Title	**Pharmacoepidemiological study (Drug Utilization Study) of JAYDESS use in routine clinical practice in Sweden**.
Protocol version identifier	
Date of last version of protocol	12 Jan, 2014
EU PAS register number	Study not registered
Active substance	Levonorgestrel (ATC code G03AC03)
Medicinal product	Jaydess Intrauterine delivery system, 13.5 mg (ATC code G02BA03) Mirena Intrauterine delivery system, 20 micrograms/24 hours (ATC code G03AC03, pilot study only)
Product reference	Jaydess: 2011-1607 47317 Mirena: 1992-0024 11668
Procedure number	Jaydess: SE/H/1186/01/DC Mirena: MAA Sweden 56794
Marketing authorisation holder(s)	Bayer Pharma AG
Joint PASS	No
Research question and objectives	Characterise new users of Jaydess and estimate time of use. Describe hormonal contraceptive methods used before and after discontinuing Jaydess.
Country(-ies) of study	Sweden
Author	Helle Kieler MD, PhD, Associate professor Head of CPE (Centre for Pharmacoepidemiology) Karolinska Institutet T2, Karolinska University Hospital SE 171 76 Stockholm Sweden
Marketing authorisation holder(s)	Bayer Pharma AG 13342 Berlin Germany
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2. List of abbreviations

LARC	Long-acting reversible contraceptive
IUD	Intrauterine device
LNG-IUS	Levonorgestrel intrauterine system
VAL/GVR-databases	Regional databases on hospital and primary care diagnoses from Stockholm County
ATC	Anatomical therapeutic chemical classification
PIN	Personal identification number
DMARD	Disease-modifying anti-rheumatic drugs
COPD	Chronic obstructive pulmonary disease
IBS	Inflammatory bowel syndrome
PID	Pelvic inflammatory disease
CIN	Cervical intraepithelial neoplasia
CIS	Cervical carcinoma in situ
DDD	Defined daily dose
PDR	Prescribed Drug Register
PR	Patient Register
MBR	Medical Birth Register
Pop R	Population Registers
CPE	Centre for Pharmacoepidemiology

3. Responsible parties

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4. Abstract

Title

Pharmacoepidemiological study (Drug Utilization Study) of Jaydess use in routine clinical practice in Sweden.

Version 4

January 12, 2014

Karolinska Institutet, Building T2, Karolinska University Hospital, SE 171 76 Stockholm, Sweden

Rationale and background

Jaydess, a levonorgestrel intrauterine system (LNG-IUS) has recently been registered but not yet marketed in Europe.It is approved for contraception for a maximum of 3 years, and the aim of the suggested studies is to assess the duration of use and indication of use of Jaydess. The only other LNG-IUS that is approved in Sweden is Mirena, which is approved for 5 years and not only for contraception, but also for idiopathic menorrhagia and in connection with estrogen menopausal hormone therapy.

Research question and objectives

Characterise new users of Jaydess and estimate duration of use. Describe hormonal contraceptive methods prior to use of, and after discontinuing, Jaydess. The study will comprise a pilot study including users of Mirena and a main study including users of Jaydess. The main study will include 3 parts using different type and level of information.

- To describe characteristics (demographic, clinical, social) of first time users of Jaydess.
- To estimate the duration of use of Jaydess.
- To study switching patterns, e.g. what are the hormonal contraceptive methods used before and what are the methods after discontinuing Jaydess.
- To study off-label use of Jaydess:
    - Duration of use of Jaydess beyond 3 years
    - Use for other indications than contraception

Study design

Observational, descriptive study using information from national and regional health care registers. Women dispensed Jaydess and living in Sweden will be included during a 3-year period and starting at launch of Jaydess in 2014 (part 1). For a subset of women living in Stockholm county more detailed information will be obtained (part 2). The women will be followed for a maximum of 7 years. For approximately 150 women dispensed Jaydess the information on indication of use and time of use as obtained from the registers will be compared with that recorded in the medical records (part 3). Initially a pilot study will be conducted aiming at assessing the viability using information from the registers to assess time of use. As Mirena is the only LNG-IUS currently marketed in Sweden the pilot study will include 100 randomly selected women who were dispensed Mirena between 2005 and 2007. Usage time according to the registers will be compared with time as noted in the medical records.

