Pharmacoepidemiological study protocol ER-9430
EPID Multiple Sclerosis Pregnancy Study

Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries

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PASS Information

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Research question and objectives	The overall research question of this study is to determine if exposure to IFN-βs before or during pregnancy has an adverse effect on pregnancy outcomes in patients with Multiple Sclerosis (MS) including, as requested by the Committee for the Medicinal Products for Human Use (CHMP), the identification of the prevalence of adverse pregnancy outcomes in women with MS unexposed to IFN-β products.
Countries of the study	Finland (FIN) Norway (NOR) Sweden (SWE)
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1 List of abbreviations

List of main abbreviations used in the study protocol

AGA	Average for Gestational Age
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CS	Caesarean Section
DDD	Defined Daily Dose
DPP	Drugs and Pregnancy Project
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUROCAT	European Surveillance of Congenital Anomalies
FIN	Finland
GW	Gestational Week
ICD	International Classification of Diseases
IFN-β	Interferon beta
LBW	Low Birth Weight
LBH	Low Birth Height
LGA	Large for Gestational Age
LMP	Last Menstrual Period
MAH	Marketing Authorisation Holder
MBR	Medical Birth Register
MCA	Major Congenital Anomaly
MS	Multiple Sclerosis
MSDMD	MS Disease Modifying Drug
NIPH	Norwegian Institute of Public Health
NCSP	NOMESCO classification of surgical procedures
NOR	Norway
PIN	Personal Identification Number
RR	Relative Risk
SD	Standard Deviation
SF	Statistics Finland
SGA	Small for Gestational Age
SID	Study Identification Number
SII	Social Insurance Institution
SWE	Sweden

THL	Finnish National Institute for Health and Welfare
TOPFA	Termination Of Pregnancy due to Foetal Anomaly
Valvira	National Supervisory Authority for Welfare and Health

2 Terminology

Birth A process resulting in a foetus or a child (one or more, ≥1) of at least 22+0 gestational weeks (GW) (≥ 22+0 GW) or weighing at least 500 grams (≥ 500 g) being born by vaginal delivery or by caesarean section (CS). The process of a child being born alive is always a birth.

Birth weight adjusted for gestational age is defined according to the gestational age and sex–specific national standards in each country (FIN: Sankilampi et al. 2013). Average for Gestational Age (AGA) is used as reference outcome in relation to Small for Gestational Age (SGA) and Large for Gestational Age (LGA).

Defect cases: Cases where 3 or more minor anomalies were detected in the same child.

Gestational age at birth is a measure of the age of a pregnancy at birth where the origin is the first day of the woman's last normal menstrual period. Preterm birth refers to gestational age less than 37 GW.

Induced abortion / elective termination of pregnancy is artificially induced termination of pregnancy which does not comply with the definition of a birth and which leads to the death of one or more foetus (≥ 1) and in which there is no indication of intrauterine foetal death before the termination.

Live birth is birth of a child that, irrespective of the duration of the pregnancy, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or movement of the voluntary muscles, whether or not the placenta is attached or the umbilical cord has been cut.

Major congenital anomaly (MCA) refers to a major congenital / foetal structural anomaly, chromosomal defect, teratoma and congenital hypothyroidism involved in a birth, an elective termination of pregnancy for severe MCA, or in a spontaneous abortion. MCAs do not include hereditary diseases and other diseases not associated with congenital anomalies, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations and common less significant congenital anomalies.

Pregnancy event refers to terminations of pregnancy, spontaneous abortions, ectopic pregnancies, stillbirths and live births.

Serious adverse pregnancy outcome is defined as a composite endpoint of pregnancy including elective termination of pregnancy due to foetal anomaly (TOPFA), MCA or stillbirth.

Spontaneous abortion / miscarriage refers to spontaneous loss of a pregnancy which does not comply with the definition of a birth or a spontaneous intrauterine death of a foetus, detected by a reliable prenatal diagnostic method, and the associated artificial expulsion of the foetus concerned before 22+0 GW (< 22+0 GW), when the foetus weighs less than 500 grams (< 500 g) according to the International Classification of Diseases, 10th revision (ICD-10) diagnosis O03 (WHO, 2014).

Stillbirth is birth of a foetus or a child that shows no evidence of life, but complying with the definition of a birth (22+0 GW or ≥ 500 g).

Pregnancy trimesters are divided as follows: 1st trimester 0-12 GW, 0-84 days from last menstrual period (LMP), 2nd trimester 13-26 GW, 85-182 days from LMP, 3rd trimester from 27 GW to delivery (approximately 40-42 GW), 183 days from LMP to delivery (approximately 280 days).

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4 Abstract

Version 2.0, 18 August 2015, Pasi Korhonen, PhD, Adjunct Professor of Biostatistics, EPID Research Oy

Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries

Rationale and background: MS is the most common chronic neurologic disability in young adult females in their childbearing ages. Little evidence is available regarding the association between exposure to IFN-β products and adverse pregnancy outcomes. Therefore the four marketing holders of IFN-β are conducting a European-wide IFN-β pregnancy registry. Additionally, the CHMP has requested a study to enable identification of pregnancy outcomes in the MS population unexposed to IFN-β products for comparison with the ongoing European IFN-β Pregnancy Registry.

Research question and objectives: The overall research question of this study is to determine if exposure to IFN-βs before or during pregnancy has an adverse effect on pregnancy outcomes in patients with MS including, as requested by the CHMP, the identification of the prevalence of adverse pregnancy outcomes in women with MS unexposed to IFN-β products. The primary objectives are to compare the prevalence of the serious adverse pregnancy outcomes between women with MS exposed to IFN-β only vs. unexposed to any MS disease modifying drugs (MSDMDs) and women with MS exposed to IFN-β only vs. unexposed to IFN-β regardless of exposure to other MSDMDs. The cohorts from this study will provide background prevalence estimates for pregnancy outcomes in MS for the European IFN-β Pregnancy Registry. However, the estimated prevalence from this study will not be directly compared with those from the European IFN-β Pregnancy Registry.

Comparison of pregnancy outcomes will be conducted by exposure status to IFN-βs before and during pregnancy (exposed vs. unexposed) and other MSDMDs.

Study design: The present study is a population-based cohort study based on register data from three Nordic countries: FIN, SWE and NOR.

