following groups (Annex 1: Tables 9 and 13):

    a. LDVE new users versus non-users of vaginal estrogen.

    b. MDVE new users versus non-users of vaginal estrogen.

    c. HDVC new users versus non-users of vaginal estrogen (HIRD only).

    d. LDVE new users versus E+P HT new users of hormone therapy.

    e. MDVE new users versus E+P HT new users of hormone therapy.

    f. HDVC new users versus E+P HT new users of hormone therapy (HIRD only).

7. HIRD only: To identify the rate of endometrial cancer in patients who may have a cumulative exposure that is higher than the intended average daily dose, the rate of endometrial cancer will be estimated among HDVC new users compared to non-users of vaginal estrogen and HDVC new users compared to E+P HT new users stratified by number of dispensings. Number of dispensings will be categorized as ≤ 2 dispensings per year and >2 dispensings per year(Annex 1: Table 10).

8. HIRD only: To evaluate possible effects of dose of vaginal estrogen on risk of endometrial cancer among vaginal estrogen new users (the full study population), the HR of endometrial cancer will be calculated for HDVC new users versus LDVE new users (Annex 1: Table 10).

9. HIRD and Sweden: A quantitative bias analysis will be conducted to evaluate the impact of potential under-ascertainment of hysterectomy and misclassification of prior use of systemic estrogens or other estrogen- or progestogen-containing products on effect estimates of endometrial cancer rate with LDVE use (Annex 1: Table 11 and Table 12). There may be women whose hysterectomy, prior estrogen use (including prior E+P HT use), or prior progestogen use is not captured in the data sources in each country prior to the index date, in which case, they would not have been excluded at baseline. This analysis will use plausible

estimates of misclassification of covariates to assess potential impact on incidence rate estimates in the PS-matched analysis.

9.7.5. Pooled Analyses

A DerSimonian and Laird random-effects meta-analysis will be performed to pool the results from the HIRD and Swedish databases at the aggregate level.[27,28] The HRs from each data source will be pooled for the comparisons in the primary and secondary analyses comparing 1) new users of LDVE versus non-users of vaginal estrogen and 2) new users of MDVE versus non-users of vaginal estrogen 3) new users of LDVE versus E+P HT new users and 4) new users of MDVE versus E+P HT new users (Annex 1: Table 12). Heterogeneity between databases will be assessed using the Q and I2 statistics, as well as a forest plot for visual inspection of the degree of variability between studies.

9.8. Quality Control

9.8.1. HIRD, US

The study will be tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues are addressed. To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

- Role Based Control Checks: Each member of the team is responsible to perform thorough quality control checks on their work; in addition, the Principal Investigator and Research Project Manager are also accountable for the quality of all deliverables.

- Quality Check Points: Regularly scheduled, centralized "checkpoints" have been implemented during the data management cycle to help ensure accurate translation of programming requests.

- Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project lifecycle.

- Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability, and accuracy for each project.

HealthCore's research team documents study progress and scientific and quality review of all study activities and deliverables (e.g., protocol, data management, data analysis, reports, manuscripts, etc.) in an Action, Decision, Issue, Notification (ADIN) log and in a Quality Control (QC) log. The ADIN log provides documentation of study progress, action items, issues/issue resolution, and notifications, and is updated weekly during internal project team meetings. The QC log documents the quality control measures performed for each study activity during the conduct of the study.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed in accordance with HealthCore Programming Standards. The HealthCore

Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore standard operating procedures (SOPs) and provide a guideline for basic, frequently used terms and definitions, and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure that Protocol criteria were met. If validation checks are not satisfied, then an examination of the problem will be performed on the dataset or datasets in question and the problem will be resolved.

9.8.2. Swedish Registers, Sweden

For Swedish analyses performed by IQVIA, the study will be conducted according to IQVIA and Pfizer SOPs. Pseudonymized data will be provided to IQVIA investigators in Sweden and a selected subset of designated project members, following signing of a confidentiality agreement, will perform the statistical analysis. Data will be analyzed locally, in accordance with legislation that data cannot be provided outside of Sweden.

At the study level, all aspects of the study from protocol development to the reporting of the results will be conducted within the framework of the IQVIA Quality Management System. A QC plan for the study will be developed and executed, which will include quality control on the study methodology, SAP, programming, data management and analysis, study results, conclusions, and interim and final study reports. Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps;
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability, and experience necessary to perform the assigned tasks;
- The result of the execution of the individual steps of the QC plan will be documented and will include the required corrective actions, if any. The execution of any required corrective action will be documented (if necessary);
- The QC plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study;
- Datasets and analytic programs will be stored according to IQVIA procedures with access restricted to study personnel; and
- IQVIA confidentiality agreements are signed by all employees and include data protection and strict prohibitions on re-identification attempts.

9.9. Limitations of the Research Methods

9.9.1. HIRD, US

The HIRD contains a dynamic population in which individuals may enter and exit as their insurance coverage changes over time. Because of this, assessment of vaginal estrogen use is limited to the period during which the individual is enrolled, and it is unknown whether individuals received vaginal estrogen prior to their enrollment. To address this concern, a study design that requires a minimum 12-month observation period prior to the start of follow-up is proposed. Individuals with vaginal estrogen use during this baseline interval will not be admitted to the study. Individuals who had a vaginal estrogen dispensing prior to enrollment may be inadvertently assigned to the non-user group. The effect of this potential exposure misclassification bias will be assessed in a sensitivity analysis restricted to patients with at least an 18-month baseline period.

In this study, diagnosis, procedure, and prescription codes will be used to reconstruct patients' medical histories. Certain risk factors for endometrial cancer such as ethnicity, BMI, pregnancy history, and lifestyle factors are not available in the HIRD or in Swedish registers. The impact of possible residual confounding will be assessed by conducting a quantitative bias analysis.

Possible outcome misclassification due to inaccurate coding of endometrial cancer will be addressed by validation of potential cases using medical records.