Population

All women dispensed Jaydess in Sweden from Q1, 2014 (launch date of Jaydess) to 2016. Only first time users of Jaydess will be included. The women will be identified through the Prescribed Drug Register.

Variables

Exposures: Jaydess

Outcomes: Sociodemographic and health related characteristics, duration of use, previous or later use of hormonal contraception, indication of use (other than contraception).

Data sources

Swedish national health registers (Prescribed Drug Register, the Patient Register and the Medical Birth Register) and the population register.

Stockholm regional and primary care databases.

Medical records

Study size

The total number first time users of Jaydess to be identified in the national registers is estimated to be around 15 00 women. The estimated number identified in the Stockholm regional and primary care databases is 300 women.

Data analysis

Descriptive data (numbers, proportions, duration of use).

Milestones

Pilot study: Q2, 2014 – Q4, 2014

Report of pilot study: Q2, 2015

Inclusion period for main study (part 1-3): Q1, 2014 – Q4, 2016

Report of Interim data analyses: Q1, 2018

End of follow-up: Q4, 2020

Validation of medical records (part 3): Q2, 2020 – Q1, 2021

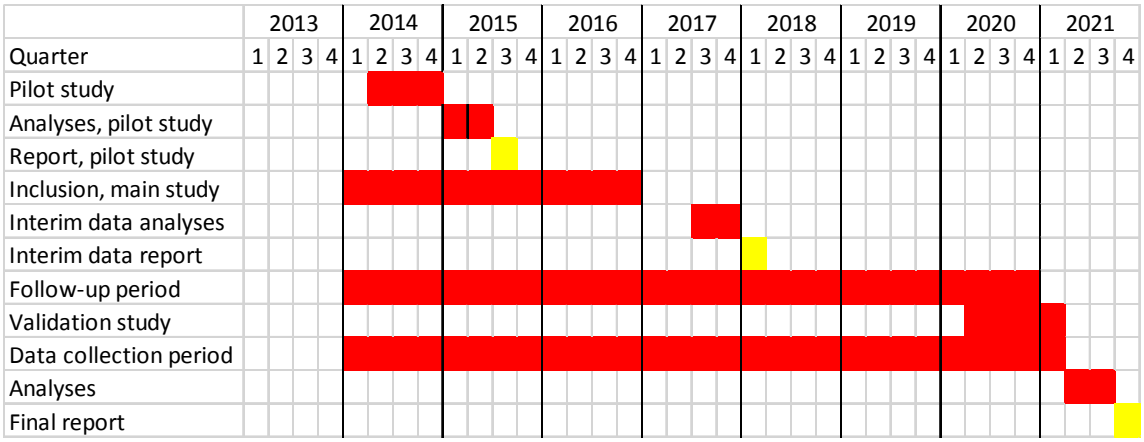
Final report: Q4, 2021

5. Amendments and updates

None

6. Milestones

Milestone	Planned date
Start of data collection	Q1, 2014
End of data collection	Q1, 2021
Interim data analyses	Q1, 2018
Registration in the EU PAS register	Q2, 2014
Final report of study results	Q4, 2021



Q Study periods and periods of analyses

Q Deliverables (study reports)

7. Rationale and background

The purpose of the proposed post-marketing pharmacoepidemiology study is to characterise new users of levonorgestrel contraceptive intrauterine system (JAYDESS) in the "Real World" setting (ie, drug utilization study). Jaydess is a 3-year long-acting reversible contraceptive (LARC). Clinical trials have shown high efficacy and that Jaydess was generally well tolerated (1). LARC methods are per NICE definition: copper-IUDs (intrauterine devices), LNG-IUS (levonorgestrel intrauterine systems), subcutaneous implant (Implanon®/Nexplanon®) and injectable progestogen-only contraceptive.

Specific areas of interest proposed to be addressed in this drug utilization study beyond routine variables are: use of Jaydess beyond the 3 year labeled use and off-label use in indications other than contraception. Considering that Jaydess was recently approved for use in Europe there are no similar studies, previously published. Previous observational studies of LNG-IUSs have found good acceptability and high continuation rates (2-4).

8. Research question and objectives

The aim of the proposed study is to describe first time users of Jaydess in a "Real-World" setting.