Population: The target study population consists of Finnish, Swedish and Norwegian women diagnosed with MS who have been pregnant during the study period from 1996 to 2014. The pregnancy may have resulted in an induced abortion, spontaneous abortion, ectopic pregnancy, stillbirth, or live birth during the study period. A pregnancy will be considered unexposed if exposure is stopped at least three months prior to LMP (exceptions: six months for mitoxantrone and cladribine). MSDMDs that will be considered aside from IFN β-1a, IFN β-1b and Peg IFN-β-1-a: human normal immunoglobulin (Anatomical Therapeutic Chemical (ATC) code, J06BA02), cyclophosphamide (L01AA01), methotrexate (L01BA01, L04AX03), cladribine (L01BB04), mitoxantrone (L01DB07), alemtuzumab (L01XC04), glatiramer acetate (Copaxone®) (L03AX13), leflunomide (L04AA13), natalizumab (L04AA23), fingolimod (L04AA27), teriflunomide (L04AA31), azathioprine (L04AX01), dimethyl fumarate (N07XX09).

Comparisons: The primary comparisons will be performed between the following study cohorts:

i) women with MS exposed to IFN-β (but not to other MSDMDs) (cohort 1) and women with MS unexposed to any MSDMDs (cohort 3), and,

ii) women with MS exposed to IFN-β (but not to other MSDMDs) (cohort 1) and women with MS unexposed to IFN-β regardless of exposure to other MSDMDs (cohort 4).

Outcomes: The primary outcome variable is a serious adverse pregnancy outcome, which is defined as a composite endpoint including elective TOPFA, MCA, or stillbirth. Other outcome variables include live births, stillbirths, elective TOPFA or elective termination due to other reasons, MCA, spontaneous abortions, ectopic pregnancies, and several other perinatal adverse health outcomes.

Data sources: The study database will be constructed from the Nordic health registers: Drugs and pregnancy Project (DPP) (FIN), Patient Registers, MS Registers, Prescription Registers, Medical Birth Registers (MBRs), Malformation Register, Causes of Death Register, and Population Registers.

Study size: The estimated number of pregnancies in MS patients is 1671, encompassing data from:

i) FIN: 1 January 1996 – 31 December 2014;

ii) SWE: 1 July 2005 – 31 December 2014;

iii) NOR: 1 January 2004 – 31 December 2014.

Of these pregnancies, 76% (n=1270) are estimated to be unexposed to any MSDMDs, 22% (n=368) exposed to IFN-β regardless of exposure to other MSDMDs, and 18% (n=294) exposed to IFN-β only. With an anticipated background rate of 7.3% for the serious adverse pregnancy outcome, the minimum detectable effect size between the study cohorts of MS women exposed to IFN-β only vs. MS women unexposed to any MSDMDs is 1.72 in terms of relative risk (RR) with an 80% power and 5% significance level.

Data analysis: The individual patient-level data from each country will be pooled into a single dataset and analyses will be conducted using the pooled dataset. The study cohorts will be characterised by country of residence, university hospital district, maternal age at LMP, year of pregnancy outcome, pre-pregnancy weight, pre-pregnancy body mass index (BMI), number of previous pregnancies, number of previous abortions, smoking status during pregnancy, number of foetuses in pregnancy (single vs. multiple), any chronic diseases, exposure to any teratogenic medications including steroids, time since MS diagnosis, and duration of MS treatment. These variables are also used as potential confounders when comparing the pregnancy outcomes between the study cohorts.

The descriptive statistics including number of events (n) and prevalence (%) will be presented for each pregnancy outcome in each study cohort separately. Descriptive analyses of the pregnancy outcomes within each study cohort will be further stratified by country, year of pregnancy outcome, maternal age at LMP, any chronic diseases, exposure to any teratogenic medication including steroids, time since MS diagnosis, duration of MS treatment, gestational age, and weight of the newborn as relevant for specific pregnancy outcomes.

The prevalence of the pregnancy outcomes will be further compared between the study cohorts using log-binomial regression with adjustments for i) baseline potential confounders (country, year, maternal age at LMP, previous pregnancies, chronic diseases, exposure to teratogenic medications including steroids) and ii) all relevant confounders. The RR estimates with 95% confidence intervals (CI) and associated p-values will be reported for these comparisons and for confounders used in the model. Confounding factors will be taken into account in the analyses according to availability and available time period from each register source.

Analyses of congenital malformations, ectopic pregnancies, spontaneous abortions, live births and stillbirths in the general population of women without MS in FIN, SWE and NOR will be based on relevant official birth health statistics available from these countries. The expected numbers of these outcomes in each study cohort will be estimated based on the age-matched population prevalence in each country and compared with the observed number of events using standardized prevalence ratios with 95% Cis.

5 Amendments and updates

Version 2.0 (dated 18 August 2015)

- Due to more data becoming available during the protocol development, end of the study period has been extended to 31 Dec 2014 in each country. Estimated cohort sizes and power calculations have been updated accordingly.
    - Dimethyl fumarate (N07XX09) has been added to MSDMD list and removed from study limitations, as it gained market authorisation on 30 January 2014.
    - Peginterferon beta-1a (L03AB13) has been added to MSDMD list as it gained market authorisation on 18 July 2014.
- Potential confounding factors
    - Maternal age has been defined at LMP instead of previous definition at LMP / spontaneous abortion / ectopic pregnancy depending on the pregnancy outcome. Missing information with regard to maternal age at LMP has been described in Section 9.9.

- Missing data (section 9.7.7)
    - Robustness of the variable selection procedure (section 9.7.3.) to missing data will be tested as part of the sensitivity analyses.

6 Milestones

Milestone	**Planned date***
Registration in the EU PAS register (reference date)	31 October 2015
Start of data collection (Data permit applications sent)	+ 1 month from the reference date
End of data collection (Data received)	+ 12 months from the reference date
Final report of study results	+ 24 months from the reference date

* Dates depend on the time required to handle data permit applications and extraction of study data from the healthcare registers which are beyond the control of the investigators.

7 Rationale and background

MS is the most common chronic neurologic disability in young adult females of childbearing age (Baird & Dalton 2013). Women with MS are confronted with questions relating to pregnancy and pharmacological MS therapy. It is commonly understood that MS relapses are fewer during pregnancy, but also that medication taken before conception or in early pregnancy could negatively affect the outcome of the pregnancy. Experience with exposure to IFN-β products during pregnancy has shown no clear association of adverse outcomes such as low birth weight (LBW), congenital anomaly or spontaneous abortion (Lu et al. 2012). However, it is contraindicated to initiate treatment with IFN-β products during pregnancy. It is also recommended that if a woman becomes pregnant during treatment, she should be informed of the potential hazards and discontinuation of therapy should be considered. In patients with a high relapse rate before treatment start, the risk of a severe relapse following discontinuation of IFN-β in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion. There are little data on newer MSDMD substances (e.g. fingolimod) (Lu et al. 2012).

This study addresses a request from the European Medicines Agency's CHMP to identify pregnancy outcomes in the MS population unexposed to IFN-β products for comparison with the ongoing European IFN-β Pregnancy Registry sponsored by the four European MAHs of IFN-βs.