Although the HIRD contains a large and geographically diverse population, there are limits to its generalizability. Because the majority of included individuals are commercially insured, most health plan members are currently employed (or are dependents of employed individuals). Findings may not be fully generalizable to individuals receiving Medicaid or Social Security Disability Insurance. Elderly individuals are included in the data environment either due to participation in Medicare Advantage plans, which are administered by Anthem and imply complete data capture in the HIRD, or due to purchase of supplementary insurance. Individuals that purchase supplementary insurance use private programs to help offset the 20% co-pay required for traditional Medicare parts A and B. Because some preventive services are covered in full by Medicare, capture in the HIRD of some diagnoses and procedures may be incomplete and are often excluded from analysis in research studies. Insofar as Medicare Advantage and traditional Medicare individuals may differ from commercially insured patients, our results may have limited generalizability in this age group.

9.9.2. Swedish Registers, Sweden

In the Swedish registers, entry is upon birth or immigration to Sweden and exit from the registers is upon emigration or death.

The Swedish registers used to identify vaginal estrogen use do not have information on daily dose. As a result, when a patient is given a prescription of a known number of vaginal estrogen tablets at a given strength per tablet, it is not clear whether they are to take one or more tablets per day. To determine the length of a treatment episode and the dosage category (LDVE or MDVE), it is assumed that patients are prescribed vaginal estrogen according to the recommended daily dosages. All vaginal estrogens under study available in Sweden are recommended to be used within the low-dose range except for Vagifem, which was available at a MDVE strength per tablet for a limited

period of time during the study period. Because stockpiling prescriptions is a common practice for patients in Sweden, if patients receive more than one vaginal estrogen prescription at a time, it is assumed that they are stockpiling and not that they are increasing their daily dose. For these reasons, the study may have a small sample size for the MDVE treatment group.

The Swedish NPR includes healthcare information from both outpatient and inpatient specialist care. It does not, however, include information from primary care visits. The lack of access to primary care information should be considered a limitation based on specific diagnoses of interest that might be captured for the first time in primary care. However, general guidelines in Sweden state that for treatment of women with menopausal issues, there should always be further investigation done for this patient group before initiating any vaginal treatment. One would expect this patient group to be referred to specialist care thereby increasing the likelihood that relevant diagnoses are captured.

As with the HIRD, diagnosis, procedures, and prescription codes from the Swedish registers will be used to inform patients' medical histories. Several factors that influence the risk of developing endometrial cancer were not able to be collected using the registers from Sweden. These factors include certain demographic factors (e.g., ethnicity, socioeconomic status) and lifestyle characteristics (e.g., BMI/obesity, exercise, diet, and smoking history). Since Sweden's healthcare is government-funded with near 100% capture within the SPDR, the likelihood of misclassifying prevalent users as true incident users is minimal. Incident cases of endometrial cancer will be identified through Sweden's established national cancer registry.

Although there has been an influx of immigration in more recent years, Sweden has a history of a homogenous population both ethnically and sociodemographically. Results from this study may not be representative of the broader European population.

Moreover, due to the availability of a few products containing various vaginal formulations of biologically weak estradiol without prescription, some information regarding exposure might not be captured in the SPDR. However, the influence on the study populations of interest is expected to be minor.

9.9.3 Other Limitations

To maximize follow-up for patients on vaginal estrogen we have not restricted follow-up to the first treatment episode, however the inclusion of multiple treatment episodes creates the potential for selection biases based on the possibility that restarting treatment may be related to a favorable outcome with past experience and that failing to re-start could be related to an unfavorable experience. This will be explored in a sensitivity analysis that censors subjects upon re-start of their index drug.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.1.1. HIRD Study

The current study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US. There is no active enrollment or active follow-up of study subjects, and no data is collected directly from individuals. HealthCore maintains Data Use Agreements and Business Associate Agreements with all covered entities which provide data to the HIRD.℠ HealthCore's access, use, and disclosure of protected health information (PHI) comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 Code of Federal Register (CFR) Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose identifiable PHI unless under a specific waiver of authorization (i.e., a HIPAA Waiver of Authorization from an Institutional Review Board [IRB]). HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

10.1.2. Swedish Study

This study involves data that exist in pseudonymized structured format. Data will be analyzed locally, in accordance with legislation that data cannot be provided outside of Sweden. Patient anonymity will be protected in the reporting and publishing of the results of the study. Results will be reported exclusively in an aggregate level where identification of individuals is not possible. Direct identifiers, such as name, address or personal identification number, are never published in any format. In addition, sensitive information will be protected, such place of residency, physical and physiological, genetic, mental, economic, cultural or social factors. Furthermore, the exact cell counts in tables, minimums or maximums may not be reported, if a recognition of individuals could be possible due to a low number of observations in a cell of a table or due to minimum or maximum values representing one or few individuals. Detailed specifications on the requirements for protecting patient anonymity is subject to the conditions demanded by data holders for accessing and processing individual level data (microdata) and other local regulations at the time of processing the data. Thus, final details on the reporting to protect patient anonymity will be detailed in the study report.

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.2.1. HIRD Study

HealthCore does not access, use, or disclose PHI other than as permitted by HIPAA and its Business Associate Agreements. The HIPAA Privacy Rule permits PHI in a limited data set to be used or disclosed for research, without individual authorization, if certain criteria are met (further described

45 CFR Part 160 and Subparts A and E of Part 164). Thus, informed consent and IRB review is not required. When using PHI for research, this typically means PHI will be used to create limited data sets for research, or when that is not feasible, a specific waiver of the HIPAA authorization requirements from an IRB may be obtained. HealthCore also takes into consideration other federal and state laws and regulations that might limit use of certain types of data more than HIPAA, including those laws related to identifiable records related to substance abuse and human immunodeficiency virus.

At no time during the conduct of this study will HealthCore provide individual or provider identifying information to the Sponsor. De-identified aggregated results will be reported to Pfizer, Inc. Pfizer will not attempt to re-identify any results provided for the study.

10.2.2. Swedish Study

As this study involves pseudonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer or IQVIA is not required.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

An IRB waiver will be requested for the portion of this study using claims data because they are de-identified and do not contain any personal health information (PHI). IRB approval is required for the validation study because PHI is used. IRB approval for the validation study will be sought in June 2021 and data collection and validation will follow.