Primary objectives

- To describe characteristics (demographic, clinical, social) of first time users of Jaydess.
- To estimate the duration of use of Jaydess.

Secondary objectives

- To study switching patterns among women using Jaydess, e.g. what are the hormonal contraceptive methods used before and what are the methods after discontinuing Jaydess.
- To study off-label use of Jaydess:
    - Duration of use of Jaydess beyond 3 years
    - Use for other indications than contraception

9. Research methods

9.1. Study design

This descriptive study will include a main study and a pilot study (6. Milestones). Information will be obtained from the Swedish national health registers (Prescribed Drug Register, the Patient Register and the Medical Birth Register) and regional databases on hospital and primary care diagnoses from Stockholm County (VAL/GVR) and socio-demographic information including information on death and migration from the registers held by Statistics Sweden. The registers, the VAL/GVR and the medical records include the Personal Identification Numbers (PINs). The PIN is a unique identifier assigned to each resident in Sweden and information from the data sources will be merged by means of the PINs. The national registers include information on all Swedish (9.5 million) inhabitants and the regional databases include information on the 2 million people living in Stockholm County. The Patient Register includes information on all in- and out-patient care at hospitals. The Prescribed Drug Register is the most recent register with full coverage of all prescriptions dispensed in Sweden since

July 2005. Accordingly, the start date for obtaining information for the present study will be 1 July, 2005.

Pilot study

Considering that Mirena currently is the only marketed LNG-IUS in Sweden, the suggested design to estimate duration of use of Jaydess in the main study will be tested in a pilot study including users of Mirena. The pilot study will include 100 randomly selected women who were dispensed Mirena and living in Stockholm county. The women will be identified through the Prescribed Drug Register as women dispensed Mirena from the start of the register in July 2005 and until July 2007. All women will be followed until December 2012. Additional information will be obtained from the Patient Register, the VAL/GVR (procedure codes for insertion and removal) and from medical records. The information on start of use by dispensing date of Mirena will be compared with the information recorded in the Patient Register or the VAL/GVR (insertion by procedure code) and date of insertion as noted in the medical records. Similarly, the information concerning removal (dispensing date of another hormonal contraceptive as recorded in the Prescribed Drug Register) will be compared with date of removal by procedure code in the Patient Register or the VAL/GVR and the date of removal as noted in the medical records. If the agreement between the information recorded in the Patient Register or the VAL/GVR and the information recorded in the medical record is poor, especially regarding information on removal, the main study may not be launched. No defined criteria have been defined to justify the main study but any changes of the design based on the Pilot study will be described in an amendment.

Main study

All women filling a prescription of Jaydess anytime during a 3-period with the start date of launch of Jaydess in Sweden will be included in the study. A woman will only contribute once during the study period, starting the first time she fills a prescription with Jaydess. The main analyses will focus on first time users, which are defined as women filling a prescription with Jaydess for the first time as recorded in the Prescribed Drug Register. Accordingly, first time users of Jaydess could previously have used Mirena. Secondary analyses will include descriptions of “naïve” users of Jaydess, i.e women without any use of hormonal contraceptive method since July 2005 (9.2 Setting). For a limited number of women (n=150) the information obtained from the registers will be validated by means of primary care records.

A three part design is suggested:

1. National study (Part 1)

Part 1 will only use information from the national registers and will include all first time users of Jaydess during a three-year period starting from launch date of Jaydess. Information on these users will be obtained from 1 July 2005 and until end of study. Though the information concerning insertion and removal will be limited to special patient groups, as IUDs are mainly handled in primary care, data on insertion or removal date of the IUD by procedure codes will be obtained from the Patient Register for the same time period. Insertion is recorded as TLC00 and removal as TLC10. The major aim of Part 1 is to describe characteristics for women in Sweden using Jaydess for the first time and their switching patterns to/from other hormonal contraceptives.

2. Regional study (Part 2)

Part 2 will include all first time users of Jaydess during a 3-year period starting from launch date and living in the county of Stockholm. The VAL/GVR will provide information on insertion and removal dates of IUDs in primary care by procedure codes. Information will be obtained from 1 July 2005 and until end of study. The aims of this part are to describe switching patterns including information on switch from/ to copper-IUDs and usage time of Jaydess as recorded by time of insertion (procedure code TLC00) and removal (procedure code TLC10). Insertion of copper-IUDs will be defined as a procedure code for insertion and no concomitant filled prescription for Jaydess or Mirena (prescription filled within 3 months before or 1 month after the insertion date).