8 Research questions and objectives

This study is a population-based cohort study based on register data from three Nordic countries: FIN, SWE and NOR. The overall research questions of this study are to determine if exposure to IFN-β before or during pregnancy has an adverse effect on pregnancy outcomes in patients with MS (ICD-10 G35) and, as requested by the CHMP, to identify the prevalence of adverse pregnancy outcomes in MS women unexposed to IFN-β products. The cohorts from this study will provide background prevalence information and context for pregnancy outcomes in MS for the European IFN-β Pregnancy Registry. However, the estimated prevalence from this study will not be directly compared with those from the European IFN-β Pregnancy Registry as: First, available information on disease severity and other confounding factors differs between the health registers and the European IFN-β Pregnancy Registry and in some cases is missing, such that the rates cannot be adjusted to be comparable. Secondly, the pregnancy cases included in the Nordic health registers are population-wide and are not based on a sample, whereas the European IFN-β Pregnancy Registry is based on spontaneous reports.

The prevalence of the various pregnancy outcomes will be estimated in the study cohorts described below and in Table 1 (see section 9.4 for definition of exposure):

1. Women with MS exposed to IFN-β only (i.e. these women have not been exposed to other MSDMDs) before or during pregnancy (cohort 1),
2. Women with MS exposed to IFN-β regardless of exposure to other MSDMDs before or during pregnancy (cohort 2),
3. Women with MS unexposed to any MSDMD before or during pregnancy (cohort 3),
4. Women with MS unexposed to IFN-β regardless of exposure to other MSDMDs before or during pregnancy (cohort 4),
5. Women exposed to MSDMDs except IFN-β or glatiramer acetate (Copaxone®) or dimethyl fumarate (Tecfidera®) (cohort 5),
6. Women from the general population in FIN, SWE and NOR without MS diagnosis (cohort 6).

Table 1: Definition of the study cohorts according to exposure to IFN-β and other MSDMDs.

Exposure status by IFN-β and other MSDMD	**Women with MS**			**Women without MS**
	Unexposed to other MSDMD	**Exposed to other MSDMD**	**Total**	
Exposed to IFN-β	**Cohort 1** Exposure to IFN-β only	Exposed to both IFN-β and other MSDMD (group not studied)	**Cohort 2** All patients with IFN-β exposure regardless of exposure to other MSDMDs	NA
Unexposed to IFN-β	**Cohort 3** No exposure to any MSDMDs	**Cohort 5** Only other MSDMD excluding IFN-β or glatiramer acetate (Copaxone®) or dimethyl fumarate (Tecfidera®) (for sensitivity analysis only)	**Cohort 4** All patients with no IFN-β exposure regardless of exposure to other MSDMDs	**Cohort 6** Women from the general population without MS diagnosis

The primary objectives are:

1. To estimate the prevalence of the following pregnancy outcomes in the above four study cohorts 1 – 4:
   - Serious adverse pregnancy outcome defined as a composite endpoint including elective TOPFA, MCA or stillbirth
   - Elective TOPFA or elective termination for other reasons (assessment not possible in SWE as no register available)
   - Stillbirth
   - Live birth
   - MCA

2. To compare the prevalence of each of the outcomes in objective 1 between:
   i) women with MS exposed to IFN-β only (cohort 1) vs. unexposed to any MSDMDs (cohort 3) and
   ii) women with MS exposed to IFN-β only (cohort 1) vs. unexposed to IFN-β regardless of exposure to other MSDMDs (cohort 4).

The secondary objectives are:

3. To compare the prevalence of the following pregnancy outcomes between:
   i) women with MS exposed to IFN-β regardless of exposure to other MSDMDs (cohort 2) vs. unexposed to any MSDMDs (cohort 3):
   - Serious adverse pregnancy outcome
   - Elective TOPFA or elective termination for other reasons (not possible in SWE)
   - Stillbirth
   - Live birth
   - MCA

4. To estimate the prevalence of a) ectopic pregnancies and b) spontaneous abortions in the study cohorts 1, 2, 3 and 4 and to compare these prevalences separately between:
   i) women with MS exposed to IFN-β only (cohort 1) vs. unexposed to any MSDMDs (cohort 3),
   ii) women with MS exposed to IFN-β only (cohort 1) vs. unexposed to IFN-β regardless of exposure to other MSDMDs (cohort 4), and
   iii) women with MS exposed to IFN-β regardless of exposure to other MSDMDs (cohort 2) vs. unexposed to any MSDMDs (cohort 3).
   This objective is subject to available data from each country, as only information on ectopic pregnancies or spontaneous abortions requiring treatment in hospitals is available in the study.

5. To estimate the prevalence of the pregnancy outcomes (i.e. serious adverse pregnancy outcome, elective TOPFA (not possible in SWE), stillbirth, live birth and MCA) in cohorts 1 – 4 stratified by country, year of pregnancy outcome, maternal age at LMP, chronic diseases, exposure to any teratogenic medications including steroids, time since MS diagnosis, duration of MS treatment, gestational age and weight of the newborn as relevant for specific pregnancy outcomes.

The exploratory objectives are:

6. To describe the following additional characteristics about pregnancy in cohorts 1 – 4:
   - Mode of delivery (CS/vaginal)
   - Preterm birth
   - Birth weight and LBW
   - Birth height and low birth height (LBH), according to country specific standards (FIN Sankilampi et al. 2013)
   - Birth weight (SGA and LGA), height and head circumference for gestational age (AGA)
   - Sex of the newborn
   - Head circumference and low head circumference (according to country-specific standards (FIN Sankilampi et al. 2013)
   - Apgar score (at 1 and 5 minutes)
   - Defect cases

7. To estimate the prevalence of i) congenital malformations in live or stillbirths, ii) ectopic pregnancies, iii) spontaneous abortions, and iv) stillbirths in the general population without MS diagnosis (cohort 6) in FIN, SWE, NOR for each pregnancy outcome separately as available in each country. The observed numbers of pregnancy outcomes in cohort 3, matched for age and country, are compared with the expected numbers through indirect standardisation under the assumption that cohort 3 had experienced the same prevalence as women in the general population without MS diagnosis (cohort 6).

9 Research methods

9.1 Study Design

The present study is a population-based cohort study using register data from three Nordic countries: FIN, SWE, NOR.

9.2 Setting

The target study population consists of Finnish, Swedish and Norwegian women with MS who have been pregnant during the study period. The study population will be identified according to the inclusion and exclusion criteria below.

9.2.1 Inclusion criteria

- Women who have had a pregnancy with a recorded outcome consisting of an induced abortion, spontaneous abortion, ectopic pregnancy, or birth during the study period in FIN, SWE or NOR with the event being documented in the relevant databases.