10.4. Ethical Conduct of the Study

10.4.1. HIRD Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Good Pharmacoepidemiology Practices* (GPP)[29] issued by the International Society for Pharmacoepidemiology (ISPE) and the US FDA Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.[30]

10.4.2. Swedish Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the following documents:

- Module XVI of the European Medicines Agency's (EMA's) *Guideline on Good Pharmacovigilance Practices (GVP) – Risk minimisation measures: selection of tools and effectiveness indicators*;[31]

- GPP issued by ISPE;[29]

- *Guidelines for Good Epidemiological Practice* issued by the International Epidemiological Association;[32]

- *International Ethical Guidelines for Health-related Research Involving Humans* issued by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization;[33]

- *Guide on Methodological Standards in Pharmacoepidemiology* issued by ENCePP;[34]

- The US FDA Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.*[30]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS (AE)/ADVERSE REACTIONS

The main study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

The Validation Study described in Annex 2 requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the Endometrial Cancer Clinical Review Form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members must complete the following Pfizer training requirements:

- "Your Reporting Responsibilities (YRR) Training for Vendors".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

A study report, which will include sections on background, methods, and results pertaining to the study objectives listed in Section 8, discussion and conclusions, will be prepared including country-level analyses for both the US and Sweden.

HealthCore, IQVIA, and Pfizer will jointly prepare and submit the first publication relating to results of the study within nine months of Pfizer's receipt of the Final Report. Any additional dissemination of study results (i.e., presentation at scientific conferences, additional publications) will be discussed by the HealthCore, IQVIA, and Pfizer Project Team.

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ANNEX 2. VALIDATION STUDY COMPONENT

This annex describes the plan for the development and validation of the algorithm that will be used in the current study to identify the occurrence of endometrial cancer (EC) as the study endpoint. As part of the current study, the performance of EC algorithms in administrative claims data will be assessed through medical record review and case adjudication for the US data source. This validation component will begin after building the analytic files for the current study, identifying the cohort of patients who meet the inclusion/exclusion criteria (as described in Section 9.2 Setting of the Study Protocol, and constructing the exposure and comparator groups. The final algorithm for EC will be determined prior to conducting analyses to estimate and compare incidence rates of EC for the exposure and comparator groups. The validated algorithm for EC will be used in the HIRD.

1. PURPOSE OF VALIDATION

A recently published validation study developed and validated an algorithm in the HIRD for EC using ICD-9 CM diagnostic codes. For EC, ICD-9-CM diagnostic codes are somewhat non-specific, including both EC and relatively rare non-endometrial uterine cancers. In the previous validation study, an initial algorithm was used to identify EC defined as at least one inpatient encounter or at least two outpatient encounters with a diagnosis of ICD-9-CM 182.x (malignant neoplasm of the body of the uterus).[35] To develop and validate the algorithm for EC, data from the HIRD were supplemented with review of full text medical records. Medical records were obtained for potential EC cases identified in the HIRD℠ among E+P HT users between 01 January 2010 and 31 August 2014. Two clinical experts reviewed and adjudicated case status to determine a diagnosis. After clinical adjudication of 315 patients with available medical records, 286 women were confirmed as having endometrial adenocarcinoma, resulting in a positive predictive value (PPV) of 90.8% (95% Confidence Interval [CI] 86.9%–93.6%).

Because the prior algorithm was developed among E+P HT users, the algorithm may not perform as well among vaginal estrogen users or non-users of hormone therapy products. Furthermore, the algorithm used ICD-9-CM codes, and ICD-10-CM codes offer greater specificity than ICD-9 codes. This study will use ICD-9-CM codes and ICD-10-CM codes and will evaluate the performance of the codes in populations being examined in the current study, i.e., users of low-dose vaginal estrogen (LDVE), moderate-dose vaginal estrogen (MDVE), high-dose Premarin VC (HDVC), estrogen and progestin hormone therapy (E+P HT), as well as non-users of these medications. The aim of this study is to generate two algorithms (one for ICD-9-CM and one for ICD-10-CM) to identify EC cases in the HIRD.

2. OBJECTIVE

To develop and assess two algorithms, one for the ICD-9-CM coding system and one for the ICD-10-CM coding system, to identify endometrial cancer cases in the HIRD.