3. Validation study (Part 3)

Part 3 will include a subset of 150 first time users of Jaydess during a 3- year period from launch date and living in Stockholm County during the study period. For this subset of women the primary care records will be scrutinized for duration of Jaydess method use together with the indication for insertion of Jaydess to obtain information on possible off-label use. The aims of Part 3 are to validate duration of use of Jaydess as established in Part 2 and assess reasons for insertion of Jaydess. This validation cannot be done until a meaningful number of women with duration of use for more than three years have been reached. One consequence of the validation might be that there is a need for a review of all primary care records.

The results from the Pilot study might render slight modifications of the design suggested for the main study. Such changes will be described in an amendment to the protocol.

9.2. Setting

A woman will be will be considered “eligible” to enter the study cohort as a first-time user of Jaydess, when she is prescribed this specific method for the first time during the study period (index date), and has never received Jaydess previously as recorded in the Prescribed Drug Register, i.e. from 1 July 2005.

Study subjects will be categorised as naïve or non-naïve according to previous use of any other prescribed contraceptive method (different from the one first prescribed at index date). “Naïve” users will be women without any use of hormonal contraceptive method for at least eight years before index date. Accordingly, “Non naïve” users will be women with use of one or more of hormonal contraceptive methods recorded at any time during the eight year period before the index date. “Non naïve” women will be further subdivided into “switchers” (exposed to another hormonal contraceptive method in the six months prior to index date and “past contraceptive users” (exposed to another contraceptive method between six months and eight years prior to index date).

The enrolment period will start immediately after Jaydess is launched in Sweden. The study period will include three years of enrolment and between four and seven years of follow-up. The minimum of four years follow-up for the whole study cohort was chosen to cover off-label use of more than three years. (6. Milestones). Nulliparous and parous status at index date will be ascertained through the Medical Birth Register.

Pilot study

100 randomly selected women who were dispensed Mirena and living in the county of Stockholm, July 2005 - July 2007.

1. National study (Part 1)

All women living in Sweden and dispensed Jaydess for the first time during a 3-year period starting from the launch date of Jaydess in 2014. The women will be identified in the Prescribed Drug Register. The women will be followed until end of study, occurrence of an event (removal, switching, pregnancy), death or emigration, whichever comes first. Accordingly, in case of no event, death or emigration a woman can be followed for a minimum of four years and a maximum of seven years.

2. Regional study (Part 2)

All women living in the county of Stockholm during the study period and dispensed Jaydess for the first time during a 3 year period starting from the launch date of Jaydess in 2014. Only women

recorded in the Prescribed Drug Register and living in Stockholm County will be included in this part of the study. Information will be merged with data in the VAL/GVR to obtain additional information from primary care on insertion and removal dates and switching to/from copper-IUD. Use of copper-IUD will be defined as a procedure code for insertion of an IUD (TLC00) with no filled prescription on Jaydess or Mirena within three months before or one month after the visit. The women will be followed until end of study, occurrence of an event (removal, switching, pregnancy), death or moving out of Stockholm County whichever comes first. Accordingly, in case of no event, death or moving out of Stockholm County a woman can be followed for a minimum of four years and a maximum of seven years.

3. Validation study (Part 3)

A total of 150 randomly selected women who were dispensed Jaydess and lived in the county of Stockholm during the study period.

9.3. Variables

The following data will be collected:

- Number of first time users of Jaydess.

- Demographic and social characteristics including: age (in categories) and parity (nulliparous and parous) at index date, sociodemographic classification by highest education.

- Numbers and proportion of users defined as “naïve”, “non naïve”, and within non-naïve: “switchers” and “past users”. Naïve users are defined as women who fill a prescription with Jaydess for the first time, with no previous prescription on hormonal contraceptives during an eight year period before the index date. Non naïve users are those who do not fulfill the criteria for being a naïve user. In Part 2, the proportion of naïve users recorded with a previous insertion of a copper-IUD will be estimated.