9.2.2 Exclusion criteria

- None

9.2.3 Study period

The study periods in the different countries are as follows: FIN, 1 January 1996 – 31 December 2014; SWE, 1 July 2005 – 31 December 2014; NOR, 1 January 2004 – 31 December 2014. The start of the study period is determined by the availability of exposure data in each country. The end of the study period is determined by the availability of data on malformations. In FIN the follow-up period for the registration of MCA is 12 months after birth, in SWE 6 months. In NOR malformations are registered in the MBR and the newborns are followed until the end of the stay at the birth clinic (usually at least 4 days).

9.2.4 Follow-up time

The cohort entry date (i.e. index date) is the date of LMP. This date is considered as the beginning of the pregnancy. The pregnancies are followed until induced abortion or birth. The births are followed-up for a maximum of 12 months for registration of MCAs (see section 9.2.3 Study period). Information on LMP, or gestational age, is not available for ectopic pregnancies or spontaneous abortions. The date of hospitalisation due to these outcomes will be used as a proxy of index date for these outcomes.

9.3 Data sources

9.3.1 Register data sources

All Nordic countries being studied (FIN, SWE, NOR) have well developed population-wide register systems with tens of years of longitudinal follow-up data. The persons are identified in the registers with a unique personal identification number (PIN) and thus the records can be linked for research purposes at the individual level between the various registers.

In the Nordic countries, births are covered by three different databases (Gissler 2010). First, all live births are registered to Central Population Registers, which are the basis for vital statistics. Second, all deaths of live born children are registered in Causes of Death Registers, maintained by statistical or health authorities. Third, all Nordic countries have introduced a separate MBR for more detailed collection of parturients, deliveries and newborns. Registers that could be used in the proposed pharmacoepidemiological study are described below in detail.

The present study will be based on data on births complemented with data obtained from Patient Registers, Prescription Registers and Population Registers. The following country-specific registers will be used: Reimbursement Register, Malformation Register (FIN), MBR (FIN, SWE, NOR), MS register (SWE, NOR) and Causes of Death Register (SWE) (Table 2).

Table 2: List of relevant data sources in different countries.

Finland		
Outcome	**Register**	**Register holder**
Ectopic pregnancies	Patient Register (Care Register for Health Care)	National Institute for Health and Welfare (THL)
Spontaneous abortions	Patient Register (Care Register for Health Care) (of previous pregnancies from DPP)	THL
Elective terminations	DPP	THL
Stillbirths with and without foetal defects	DPP	THL
Live births with and without congenital anomaly	DPP	THL

Exposure	DPP National Prescription Register National Reimbursement Register	THL Social Insurance Institution (SII)
MS population	DPP, Patient Register (Care Register for Health Care)	THL
General population	Population Register	Statistics Finland (SF)
Sweden		
Outcome	**Register**	**Register holder**
Ectopic pregnancies	Patient Register	National Board of Health and Welfare
Spontaneous abortions	Patient Register	National Board of Health and Welfare
Elective terminations	not recorded in SWE	N/A
Stillbirths with and without foetal defects	MBR	National Board of Health and Welfare
Live births with and without congenital anomaly	MBR	National Board of Health and Welfare
Exposure	Prescribed Drug Register	National Board of Health and Welfare
MS population	Patient Register, MS Register	National Board of Health and Welfare
General population	Population Register	Swedish Tax Agency
Norway		
Outcome	**Register**	**Register holder**
Ectopic pregnancies	Patient Register	Norwegian Directorate of Health
Spontaneous abortions	Patient Register (of previous pregnancies in MBR)	Norwegian Directorate of Health Norwegian Institute of Public Health (NIPH)
Elective terminations	MBR	NIPH
Stillbirths with and without foetal defects	MBR	NIPH
Live births with and without congenital anomaly	MBR	NIPH
Exposure	Prescription Register	NIPH
MS population	MS Register	Helse Bergen
General population	Population Register	Statistics Norway

9.3.1.1 MS diagnosis and Exposures

MS Registers (SWE, NOR)

Information on MS diagnoses will be obtained from MS registers in SWE and NOR. The Norwegian MS Register was established in 1998 (Myhr et al. 2012). In 2012, the register included information on more than 5000 patients regarding demographics, diagnosis, disease modifying treatment and follow-up, as well as disease activity with clinical scoring and several patient-reported outcome measures. The register includes also information on patients' comorbidity, co-medication, and siblings with MS. During 2007 the registry was expanded to include a biobank for collection of blood samples (DNA and serum).

The Swedish MS Register was officially launched in 2001 and contains data since 1996. Since 2011 the register has been part of the Swedish Neuro Register. The register is a nationwide quality registry for patients diagnosed with MS. Most MS specialists in SWE use the Swedish MS Register to enter information on age at onset and sex as well as clinical parameters, such as disease course, relapses, and treatment. The register dates back to 2002 and contains mostly prospective cases, although some clinics have entered data retrospectively.

Register on Reimbursed Medications (FIN)

In FIN, information on chronic diseases can be obtained from the separate register on special medical reimbursements for treatment of chronic disease. Information on maternal MS diagnoses obtained from the DPP (FIN) is based on this Register on Reimbursed Medications maintained by the SII of Finland. All the patients who are entitled for special reimbursement due to MS diagnosis are included in the register. Reimbursement for MS requires a medical certificate demonstrating that the diagnosis is based on clinical examinations, fulfils international criteria, and is made by a board-certified physician. The medical certificate is issued when the MSDMD treatment is started.

Prescription Registers (FIN, SWE, NOR)

Information on maternal MSDMD exposure before and during pregnancy will be obtained from the Prescription Registers based on reimbursed drug purchases (information is linked to DPP in FIN). The Prescription Registers contain information on outpatient medication purchases in pharmacies (established FIN 1994, SWE 2005, NOR 2004). Prescription-only medicines are only sold in pharmacies, and dispensing requires a prescription issued by a physician or a dentist in FIN, SWE and NOR. In FIN, the register contains information on all purchased prescribed medicines that are reimbursed by the government. This excludes, for instance, most contraceptives. In SWE and NOR, all prescribed medicines purchased in community pharmacies are included irrespective of reimbursement status. The prescription data in the registers includes patient's ID, the generic name of the drug, ATC code, the brand name, the formulation and package, the amount as the defined daily dose (DDD), the date of purchase, the prescribing practice (primary vs. secondary healthcare), and the prescribing physician's area of specialisation.

9.3.1.2 Outcomes

Medical Birth Registers (FIN, SWE, NOR)

Information on live births and stillbirths will be obtained from the MBR in each country (via DPP in FIN). Furthermore, information on abortions and MCAs will be obtained from MBR for NOR. The MBR's purpose for collecting data is to develop and organise maternity care, obstetrical services and neonatal care.