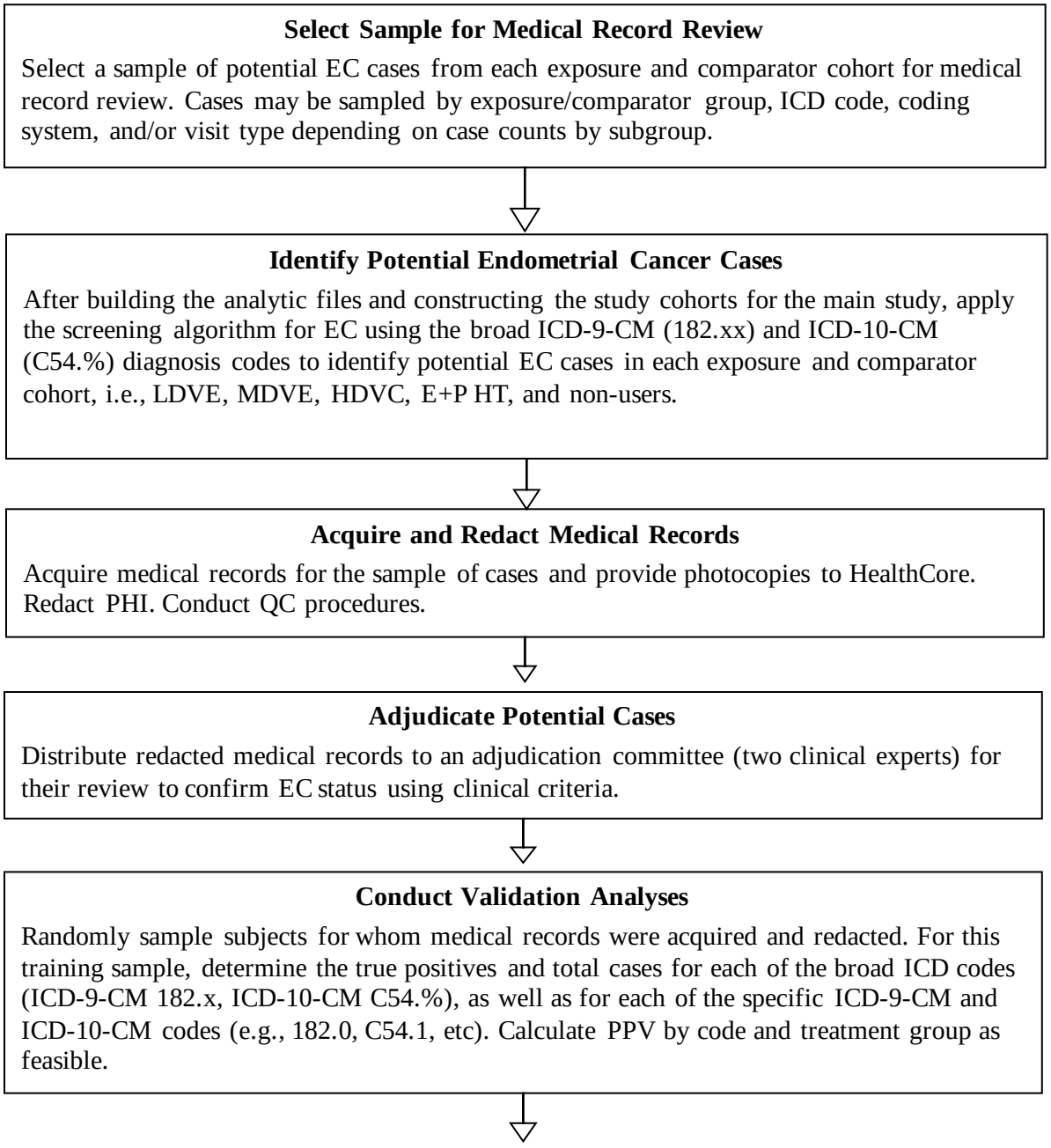
3. OVERVIEW OF VALIDATION STEPS

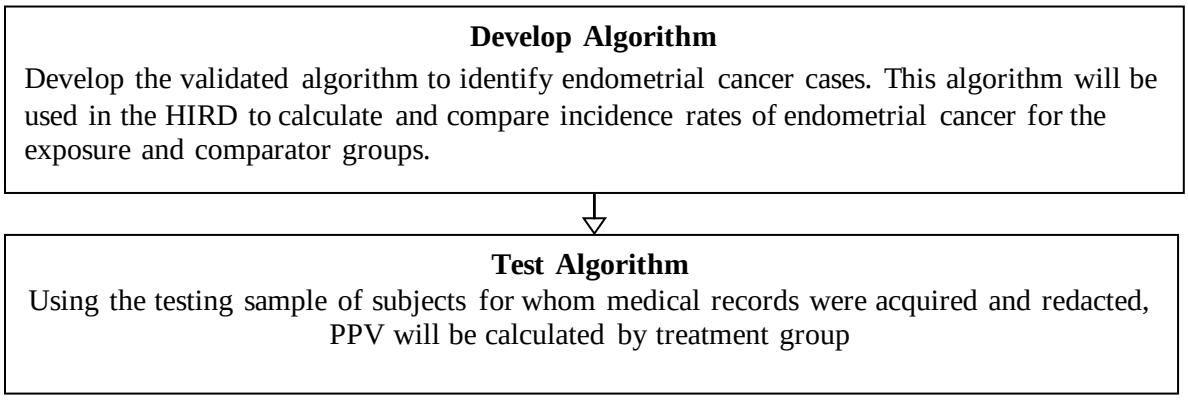
Medical records will be obtained for a sample of women with EC identified in the claims data and will undergo expert clinical review to confirm whether the women had EC. For validation of EC, the gold standard against which the claims-based algorithm's performance will be measured is the

diagnosis derived from clinical expert review of the evidence available in the medical record, which includes all available results of endometrial biopsies, clinician evaluations, treatment, and medical history. The results of the adjudication will provide information on the PPV of the claims-based event identification criteria to inform decisions for identifying outcomes in the main analyses.

The steps of event identification and adjudication are summarized in Figure 1 below:

Figure 1. Overview of Validation Steps





Abbreviations: E+P HT, Estrogen and progestin hormone therapy; EC, endometrial cancer; HDVC, High-dose Premarin Vaginal Cream; LDVE, Low-dose vaginal estrogen; MDVE, Moderate-dose vaginal estrogen; PHI, protected health information; PPV, positive predictive value; QC, quality control; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

4. ENDOMETRIAL CANCER CASE IDENTIFICATION

4.1. Claims-Based Identification of Potential Endometrial Cancer Cases

Potential cases of endometrial cancer in the current study will be identified via a screening algorithm in each exposure and comparator cohort, i.e., LDVE, MDVE, HDVC, E+P HT, and non-users, using ICD-9 and ICD-10 codes. The screening algorithm will be defined as at least one ICD-9-CM or ICD-10-CM diagnosis code listed in Table 1 in any position (primary, secondary, etc.) and any location (outpatient, inpatient, ED, etc.) during the follow-up period. This algorithm was informed using preliminary case counts of patients in the HIRD with codes beginning with 182 and C54. Endometrial cancer is the most common cancer with codes starting with 182 or C54 and the vast majority of patients had either the code 182.0 or C54.1. The codes 182.8, C54.8 and C54.9 were also included to improve the capture of all possible cases of EC. Therefore, with this screening algorithm, an assumption is that all possible cases of EC have been captured. The index date of diagnosis will be the date of the first encounter with a diagnosis code in Table 1. Cases diagnosed during baseline will be considered prevalent cases and excluded from analysis.