- Duration of use of Jaydess. Duration of use can be assessed as the period between the date of filling of a prescription with a Jaydess and/or a recorded insertion (procedure code TLC00) and a recorded removal (TLC10). Duration of use for shorter time periods than the maximum approved period can also be assessed for women giving birth within 3 years from starting with Jaydess. Similar information can be obtained for those who later filled a prescription with a hormonal contraceptive.

- Type and number of different hormonal contraceptive methods prescribed before index date among the “non naïve” group.

- Use of other prescribed medications based on information from the Prescribed Drug Register in the year prior to index date will be collected. This will include: fertility medications (procedures if available), hormone replacement therapy, cardiovascular drugs (antihypertensive, antiplatelets, anticoagulants, antiarrhythmics), antidiabetic agents, antibiotics, tranexamic acid, NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs), asthma drugs, analgesic drugs, antimigraine drugs, antidepressant drugs, antihypertensive medication and emergency contraception.

- Medical history at any time before start date will be obtained from the Patient Register and the VAL/GVR registers and will include information on: rheumatoid arthritis, osteoarthritis, venous thromboembolism, acute coronary syndrome, cerebrovascular disease, cardiovascular risk factors (hypertension, diabetes, hyperlipidemia), peripheral arterial disease, gallbladder disease, liver disease, smoking related disease (COPD, emphysema), respiratory failure, gastrointestinal disease (peptic ulcer disease, gastrointestinal hemorrhage, gastritis and duodenitis, dyspepsia, and IBS), cancer related to sex hormones, alcohol related disorders, pelvic inflammatory disease (PID), endometriosis, pre-malignant disease of the cervix and endometrium (endometrial polyps, endometrial hyperplasia, cervical polyps, cervical intraepithelial neoplasia-CIN, and cervical carcinoma in situ-CIS), benign tumors of the female genital tract such as fibroids/myoma, anxiety, depression, acne, premenstrual syndrome, menorrhagia, previous ectopic pregnancy, history of sterilization and interventions for heavy menstrual bleeding (eg. endometrial ablation).

Information on prescribed medications will be obtained from the Prescribed Drug Register, information on education from the Population Register and information on medical history from the Patient Register.

9.4. Data sources

The Prescribed Drug Register contains information on all filled prescriptions in Sweden since July 2005, the Patient Register covers all publicly run inpatient care in Sweden from 1987 and out-patients treated at hospitals since 2001 and the Medical Birth Register includes information on all births from gestational week 22. VAL/GVR includes information on diagnoses and procedures from hospitals and consultations in primary care in the county of Stockholm since 2002 (see section 9.10 for detailed description of the registers). Socioeconomic data in the population registers of Statistics Sweden includes patient education and migration.

All the registers and VAL/GVR include the Personal Identification Numbers (PINs). The PIN is a unique identifier assigned to each resident in Sweden and information from the data sources will be merged by means of the PINs.