Each of the countries included in this study has kept medical birth registers for decades (established: FIN 1987, SWE 1973 and NOR 1967), with compulsory notification (Langhoff-Roos et al. 2014). All live births and stillbirths from varying gestational ages in the different countries are notified to the registers. There is some variation in content between the Nordic MBRs, but all the registers include some information on maternal socio-demographic background (e.g. marital status, age, smoking status), previous pregnancies and deliveries, maternal diagnoses (ICD-10 codes), care and interventions during pregnancy and delivery, and information on newborn health, diagnoses, care and interventions (Gissler 2010). Diagnoses are registered as ICD-8, ICD-9 and ICD-10 codes. The international origin of the codes for some main groups created through the registers allows for cross-country research on large populations within the Nordic countries. However, codes for each individual case are assigned nationally and this may involve minor differences between the countries. Birth notification forms are linked to MBRs and to population census offices.

The follow-up ends usually when the child is discharged from the hospital or, at the latest, until the end of perinatal period, i.e. the first week of living. Information on deaths, however, can cover the whole infant period until one year of age (Gissler 2010).

Malformation Register (FIN)

Information on MCAs (FIN) will be obtained from the DPP, based on information from the Finnish Malformation Register. The Malformation Registers are usually closely linked to the MBR (FIN), or as a part of the MBR (NOR). Their follow-up period is usually from six to twelve months, and these registers also cover induced abortions due to foetal problems, except in SWE (Gissler 2010).

Register on Induced Abortions (FIN)

In the Nordic countries, statistics on induced abortions are based on case data on an individual level (Gissler 2010). In SWE, however, the data collection is anonymous, and in NOR, the data collection is anonymous before 12 weeks of gestation. In FIN there is a separate Register on Induced Abortions and Sterilisations.

Patient Registers (FIN, SWE, NOR)

Information on hospitalisations due to MS, spontaneous abortions, and ectopic pregnancies will be obtained from the Patient Registers in this study. The Patient Register includes individual-level inpatient data in FIN SWE and NOR (established: FIN 1969, SWE 1987, NOR 2008). Outpatient visits are available since 1998 in FIN, 2001 in SWE and 2008 in NOR. The registers include data on hospitalisations with information on diagnosis (ICD-10), start and end date of the hospitalisation period, operations and other procedures performed, and identification of the hospital and the hospital district. In addition, outpatient visits in the secondary healthcare units and day surgeries are included the registers. No primary care data are currently available.

Causes of Death Register (NOR)

The Causes of Death Register provides data on dates and causes of death with PIN, sex, age, place of residence and causes of death reported by ICD-10 diagnosis codes.

Drugs and Pregnancy Project (FIN)

DPP will be a data source for the Finnish data regarding information on maternal MS diagnosis, MSDMDs, TOPFAs, live births, stillbirths, and MCAs. The purpose of the Finnish DPP, initiated in 2003, is to evaluate the pattern of drug use during pregnancy and estimate the effect of drug use on pregnancy outcomes. The research data are based on information obtained from the Finnish national health registers: the MBR, the Register on Induced Abortions and the Malformation Register, all maintained by THL (Artama et al. 2011). Information on maternal drug use and drug reimbursements is obtained from the Prescription Register and the Register on Reimbursed Medications, both maintained by the SII. The research database enables evaluation of the frequency and type of maternal drug use during pregnancy retrospectively from the year 1996 onwards (at the time of data extraction until the end of 2014). Drug purchases are recorded covering a time period from one month prior to pregnancy to the end of pregnancy in the DPP.

9.3.2 Validity of the data sources

The Nordic national health registers have a population-wide coverage within each country, and the overall quality of the registers is high. The large size of the health register databases of these countries enable the precise estimates of number of different health indicators, and combined together, they also enable evaluation of rare exposures and outcomes. Use of PINs increases the validity of the information, and the register-based method helps to avoid certain biases, such as recall or reporting bias.

9.3.2.1 MS diagnosis and Exposures

MS diagnosis

The Swedish MS Register includes information on approximately 15 000 patients (as in September 2014), with the coverage of about 70% of MS patients in SWE (Ludvigsson et al. 2011). The diagnostic accuracy for patients included in the Swedish MS Register is over 90% (Bahmanyar et al. 2009).

The Register on Special Reimbursement (FIN) includes all the patients who are entitled for special refunds of medicine expenses based on their chronic condition, including MS diagnosis. In practice, only persons who refuse the special reimbursement are excluded from the register. The proportion of these cases is very low, as usually costs for chronic disease related drugs are high.

Exposure to MSDMDs

The Prescription registers in FIN, SWE and NOR cover the whole population, and completeness and accuracy of the registers on reimbursed medications is high (Furu et al. 2009, Furu 2008, Wettermark 2007). For quality assurance, a number of routine data checks are carried out frequently in these registers to identify possible errors or inconsistencies in registers in FIN, SWE and NOR. In FIN the register on reimbursed medications comprises all purchases of medicines directly reimbursed upon purchase at the pharmacies (e.g. 99% in 2007) (National Agency for Medicines and Social Insurance Institution, 2007).

However, there are some limitations to the data collected on exposure:

- Patient-level data on drug use in hospitals and other institutions such as outpatient clinics are not collected routinely in the Prescription Register in FIN, SWE, or NOR, creating observation gaps (Furu et al. 2009). Some drugs are dispensed only through outpatient clinics (for example, antiretroviral drugs), and some new drug groups including some biological drugs (for example, infliximab) are mainly administered in hospitals, and are therefore not usually included in the prescription databases (Table 3). Nonetheless, in FIN information on patients who have a special reimbursement, for example, intramuscular injection, and who want to be injected by a healthcare professional, is included in the prescription register as the patient buys the medicine from pharmacy (personal communication with Leena Saastamoinen, SII on Finland Jan 5, 2015). However, infusion medicines are always obtained from the hospital pharmacy, and therefore information is not included in the Prescription Register (see section 9.7.6 Sensitivity analyses).

9.3.2.2 Pregnancy outcomes

Medical Birth Register

The MBR data are collected from all maternity hospitals in FIN, SWE and NOR. Data are checked, and any data that are missing or inferred to be incorrect are confirmed by contacting the treating hospitals on maternity hospital records. Furthermore, these data are supplemented from birth and death certificates. Information on perinatal deaths (stillbirths or deaths during the first week of life) is revised and supplemented from the Causes of Death Register. After these additions, the statistics in practice have coverage of 100% of births. According to data quality studies, the majority of the register content corresponds well or satisfactorily with hospital record data depending on the type of information (Teperi 1993, Gissler et al. 1995, Gissler 2010). There have been changes to the data content of the MBRs in order to improve reliability of the register. Also, updates of the notification forms have been conducted to bring the collected information more in line with current care practices.