Table 1. Endometrial Cancer Diagnosis Codes for Provisional Case Definitions

ICD-9-CM		ICD 10-CM	
Code	**Description**	**Code**	**Description**
182.0	Corpus uteri, except isthmus [Endometrium] [Myometrium] [Fundus] [Cornu]	C54.1	Malignant neoplasm of endometrium
182.8	Other specified sites of body of uterus [Malignant neoplasm of contiguous or overlapping sites of body of uterus whose point of origin cannot be determined]	C54.8	Malignant neoplasm of overlapping sites of corpus uteri
N/A	N/A	C54.9	Malignant neoplasm of corpus uteri, unspecified

4.2. Identification of Validation Sample

Patients who meet the inclusion/exclusion criteria for the current study and fulfill the screening algorithm during follow up will qualify for inclusion in the validation study sampling. Table 2 will be populated with the counts of provisional cases identified with the screening algorithm. Preliminary feasibility counts for EC based on the screening algorithm show that approximately 500 cases are included across the vaginal estrogen exposure groups and approximately 100 cases in the E+P HT comparator group. The target number of cases to be sampled will be 300 across vaginal estrogen users (LDVE, MDVE, HDVC), all E+P HT, and 300 non-users. Cases will be sampled by exposure/comparator group, ICD code, and coding system, and/or visit type depending on case counts by subgroup (Table 2). Preference will be given to requesting medical records for provisional cases coding with ICD-10-CM codes because no validation study has been published for that coding system. If case counts are lower than expected, then medical records for all provisional cases will be sought. A yield of approximately 65% of requested medical records is expected and also that 10% of medical records returned will not be evaluable (e.g., missing data, wrong time period, etc.). Therefore, to obtain medical records for 300 provisional cases among vaginal estrogen users, records from all patients identified with the screening algorithm will be requested. A similar number of records will be requested from the non-user cohort.

Table 2. Number of Provisional Endometrial Cancer Cases by Diagnosis Code, Exposure/comparator group, and Visit Type

		Number of Endometrial Cancer Cases							
			Exposure/Comparator					Visit Type	
ICD Version	Code	Total	LDVE	MDVE	HDVC	Non-Users	E+P HT	Inpatient	Outpatient
ICD-9-CM	182.0								
ICD-9-CM	182.8								
ICD-10-CM	C54.1								
ICD-10-CM	C54.8								
ICD-10-CM	C54.9								

5. MEDICAL RECORD ACQUISITION AND REDACTION

5.1. Vendor Identification and Contracting

HealthCore will contract with a vendor who has extensive training and experience in performing medical record acquisition and redaction. HealthCore contracts only with vendors who follow federal and state laws and regulations, including but not limited to privacy and security rules such as HIPAA.

5.2. Medical Record Acquisition

For a sample of patients who meet the EC screening algorithm, at least one medical record per patient will be requested. To increase the likelihood that the medical record includes data required for adjudication, providers and/or facilities who have the patient's medical records based on the type of visit in claims will be ranked, such as:

1. Hospital or ED visit with EC; or

2. Physician office(s) with at least one claim for EC.

If no medical records can be obtained for a patient, an alternate patient will be selected from the list of eligible patients to meet the target number of medical records per subgroup for case validation. In addition, medical records obtained by the vendor that are missing key information, e.g., documentation from biopsy or pathology reports, will be considered non-evaluable. These patients will not count towards the target sample of 300 cases per exposure/comparator cohort, and records for an alternate patient will be requested.

5.3. Electronic Copies of Medical Records

The vendor will provide HealthCore with scanned/electronic copies of the medical records that were successfully retrieved. They will also provide scanned/electronic copies with the PHI redacted.

5.4. Quality Control

HealthCore will take steps to maximize the validity of the data obtained from the medical record review process. HealthCore will train the vendor responsible for acquiring the medical records to ensure standardization and consistency across time. Prior to initiating record acquisitions, HealthCore will hold a kick-off meeting/training session with the vendor to clarify any details related to record acquisition. Upon receipt of the copied and masked medical records, HealthCore will review each medical record to ensure completeness and the appropriate blinding of identifiable information. If any issues are identified in the review, the medical record will be returned to the vendor for correction and resubmission. Adjudicators will be blinded to exposure group, physician, and personal identification information.

6. EVENT ADJUDICATION

6.1. Endpoint Adjudication Committee

An Endpoint Adjudication Committee (EAC) comprising clinicians not employees of HealthCore or Pfizer will be formed to review the medical records and adjudicate the EC cases identified in the

claims. The EAC will comprise of two clinical experts with obstetrics and gynecology (OB/GYN) and/or oncology specialties (e.g., gynecologic oncologist).

The EAC will be identified prior to the initiation of medical record acquisition and adjudication. The members will provide clinical guidance to support finalization of the algorithm to identify EC. A training session will be provided to the EAC prior to initiation of adjudication. All members of the EAC must sign a conflict of interest form prior to this training. EAC members will also be required to disclose any conflicts of interest that arise during the course of the study.

The training session will include a review of the validation plan, as well as the policies and procedures for adjudicating the events. This training session will be a collaborative approach to illustrate the information that physician reviewers will use to determine EC events. After a thorough discussion has ensued, a document will be circulated among the study team and reviewing physicians to exemplify complete documentation of the EC adjudication process. Any changes made to the adjudication criteria or Clinical Review Form due to clarifications requested during the training session will be documented in an amendment to validation plan.

All members of the EAC are responsible for completing the following activities:

- Attend the training session prior to the initiation of adjudication.
- Understand the current case definition for the study endpoint to be adjudicated.
- Read and understand the contents of the validation plan and all future amendments to the validation plan.
- Complete the Clinical Review Form (Appendix A) for all events that require adjudication in the time frame specified in the consulting work order.
- Attend any scheduled conference calls or meetings for the final adjudication of events and the conduct of committee business, as needed.
- Participate in the orderly conduct of teleconferences and meetings (with technical assistance from HealthCore as needed).

6.2. Clinical Criteria for Endpoint Adjudication

The clinical criteria for adjudicating EC events identified in claims includes the presence of the following in the medical record:

1. Documentation of an EC diagnosis (any stage) by a treating healthcare provider.

AND

2. Positive results from an endometrial biopsy, pathology report, or surgical procedure, OR treatment with medications consistent with EC care.