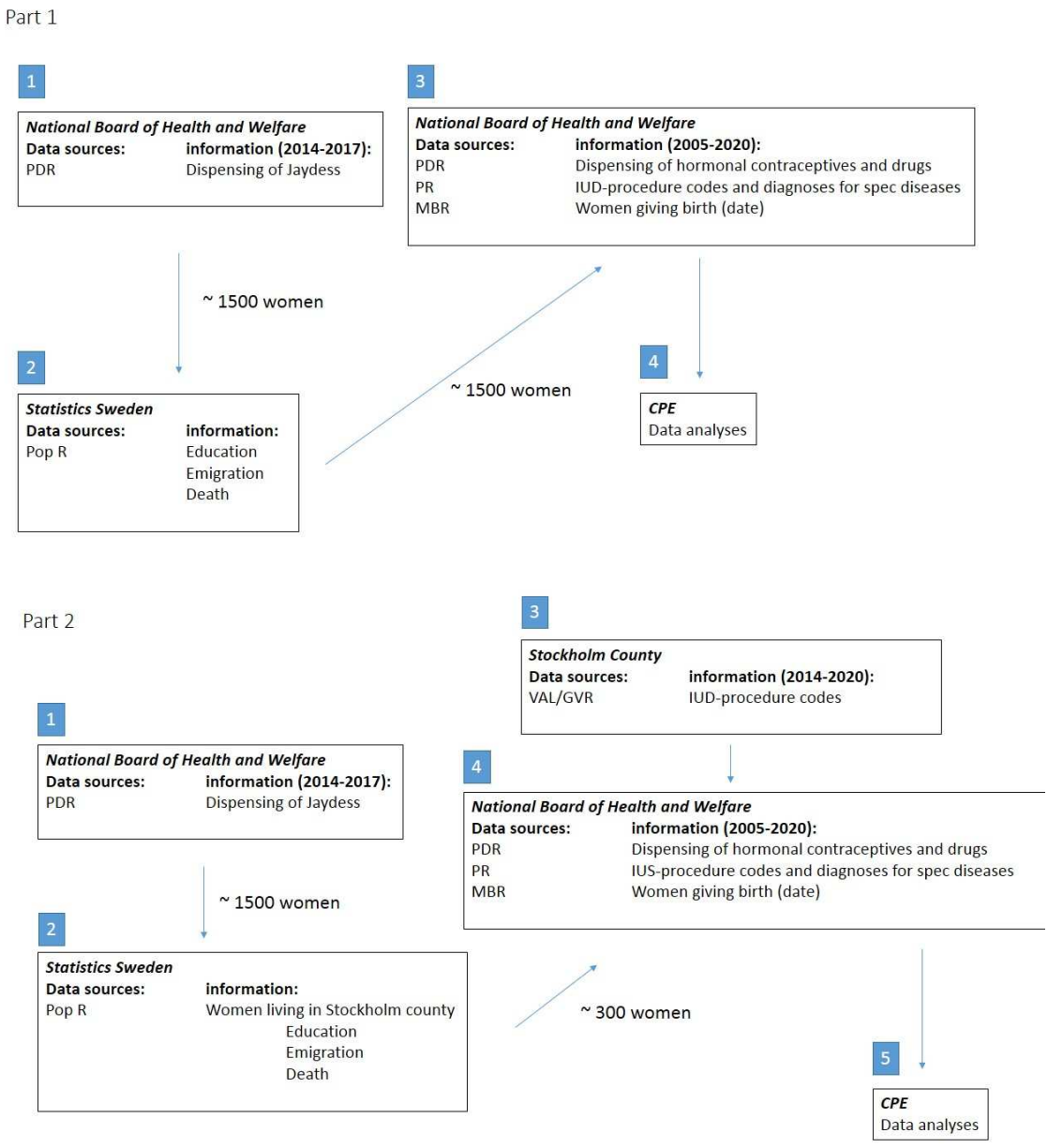
9.5. Study size

The inclusion period is set to three years with a minimum of four years of follow up (see 6. Milestones). The inclusion period may be extended if fewer women than expected are included during the three-year period. Annually around 5000 women in Sweden will have a Mirena inserted for the first time. Estimating that after Jaydess is introduced to the market 10% of the first time users of Mirena would instead have Jaydess a total of 1500 women with Jaydess can be included during a three-year period in Part 1 (national study). Considering that around 20% of the Swedish population lives in Stockholm, the corresponding number for the regional study (Part 2) will be 300 with Jaydess.

9.6. Data management

The Swedish national health registers are held by the National Board of Health and Welfare, the population registers by Statistics Sweden and the VAL/GVR by the county council in Stockholm. All data are stored electronically and can be obtained for research purposes after obtaining an approval of the study from one of the regional research committees. Data from the registers are merged at the register holder, which normally removes the PINs before sending the encrypted data to the research group. After ethical approval, permission to obtain the PINs for a limited number of individuals recorded in the registers to obtain further information from the medical records can be granted. The head of department or the responsible physician at the primary care centre must, in addition to the ethical approval, grant her or his permission to access the medical records, which are stored electronically at the hospitals or at the primary care centres. Data are obtained from the registers as a “SAS-file” and analysed using this software after removal of the PINs. Information on insertion and removal dates of IUDs for the 100 women included in the Pilot study and the 150 included in the Validation study will be entered into the free-ware program “Epi-data”. The data from the medical records will then be merged with data from the registers before the PINs are removed. All data will be stored at a server at the research unit (Centre for Pharmacoepidemiology) at the Karolinska University Hospital and the data can only be accessed by the research group The review of medical records as part of the Pilot study and the Validation study will be performed by data abstractors (research nurses) employed at the Centre for Pharmacoepidemiology.