Validation of MBR variables for specific studies has been carried out in all Nordic registers, but they cover different periods and have only been applied to selected conditions (Kristensen et al. 1996, Gissler & Shelley 2002, Klemmensen et al. 2007, Baghestan et al. 2007). These validation studies have been important for each specific study but are of less value for validating general birth registration details, since the true (correct) values do not replace missing or erroneous variables in the medical birth registers, nor do they apply to changes in coding that might have occurred. The results from the validation studies have been used to improve notification routines and quality controls (Langhoff-Roos et al. 2014). Some variables may be over-reported to patient registers, with implications for the medical birth registers that use the general patient registers based on admission data as a primary source.

Congenital malformations

The Finnish Malformation Register receives data on congenital anomalies from hospitals, healthcare professionals and cytogenetic laboratories. It also draws data from the MBR, the Patient Register for Health Care (including Information on Outpatient Services in Specialized Health Care), the Register on Induced Abortions, and the Register of Visual Impairment, all maintained by THL, as well as from the data provided by the National Supervisory Authority for Welfare and Health (Valvira), and from the Causes of Death Register, maintained by SF. The diagnoses obtained from these data sources are confirmed by contacting the hospitals that have given treatment to the infant/foetus. Although the Register mainly collects data from the first year of the infant for monitoring, it also collects data on subsequently detected congenital anomalies for statistics and research. Data check-ups are made regularly, missing cases and case-specific data are added from the MBR, for instance, and any unclear cases and diagnoses are checked and ascertained by contacting the treating hospitals.

The data content and the data collection practices of the Malformation Register were revised in 1985, 1993 and 2005. From 1993 onwards the data coverage can be regarded as very good although there have been no coverage analyses since the 1993 revision. The prevalence of cases with congenital anomalies corresponds to the normal prevalence described in the literature and reported internationally. The prevalence rates of different types of congenital anomalies have also been consistent with the findings of other national and international studies on congenital anomalies. Since 2005, data on congenital malformations have also been derived from the statistics on information on Outpatient Services in Specialized Health Care, which has further improved the total coverage of the Malformation Register to some extent.

Elective terminations of pregnancy

Information on TOPFA and abortions due to other reasons will be obtained from the DPP (FIN) and MBR (NOR). The Finnish Abortion Register, which is the data source for the DPP regarding pregnancy terminations, collects data on all terminations performed in FIN since 1977. The national abortion legislation requires permission with a legal indication for terminating a pregnancy. The data of the Abortion Register are obtained from hospitals and Valvira. The information is completed with information from the national Hospital Discharge Register. More than 99% of all elective TOPs (regardless of reason of the termination (maternal social or health related, foetal related health) registered in hospital records are included in the Abortion Register (Gissler et al. 1995, Gissler et al. 1996). In NOR, abortions are included in the MBR from 12 GW onwards. SWE does not have a register on abortions.

Spontaneous abortions and ectopic pregnancies

Information on spontaneous abortions and ectopic pregnancies will be obtained from the Patient Register. The quality of the data of the Patient Registers is dependent on the quality of the master data that is registered by the sector. According to validity studies focused on the quality of the Swedish (Ludvigsson et al. 2011) and Finnish (Sund 2012) patient register data comparing the data to external information sources, the overall completeness and accuracy seemed to vary from satisfactory to very good in these registers. In the Finnish study more than 95% of discharges could be identified from the register (Sund 2012). The positive predictive value (PPV) for common diagnoses was between 75-99% (Sund 2012). Correspondingly, the PPV varied between the diagnoses, but was generally between 85-95% in the Swedish study (Ludvigsson et al. 2011). No specific validity studies have been conducted regarding information on maternal diagnoses of spontaneous abortions or ectopic pregnancies included in the Patient Registers.

9.3.3 Linkage methods

Study permit approvals and access to the study data will be applied for by EPID Research in FIN and by academic collaborators in SWE and NOR. After receiving the permits, EPID Research and the collaborators will send data requests to the data holders, who identify the study population and use the unique PINs to extract all the relevant data for the study population. The data holders will also create a unique dummy study identification number (SID) for each PIN. EPID Research will then receive the data where the PINs have been replaced by SIDs and these will be used for data linkage at the patient level. Therefore, the researchers at EPID Research have access to anonymous data only.

9.4 Variables

Exposures: Maternal MS and related medication exposure before and during pregnancy are the basis of the exposure status of the study subjects in this study.

Pregnancies are considered unexposed if no MSDMDs of interest have been used within three months (except six months for mitoxantrone and cladribine) prior to LMP or during pregnancy. As the maximum reimbursable amount per purchase is the supply for three months of treatment, a pregnancy is defined as unexposed to MSDMDs if there are no purchases of MSDMDs within six months (except nine months for mitoxantrone and cladribine) prior to LMP or during pregnancy. Otherwise a pregnancy is defined as exposed to MSDMDs. Similarly, a pregnancy is defined as unexposed to IFN-β if there have been no purchases of IFN-β containing medications within six months prior to LMP or during pregnancy and otherwise a pregnancy is defined as exposed to IFN-β.

The following MSDMDs and their ATC codes are included in this study: IFN-β-1a (L03AB07), IFN-β-1b (L03AB08), Peg IFN-β-1-a (L03AB13), human normal immunoglobulin (J06BA02), cyclophosphamide (L01AA01), methotrexate (L01BA01, L04AX03), cladribine (L01BB04), mitoxantrone (L01DB07), alemtuzumab (L01XC04), glatiramer acetate (Copaxone®) (L03AX13), leflunomide (L04AA13), natalizumab (L04AA23), fingolimod (L04AA27), teriflunomide (L04AA31), azathioprine (L04AX01), dimethyl fumarate (N07XX09).