HealthCore will consult with the EAC to further develop these criteria as necessary during the training session that will be held prior to the start of adjudication for the pilot study. The definition may also be revised based on feedback from the EAC following review of a pilot group of cases.

6.3. Independent Event Adjudication

Medical records for each potential EC case selected for validation will be reviewed independently by both expert clinicians on the EAC. The EAC members will use a structured questionnaire, i.e., the Clinical Review Form (Appendix A), to assess the criteria for endpoint adjudication and to record key clinical findings (e.g., biopsy results, diagnostic procedures and treatments, stage, and pre-existing cancers, histology). Each EAC member will adjudicate case status by medical record review based on their expert opinion informed by the prespecified clinical criteria found in Appendix A: The endometrial cancer clinical review form. They will each classify EC case status as either confirmed (true positive), not confirmed (false positive), or non-evaluable. Reviewers will document the reason why a potential case was not confirmed as EC or non-evaluable.

6.4. Final Event Adjudication

All decisions made from the final event adjudication will be entered into a case verification form.

If the reviewers agree on the information collected in the Clinical Review Form, no further action is required. The EAC will meet if there are any discordant results to reconcile. To maximize efficiency and reduce the number of meetings, the EAC will hold adjudication meetings after a specific number of discordant results have been identified. This number will be mutually agreed upon by HealthCore and the EAC. During the final adjudication, the case verification form will be updated with a final decision by the EAC as to the final classification of cases (confirmed, not confirmed, or non-evaluable).

The EAC will document the final decision on the adjudication of each case based on a consensus of the committee members after considering the information recorded in the Clinical Review Form for each discordant case. The final decision on adjudication status for potential EC cases selected for validation will be documented in the case verification form as one of the following:

- Confirmed (true positives) – claims-based event represents true case of EC based on fulfilling the validation criteria.
- Not confirmed (false positives) – claims-based event did not fulfill the validation criteria for EC.
- Non-evaluable – claims-based event could not undergo validation due to insufficient information to confirm case status.

The following information will also be documented in the case verification form:

- Reason(s) for non-confirmed classification.
- Reason(s) for non-evaluable classification.

6.5. Medical Record Distribution and Tracking

The redacted copies of the medical records will be shared with the two EAC clinical experts. Redacted medical records will be distributed electronically to the members of the adjudication committee via an online portal or Secure File Transfer Protocol (SFTP) transfer. All medical records will be assigned to both of the clinical experts. Each member of the EAC will be provided with a listing of the specific cases for which he or she is responsible and a schedule for reviewing the current batch of medical records.

Once received by reviewers, a window of 21 days will be allowed for physicians to complete their reviews. If not completed, or if only a portion of physicians' total medical records have been reviewed by this time, HealthCore will send a reminder message about the deadline. These reminders will be sent once a week for every week when outstanding medical records have not been reviewed and submitted.

Physicians will also be provided access to an electronic database via SFTP to record their responses to the Clinical Review Form (Appendix A). Each form within the database will have a medical record number, which will correspond to the same number on the electronic medical record. The database will allow physicians to track their progress through the review process by distinguishing between medical records they have already seen and those that still need their attention.

6.6. Data Management

The Clinical Review Form shown in Appendix A will be converted into an electronic format to facilitate data entry. The collected information will be entered into a secure electronic database. The research database will be hosted on servers contained within HealthCore's Data Coordination Center (DCC) which is located in a locked suite within HealthCore's facility. Access to this database will be via password protected 128-bit secured encrypted connections (Secure Socket Layering pages). HealthCore will use the data entered into the secure database to complete the validation analyses.

7. VALIDATION ANALYSES

7.1. Calculate Positive Predictive Value

Following medical record redaction and adjudication, a random set of adjudicated EC cases stratified by treatment group will be sampled. This random sample will be training set used to generate the PPVs for various algorithm components and to build the EC algorithm. The provisional cases who were not randomly sampled will be the testing set used to validate the algorithm developed on the sampled subjects. If enough medical records have been retrieved (e.g., 300 for the vaginal estrogen group), a split-sample validation procedure will be used. The training set will consist of a random selection of two-thirds of provisional cases for each treatment cohort (vaginal estrogen users, E+P HT users, and non-users) and the testing set will be the last third of medical records. If too few records are retrieved to use this method, then a re-sampling technique such as k-fold validation will be used.

Descriptive characteristics of patients with provisional EC, those whose medical records were returned, those for whom medical records could not be obtained and those in the training set and testing set in Table 3 will be presented. Baseline characteristics will be compared across the study cohorts to assess comparability. The information to be compared across cohorts includes demographics, key medical characteristics (current therapies), facility types and reasons that the medical record was unavailable (e.g., unidentifiable/out of network provider, unable to identify the patient, facility refusal).

Table 3: Characteristics of Patients with Provisional Endometrial Cancer

Characteristic	All provisional cases	Patients with retrieved medical records	Patients whose medical records could not be obtained	Patients in the training set	Patients in the testing set
Total					
Age Mean (sd)					
Region					
North					
Midwest					
South					
West					
Current medications					
Non-study vaginal estrogens					
Estrogen hormone replacement therapy					

Characteristic	All provisional cases	Patients with retrieved medical records	Patients whose medical records could not be obtained	Patients in the training set	Patients in the testing set
(oral, transdermal, injectable), single entity					
Estrogen hormone replacement therapy (oral, transdermal, injectable), combination, excluding E+P HT products					
Progestogen contraceptives (oral, transdermal, injectable, implant, IUD), single entity					
E+P contraceptives (oral, transdermal, injectable)					
E+P contraceptives (vaginal)					
Progestogens (oral, transdermal, injectable)					
Progestogens (vaginal)					
Selective estrogen receptor modulators					
Androgens					
Anabolic steroids					
Corticosteroids (oral and injectable)					
Lipid lowering agents					
Antihypertensives					
Antidiabetics					
Antidepressants					
Sedatives/hypnotics					
Anticonvulsants					
Antifungals					
Antivirals					
Macrolides					
Facility types					
Outpatient					

Characteristic	All provisional cases	Patients with retrieved medical records	Patients whose medical records could not be obtained	Patients in the training set	Patients in the testing set
Inpatient					
ED					
Other					
Reason medical record was not available					
[TBD]	N/A	N/A		N/A	N/A

Abbreviations: E+P HT, Estrogen and progestin hormone therapy; ED, emergency department; IUD, intrauterine device; N/A, not applicable; sd, standard deviation; TBD, to be determined.