Data obtaining process



9.7. Data analysis

Only descriptive data (numbers, proportions, time on drug) will be presented. A Statistical Analysis Plan, describing the analyses in more detail will be developed.

9.8. Quality control

Information concerning the ability and to use the registers to determine usage time will be validated by means of medical records for two subsets (Pilot study and Validation study). The register holders perform regular quality controls of their register data (9.10 Other aspects).

9.9. Limitations of the research methods

Information will mainly be obtained through national and regional registers. Administration of LARCs is mostly done in primary care and therefore information concerning insertion and removal of these contraceptives will not be fully covered in the National Patient Register, which includes information from hospital contacts only. Those identified as having an IUD inserted or removed at the hospital might not be representative of users of IUDs in general. Insertion at the hospital could be in connection with an abortion and a removal could be performed because of special complications, such as dislocation of the IUD. The regional register: VAL/GVR, contains information on primary care contacts, but a preliminary investigation for this proposal indicated underreporting of codes related to IUDs. Copper-IUDs are not included in the Prescribed Drug Register as they are not dispensed by prescriptions. Information on insertion of copper-IUDs can, however, be obtained by a procedure code as recorded in the Patient Register or the regional database, without a concomitant filled prescription for Jaydess or Mirena. Another limitation is the time lag of the Patient and Birth registers of 9 and up to 14 months, respectively, which means that to include the latest available information an additional year (or 14 months) will need to be added after the end of the inclusion period before linkage of data and analyses can be performed.

The strengths include full coverage of the populations to be included as all women filling a prescription with Jaydess will be identified in the Prescribed Drug Register. Another strength is the possibility to assess populations by varying data sources (national registers, regional registers and primary care records).

9.10. Other aspects

Detailed description of the national health registers and their content together with short descriptions of the data in the Stockholm county regional database and the register of the total population to be used in the proposed study.

Swedish Prescribed Drug Register

The Prescribed Drug Register (5-7) includes information on all prescribed drugs, including antibiotics, sold in Sweden since July 1, 2005. The register contains patient level data on dispensed medicines for the entire Swedish population, including information on the dispensed drug (product, quantity, price) as well as the dates of prescription and dispensing. Data on total and reimbursed expenditure and certain characteristics of the prescriber and the workplace of the prescriber are also recorded. All drugs are classified according to the World Health Organization ATC classification and the register is updated monthly.

Present register content:

Patient

County (county code)

Personal Identification Number (PIN)

Age

Sex

Residence - community

Prescriber

Profession

Level of education (code)

Speciality (code)

Pharmacy

County

Owner (public/private)

Type/level (primary/hospital, speciality)

Drug

Dispensing date

Prescribed date

Type (drug/device/food substitute)

Reimbursement type

Prescriber category (MD, nurse, dentist etc)

Start package (Y/N)

Exchange to generic drug

Brand name

Substance name

ATC

DDDs

No of tablets/capsules/vials per package

No of packages/dispensing

Total costs

Patient costs

Public costs

Swedish Patient Register

In the 1960s, the National Board of Health and Welfare started to collect data on individual in-patients at public hospitals. Since 1987, the Patient Register(8) has covered all public in-patient care in Sweden and since 2002 there is almost full coverage of all out-patient hospital visits. For the period 1964-2003, the register includes 47 million discharges.

Information available in the register includes the following:

- Patient data (personal identification number, sex, age and place of residence)
- Hospital data (county council, hospital and department)
- Administrative data, including:
    - date of admission
    - date of discharge

- length of stay
- acute/planned admission
- admitted from
- discharged to

- Medical data, including:
  - main diagnosis
  - secondary diagnoses
  - external cause of injury and poisoning
  - surgical procedures

Information to the register is delivered once a year to the National Board of Health and Welfare from each of the 21 county councils in Sweden.

Regarding quality of data and underreporting, very rapid changes of hospital organization in Sweden make estimations of underreporting difficult, especially for psychiatric and geriatric care. The total number of drop-outs for somatic short-time care for the period 1987-1991 has been estimated to be less than 2 per cent. For all records reported to the register a data control is run. A check is made that compulsory variables are reported, eg, personal identification number, hospital and main diagnosis. A check is also made that codes for different variables and dates have valid values. Some obviously incorrect data is corrected in connection with the quality controls.