Table 3: More detailed information on individual MSDMD agents, including information on availability and reimbursement in FIN, SWE and NOR.[7]

MSDMD agent		ATC code	Reimbursed in FIN in Jan 2015 (yes / no)[1]	Marketing authorisation date			Administration in hospital only[4]
				FIN	SWE	NOR	
IFN-β natural		L03AB02		no	no	no	
IFN-β-1-a	Avonex®	L03AB07	yes	13.3.1997	13.3.1997	5.7.2002	no
	Rebif®			4.5.1998	4.5.1998	19.8.2003	no
IFN-β-1-b	Betaferon®	L03AB08	yes	30.11.1995	30.11.1995	1.9.2006	no
	Extavia®			20.5.2008	20.5.2008	20.5.2008	no
Peg IFN-β-1-a	Plegridy®	L03AB13	yes	18.7.2014	18.7.2014	18.7.2014	no
intravenous immunoglobulin		J06BA02	no	16.10.1991	10.10.1981	9.10.1996	yes
cyclophosphamide		L01AA01	no	4.6.1986	28.4.1959	6.4.1959	injection yes tablet no
methotrexate		L01BA01 L04AX03	yes[2] / no[3]	25.2.1981	23.6.1964	14.4.1971	tablet no infusion yes injection yes/no[5]
cladribine		L01BB04	no	25.9.2000	19.11.1993	14.11.1996	injection no infusion yes
mitoxantrone		L01DB07	no	30.8.1993	29.10.1987	1.8.1988	yes
alemtuzumab		L01XC04	no	12.9.2013	no	no	yes
glatimer acetate (Copaxone®)		L03AX13	yes	8.3.2004	21.9.2001	24.2.2004	no[6]
leflunomide		L04AA13	yes	2.9.1999	2.9.1999	5.11.2004	no
natalizumab		L04AA23	no	27.6.2006	27.6.2006	27.6.2006	yes
fingolimod		L04AA27	yes	17.3.2011	17.3.2011	17.3.2011	no
teriflunomide		L04AA31	yes	26.8.2013	26.8.2013	26.8.2013	no
azathioprine		L04AX01	yes	31.1.1968	14.3.1968	9.8.1968	no
dimethyl fumarate		N07XX09	no	30.1.2014	30.1.2014	30.1.2014	no

[1] Information on only reimbursed medication can be acquired from the National Prescription Register in Finland.
[2] Pre-filled syringes/pens and tablets.
[3] Injection and infusion solutions - except Trexan injection solution, which is reimbursed.
[4] Information on drug use in hospitals and outpatient clinics are not collected in the Prescription Registers and thus information on exposure to these types of medication is not available.
[5] Some of the injections are given in hospital and some can be self-administered at home.
[6] Earlier there may have been also products that have been administered in hospital.
[7] Sources (accessed on 3.2.2015):
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124,
http://www.fimea.fi/laaketieto/valmisteyhteenvedot/laakkeet
http://www.lakemedelsverket.se/LMF
http://www.legemiddelverket.no/Legemiddelsoek/

Outcome variables: The primary (P), secondary (S) and exploratory (E) outcomes are presented here according to pregnancy timeline.

Ectopic pregnancies (S) (ICD-10: O00) and spontaneous abortions (S) (ICD-10:O03):

- Information will be obtained from Patient Register (FIN, SWE, NOR) based on hospital visits due to these diagnoses

Elective termination of pregnancy (P) (ICD-10: O04):

- Information will be obtained from the DPP (FIN) and from MBR (NOR), where the abortions are registered from GW 12.
- This information is not available from SWE.

Stillbirth (P):

- Information will be obtained from the DPP (FIN) and MBR (SWE, NOR). The Finnish DPP and Norwegian MBR include information on all stillbirths of foetuses with a birth weight of at least 500 g or with a gestational age of at least 22+0 GW. The Swedish MBR includes data on stillbirths after 28 GW.

Live Birth (P):

- Information on live births will be obtained from the DPP (FIN) and MBR (SWE, NOR)

MCAs (P):

- Information will be obtained from the DPP (FIN), Patient Register (SWE) and MBR (SWE, NOR). The study will concentrate on MCAs. These outcomes are registered according to ICD-9 classification into 25 groups (ICD-codes 740-759). Minor anomalies will principally be excluded according to the European Surveillance of Congenital Anomalies (EUROCAT).

Defect cases (E):

- Information will be obtained from the DPP (FIN), Patient Register (SWE) and MBR (SWE, NOR). Defect cases with 3 or more minor anomalies will be defined according to the European Surveillance of Congenital Anomalies (EUROCAT).

Serious adverse pregnancy outcome (P):

- A composite endpoint including presence of elective TOPFA, MCA or stillbirth.

Mode of delivery (CS/vaginal)(E):

- Information will be obtained from the DPP (FIN), MBR (SWE, NOR).

Preterm birth (E):

- Information on gestational age will be obtained from the DPP (FIN) and MBR (SWE, NOR). Preterm birth is defined as length of gestation less than 37 completed GW.

Birth height (E):

- Information will be obtained from the DPP (FIN) and MBR (SWE, NOR). LBH is defined according to national standards in each country as available (FIN: Sankilampi et al. 2013).

Birth weight (E):

- Information will be obtained from the DPP (FIN) and MBR (SWE, NOR). LBW (E) is defined as birth weight less than 2500 grams. High birth weight is defined as 4500 grams or more.

Birth weight for gestational age (E):

- Information will be obtained from the DPP (FIN) and MBR (SWE, NOR). It is defined according to the gestational age and sex-specific national standards in each country as available (FIN: Sankilampi et al. 2013). AGA is used as reference outcome in relation to SGA and LGA.

Sex of the newborn (E):

- Information will be obtained from the DPP (FIN) and MBR (SWE, NOR)

Head circumference (E):

- This information will be obtained from the DPP (FIN) and MBR (SWE, NOR) and is measured as centimetres. Low head circumference is defined according to national standards in each country as available (FIN: Sankilampi et al. 2013).

Apgar scores (E):

- These are registered at 1 and 5 minutes after birth. Low Apgar score is defined as less than 7 in 1-minute and 5-minutes score. Information is available from the DPP (FIN) and MBR (SWE, NOR).

Any chronic diseases:

- Information on chronic diseases available from the DPP (FIN), MBR (FIN, SWE, NOR), MS Register, Patient Register (SWE, NOR), Prescription Register (FIN, SWE, NOR) will be used to define pharmacological treatment for comorbidities. The comorbidities listed in Table 4 existing before, or during pregnancy will be identified based on diagnoses or specific medications for chronic diseases. These represent the most common chronic diseases among women who have been pregnant (information source the DPP, years 1996-2010). Information is based on pre-pregnancy diagnoses. From these comorbidities a binary variable will be created to indicate if the mother has had any chronic diseases before or during pregnancy (Yes, No). Lifetime pre-pregnancy diagnoses are included from the time period included in the data sources.

Table 4: List of chronic diseases diagnosed before LMP and during pregnancy.