The validation results will include true positive and false positive cases separately for the EC screening algorithm by exposure/comparator group (Table 4). The number of provisional cases, confirmed cases, not confirmed cases, non-evaluable cases, and PPV and 95% CI for each algorithm component will be calculated. The PPV will be calculated as the number of events confirmed as true cases via medical record review, divided by the total number of events that were evaluated for validation.

$$PPV = \frac{true\ positives}{true\ positives + false\ positives}$$

The PPV will initially be evaluated for the broad EC screening algorithm for the full sample and by treatment group. Changes in PPV will be evaluated by shifting to more specific codes and counts of encounters. Sites of care will not be analyzed because preliminary case counts in the HIRD suggest that approximately 90% of subjects with an inpatient encounter also have an outpatient visit. In a sensitivity analysis, the non-evaluable cases will be added to both the numerator and denominator.

Table 4. Positive predictive values for endometrial cancer algorithm components

Algorithm Development	Total Cases N	Confirmed n (%)	Not Confirmed n (%)	Non-Evaluable n (%)	PPV % (95% CI)
Overall	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Exposure Groups					
LDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
MDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
HDVC	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Comparator Groups					
E+P HT	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Non-users	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
ICD-9-CM					
182.0	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
182.8	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
ICD-10-CM					
C54.1	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
C54.8	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
C54.9	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Number of separate encounters at any location with ICD-9 codes 182.0 or 182.8					
1	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
≥2	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
≥3	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Number of separate encounters at any location with ICD-10 codes C54.1, C54.8, or C54.9					
1	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
≥ 2	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
≥ 3	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)

Abbreviations: CI, confidence interval; E+P HT, Estrogen and progestin hormone therapy; HDVC, High-dose Premarin Vaginal Cream; LDVE, Low-dose vaginal estrogen; MDVE, Moderate-dose vaginal estrogen; N, number; PPV, positive predictive value; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

7.2. Development of the Algorithm

Based on the validation results in Table 4, separate algorithms for ICD-9-CM and ICD-10-CM coding systems will be developed because it is not certain that the crosswalk between ICD-9 to ICD-10 will yield an algorithm with comparable performance. The algorithms will be generated by choosing codes and the number of encounters that will maximize the detection of EC cases. For example, if Table 4 shows that there are true EC patients receiving the codes C54.8 or C54.9 then those codes will be included in the algorithm (Table 5). These algorithms will then be validated using the testing sample of provisional cases (Table 6). If there are enough cases in each exposure group (LDVE, MDVE, and HDVC) then the PPVs will be assessed by each vaginal estrogen treatment group and used to correct our estimates for measurement error. Otherwise, one PPV will be assessed for all three exposure groups. The PPVs for each treatment group will be used to correct estimates of association for measurement error in the main analysis. A sensitivity analysis will be conducted using the non-evaluable records. The PPVs for the final algorithm will be calculated assuming the non-evaluable records are cases and again assuming they are non-cases.

Table 5: Positive Predictive Values for Endometrial Cancer Algorithms by Exposure/comparator Group

Algorithms assessed	**Total Cases**	**Confirmed**	**Not Confirmed**	**Non-Evaluable**	**PPV**
	N	**n (%)**	**n (%)**	**n (%)**	**% (95% CI)**
ICD-9-CM algorithm: *[algorithm definition including ICD-9 EC codes and number of encounters]*					
Overall	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Exposure Groups					
LDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
MDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
HDVC	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Comparator Groups					
E+P HT	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Non-users	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
E+P HT	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Non-users	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
ICD-10-CM algorithm: [*algorithm definition including ICD-10 EC codes and number of encounters]*					

Algorithms assessed	Total Cases	Confirmed	Not Confirmed	Non-Evaluable	PPV
	N	n (%)	n (%)	n (%)	% (95% CI)
Overall	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Exposure Groups					
LDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
MDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
HDVC	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Comparator Groups					
E+P HT	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Non-users	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)

Abbreviations: CI, confidence interval; E+P HT, Estrogen and progestin hormone therapy; EC, endometrial cancer; HDVC, High-dose Premarin Vaginal Cream; LDVE, Low-dose vaginal estrogen; MDVE, Moderate-dose vaginal estrogen; N, number; PPV, positive predictive value; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Table 6: Positive Predictive Values for Final Endometrial Cancer Algorithms by Treatment Group in the Testing Set

Algorithms assessed	Total Cases	Confirmed	Not Confirmed	Non-Evaluable	PPV
	N	n (%)	n (%)	n (%)	% (95% CI)
ICD-9 algorithm: [algorithm definition including ICD-9 EC codes, number of encounters with EC code, and sites of care]					
Overall	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Exposure Groups					
LDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
MDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
HDVC	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Comparator Groups					
E+P HT	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Non-users	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)

Algorithms assessed	Total Cases	Confirmed	Not Confirmed	Non-Evaluable	PPV
	N	n (%)	n (%)	n (%)	% (95% CI)
ICD-10 algorithm: [algorithm definition including ICD-10 EC codes, number of encounters with EC code, and sites of care]					
Overall	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Exposure Groups					
LDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
MDVE	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
HDVC	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Comparator Groups					
E+P HT	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)
Non-users	X	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx, xx)

Abbreviations: CI, confidence interval; E+P HT, Estrogen and progestin hormone therapy; EC, endometrial cancer; HDVC, High-dose Premarin Vaginal Cream; LDVE, Low-dose vaginal estrogen; MDVE, Moderate-dose vaginal estrogen; N, number; PPV, positive predictive value; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

The validated algorithms will be used in the analyses for the main study to identify EC as the primary endpoint of interest, and sensitivity analyses will be used to assess the impact of misclassification based on algorithm performance characteristics such as PPV.