Swedish Medical Birth Register

The Swedish Medical Birth Register(9-11) was established in 1973 by an act of the Swedish Parliament, for the purpose of compiling information on ante- and perinatal factors and their importance for infant health. The basic structure of the register has remained unchanged since 1973. Since 1982 the information recorded in the register is based on copies of the medical records used in connection with pregnancy, delivery and the neonatal period. Pre-specified data is extracted from the records and forwarded electronically to the National Board of Health. Specific diagnoses are noted with the currently* used version of ICD (International Classification of Diseases) and certain other conditions are captured by means of check boxes. Since 1995 drugs used during pregnancy are included in the birth register. The information mainly includes drugs used in early pregnancy and is

based on the information provided by the pregnant woman at the first visit to antenatal care. Drugs used or prescribed later in pregnancy should also be reported, but is under reported.

*< 1987: version 8, 1987-1997: version 9, > 1997: version 10

Summary of the present register content:

A. Identification of patient

Maternal personal identification number (PIN), infant PIN, maternal place of residence (parish) at delivery, delivery hospital, prenatal-care center.

B. Social factors

Cohabitation, work outside home, occupation, parents' nationality, mother's country/county of birth, smoking before pregnancy, smoking in early pregnancy, smoking in late pregnancy, use of snuff before, snuff in early pregnancy, snuff in late pregnancy.

C. Maternal history

Previous pregnancies and births: spontaneous abortions, ectopic pregnancies, stillbirths, live births, perinatally dead infants, later dead infants; pre-pregnancy weight, weight at delivery, height, involuntary childlessness, number of years, method for assisted conception, use of contraceptive pills or IUD before pregnancy, previous cesarean section, including year.

D. Pregnancy

Last menstrual period (LMP) date; expected date of delivery according to LMP and ultrasonography, chorionic villus sampling (CVS) or amniocentesis, including date and outcome, selected diseases at first visit to prenatal clinic (urinary infections, hypertension, chronic kidney disease, diabetes, epilepsy, pulmonary disease and asthma, inflammatory bowel disease, systemic lupus as noted in the check boxes), drugs used during pregnancy, number of prenatal visits, date of first prenatal visit, in- and out-patient visits during pregnancy (ICD-code and date)

E. Delivery

Date of admission to delivery unit, pregnancy duration (weeks, days), presentation of infant, delivery diagnoses (ICD-code), cesarean section, forceps, vacuum extraction, analgesia, anesthesia with specification, induction of delivery, placental weight, number of umbilical arteries, ruptures, perineotomia.

F. Infant

Date and time of birth; stillborn/live-born; date of death, underlying cause of death, sex, birth weight, birth length, head circumference, multiple birth (including number), Apgar score at 1, 5, and 10 minutes, infant diagnoses (ICD-code) operations and other treatments of infant.

The Stockholm county regional database (VAL/GVR)

The database includes information on diagnoses and procedures from hospitals and from consultations in primary care in the county of Stockholm since 2002. In addition the database includes information on drugs and sociodemographic variables. The county has 2 million inhabitants.

The Total Population Register

The register includes data on demographic variables for all Swedish residents including information on migration, death and education.

10. Protection of human subjects

The Centre for Pharmacoepidemiology is an ENCePP center and all studies performed at the centre are done in accordance with the ENCePP code of conduct, the good clinical practice guidelines, and the ISPE guidelines for good pharmacoepidemiology practice. All data are handled in accordance with Swedish law and EU regulations.

11. Management and reporting of adverse events/adverse reactions

Since this a non-interventional study design based on secondary data, reporting of adverse events is not required. For this drug utilization study there will be no specific investigation of adverse events. If adverse events are noted through review of the medical records, they will summarised in the reports in accordance with the EMA guidelines.

12. Plans for disseminating and communicating study results

The study results will be reported to the MAH and the EMA. In addition, any results of interest for a broader public will be published in peer reviewed scientific journals.

13. References

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Annex 1. List of stand-alone documents

Not applicable.

Number	Document reference number	Date	Title

Annex 2. ENCePP checklist for study protocols

Attached.

Annex 3. Additional information

Future amendments and deviations will be added here if applicable.