8. ARCHIVING

Archiving of study data and materials will be performed by HealthCore in accordance with standard internal procedures.

9. STUDY ETHICS

As part of the validation study, the medical and pharmacy claims data will be augmented with information obtained from medical records. In order to conduct medical record acquisition and abstraction, HealthCore must access PHI (see Section 10 Protection of Human Subjects of Study Protocol). Therefore, a HIPAA Waiver of Authorization will be applied for from an IRB. HealthCore will submit the protocol and Clinical Review Form to a central IRB for review and approval. Approval is typically provided within two to three weeks of submission. Once IRB approval is obtained, HealthCore's vendor will proceed with the conduct of medical record acquisition in accordance with the limitations and requirements stipulated by the IRB. If changes to the protocol and Clinical Review Form are required, HealthCore will submit an amendment to the IRB. As the

IRB is independent, HealthCore cannot control the approval or whether there are conditions for the approval.

HealthCore will engage a vendor for medical record acquisition and abstraction and provide the vendor only the minimum amount of patient information that is necessary. HealthCore only utilizes vendors that have agreed to follow federal and state laws and regulations, including but not limited to privacy and security rules such as HIPAA prior to contracting.

At no time during the conduct of this study will HealthCore provide patient identifying information to the study Sponsor. Deidentified and aggregated results will be reported to the study Sponsor. The study Sponsor will not attempt to re-identify any results provided for the study.

10. APPENDIX A. ENDOMETRIAL CANCER CLINICAL REVIEW FORM

HealthCore CLINICAL REVIEW FORM

Clinical Review Form, Endometrial Cancer

Reviewer:

Patient ID:

Age (years):

Clinical Review Form, Endometrial Cancer

Section 1: Medical record documentation

1. Was there documentation of an endometrial cancer diagnosis in the medical record?	Yes/No
a. If yes, highest stage recorded?	[IA]
b. If yes, was the diagnosis listed as questionable or rule-out?	Yes/No
2. Please describe histology findings.	[Grade 1, endometrioid]
3. Was there documentation of any other type of cancer?	Yes/No
a. If yes, what type(s)?	[free text]
b. If yes, which type of cancer was diagnosed first?	Endometrial cancer Other (specify)
4. Please indicate whether documentation of the following was found in the medical record:	
a. Consultation with an oncologist.	Yes/No
b. Endometrial biopsy.	Yes/No
c. Physician prescribed treatment consistent with endometrial cancer.	Yes/No
d. Hysterectomy performed.	Yes/No

Section 2: Clinical reviewer impression

1. Do you believe that this was an endometrial cancer case?	Yes/No [Well documented case of Stage IA, grade 1 endometrioid adenocarcinoma of the endometrium]
2. Please provide any additional comments.	

ANNEX 3. ESTIMATION OF STUDY SIZE AND POWER FOR SWEDEN

For Sweden, preliminary patient counts are not available because a formal protocol is needed to obtain data from national registries. The size of the exposed cohort was estimated using the statistics databases of the National Board of Health and Welfare of Sweden (1) and Statistics Sweden, (2) and an estimate for the prevalence of vaginal estrogen use reported for peri- and postmenopausal women in Denmark in 2013. (3)

In Sweden, the LDVE cohort (All users) is estimated to include 132,372 women and the LDVE cohort (new users) is estimated to include 100,800 women (estimation process is summarized in Table 2).

The LDVE non-user cohort (Comparator 1) is estimated to include 1,378,928 women (estimation process is summarized in Table 3).

Table 2. Steps for Estimating the LDVE Cohort (exposure group) Size.

Group	Estimated group size
Swedish women aged 50 years or older between 2007-2019.(3)	2,508,789
Swedish women aged 50 years or older using LDVE during study period (assuming a prevalence of 10.2% for vaginal estrogen use (excluding estriol), as reported for peri- and postmenopausal women in Denmark in 2013.(4))	255,895
Swedish LDVE cohort (exposure group), All Users (using an estimate for the impact of excluding women using E+P HT, non-study estrogen [except contraceptives] or non-study progestogen [except contraceptives]; based on publicly available data.(2))	132,373
Swedish LDVE cohort (exposure group), New Users only (assuming 76.1% of all users are new users, based on HIRD study size estimates)	100,800

Table 3. Steps for Estimating the LDVE Non-User Cohort (Comparator 1) Size.

Group	Estimated group size
Swedish women aged 50 years or older between 2007-2019.(3)	2,508,789
Median of yearly counts of women aged 50 years or older purchasing any estrogen or progestogen products during the study period.(2)	392,565
Twofold median of the count on previous row (used as a conservative estimate for the number of women using any estrogen or progestogen products, among women aged 50 years or older between 2007-2019)	785,130
Swedish women aged 50 years or older between 2007-2019, estimated not to have bought any estrogen or progestogen products (calculated by subtracting the count on the previous row from the total number of Swedish women aged 50 years or older between 2007-2019)	1,723,659
Swedish Non-Users cohort (assuming that 80% of the women contributing to the count in previous row had a gynecological visit between 2007-2019, based on an estimate in.(4))	1,378,928

References

1. National Board of Health and Welfare of Sweden. Statistikdatabas för läkemedel [Internet]. [cited 2020 Mar 23]. Available from: https://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel

2. Statistics Sweden [Internet]. Statistiska Centralbyrån. [cited 2020 May 11]. Available from: http://www.scb.se/en/

3. Meaidi A, Goukasian I, Lidegaard O. Use of vaginal estrogen in Danish women: a nationwide cross-sectional study. Acta Obstetricia et Gynecologica Scandinavica. 2016;95(3):280–4.

4. Sverige, Socialstyrelsen. Screening för livmoderhalscancer: rekommendation och bedömningsunderlag. Stockholm: Socialstyrelsen; 2015.

ANNEX 4. ADDITIONAL INFORMATION

Not applicable