Comorbidities	ICD-10	Proportion of women with the disease among parturient (%) in Finland 1996-2010 [1]
Asthma and related conditions	E84.0, J41–J45, P27.1	2.77
Hypothyroidism (thyroid insufficiency)	C73, E03, E89.0	0.82
Epilepsy	C71, G40, G41	0.80
Rheumatoid arthritis and related conditions	A04.6, A39.8, A50.5, D76.0, D76.3, H20.1, H30, I33.0, J84, K50.9, K51.9, K73.2, K74.3, K83.0, L40.5, M02, M05, M06, M08, M13.9, M30–M35, M45, M46.1, M46.9, M94.1, N03, Q44.2	0.61
Diabetes Mellitus (type I and type II will be considered separately)	E10-E14, E89.1	0.52
Colitis Ulcerosa, Crohn´s disease	K50, K51	0.50
Hypertensive diseases	I10–I13, I15, I27.0	0.38
Severe psychosis and other severe mental disorders and related conditions	A52.1, A69.2, A81.0, B22.0, B56.9, B57.2, E01.8, E03.9, E52, E53.8, E75.6, E83.0, E83.5, F01, F03, F06.0-F06.3, F20-F25, F28, F29, F30.1, F30.2, F31, F32.3, F33.3, F84, G10, G20, G30.0, G30.1, G30.8, G30.9, G31.0, G35, G40.9, M30.0, M32.8	0.32
Leukaemia and related conditions	C81–C85, C88, C90–C96, D45–D47, D72.1, D75	0.06
Hypercholesterolemia and mixed hyperlipidemia	E78.0, E78.2	0.05
Hypogonadism	E28.3, E29.1, E89.4, E89.5, Q96, Q98	0.04
Hypertensive heart disease with heart failure and related conditions	I11.0, I13, I50, I97.1, P29.0	0.04
Chronic arrhythmia of the heart	I47–I49	0.04
Glaucoma	H40	0.03
Pernicious anemia and deficiency of specified B group vitamins	C16, D51, E53.8	0.03

Comorbidities	ICD-10	Proportion of women with the disease among parturient (%) in Finland 1996-2010 [1]
Hypothyroidism parathyroid gland, chronic (parathyroid insufficiency)	E20, E31.0, E89.2	0.02
Deficiency of coagulation, hemophilia	D66, D67, D68.0–D68.2	0.01
Myasthenia gravis	G70.0	0.01
Maternal pregnancy-related disorders	O10-O29	not available from DPP
Other malignancies	C00-C80	not available

[1]Lahesmaa-Korpinen et al. 2014

Exposure to any teratogenic medications (including steroids)**:**
Information on co-medication will be obtained from Prescription Registers (FIN, SWE, NOR). The medications included consist of high-risk medicines during pregnancy according to the Swedish Catalogue of Approved Drugs (FASS) (Berglund 1984, FASS 1993). This classification comprises 4 separate categories (A, B, C, D): A includes the safest drugs; B is divided into 3 subgroups (B1, B2, B3); and C and D categories are used for drugs which may have different risks for the foetus depending on the evidence on which the risk is based. In this study, drugs from categories C and D will be included as potentially teratogenic drugs or teratogenic drugs (see Annex 3 for the classification of teratogenic medications and for a detailed list of specific ATC codes). From these medications a binary variable will be created to indicate if the mother has been exposed to any teratogenic medications (including steroids) before or during pregnancy (Yes, No). Pregnancies are considered unexposed to an MSDMD if the medication has not been used within 3 months prior to LMP or during pregnancy (except for mitoxantrone and cladribine, for which 6 months must be allowed).

Potential confounding factors and effect modifiers:
The following confounding factors and effect modifiers will be taken into account in the analyses according to availability and available time period from each register source: any chronic diseases, exposure to any teratogenic medications including steroids, country of residence of the mother, university hospital district, maternal age at LMP, year of pregnancy outcome, pre-pregnancy weight, pre-pregnancy BMI, number of previous pregnancies, time since MS diagnosis, duration of MS treatment, number of previous abortions, smoking status during pregnancy and number of foetuses in the pregnancy (single or multiple).

9.5 Study size

Based on the feasibility study (cf. Annex 1) it is estimated that a total of 1671 MS pregnancies would be available for the current study from FIN, SWE and NOR. This total sample size was estimated as follows: In FIN 433 MS pregnancies were observed between 1 January 1996 and 31 December 2010 of which 86 were in 2010. For the actual study, data from FIN from 1 January 2011 to 31 December 2014 will also be used, and therefore the total number of available MS pregnancies was estimated to be 777 (433 + 4*86, where 86 is the number of MS pregnancies in 2010). In SWE 329 MS pregnancies were observed during the time period 1 July 2005 – 31 December 2011 (329/6.5 years = 51 per year). Because the study period in SWE is from 1 January 2005 to 31 December 2014, the estimated number of MS pregnancies in SWE is 482 (329 + 3*51). In NOR, 330 MS births were expected to occur in the time period 1 January 2004 – 31 December 2014, which was estimated to be 80% of all MS pregnancies excluding terminations of pregnancies. The number of MS pregnancies available in the study from NOR was thus estimated to be 412 (330/0.8). The total number of 1671 MS pregnancies available for the study is obtained as the sum of these estimated numbers (777 + 482 + 412).

From the 433 MS pregnancies in FIN, 102 (24%) and 331 (76%) were identified as exposed and unexposed to any MSDMD, respectively (in SWE, the proportion of unexposed to any MSDMDs was 77%). Furthermore, of the 433 MS pregnancies in FIN, 95 (22%) and 338 (78%) were identified as exposed and unexposed to IFN-β regardless of exposure to other MSDMDs, respectively (personal communication with Anna-Maria Lahesmaa-Korpinen, THL, 15 May 2014). Based on these numbers, it was estimated that 76% (= 331/433) of all MS pregnancies will be unexposed to any MSDMD and 78% (= 338/433) of all MS pregnancies will be unexposed to IFN-β (regardless of exposure to other MSDMDs). Based on a systematic review of MSDMD usage (La Mantia et al. 2014), it was estimated that 80% of those identified as exposed to IFN-β would not be using other MSDMDs (368*0.8 = 294). Table 5 presents the study population size by exposure to IFN-β based on these assumptions.

The estimated background prevalence for the composite endpoint of serious adverse pregnancy outcome, consisting of TOPFAs, live births with MCA and all stillbirths, was 6.5% (personal communication with Anna-Maria Lahesmaa-Korpinen, THL, 15 May 2014) and 7.3% (= 24/331, based on the feasibility study in Finland, cf. Annex 1) in women with MS unexposed to IFN-β (regardless of exposure to other MSDMDs) and unexposed to any MSDMD, respectively. Because these numbers best correspond to the study setting, they were taken as the most relevant baseline prevalences of serious adverse pregnancy outcomes in the sample size calculations. Lower outcome prevalences were investigated to test how sensitive the findings of minimum detectable effect sizes are to these assumptions. For comparison, in the Finnish feasibility study the prevalence of serious adverse outcomes was 3.7% = (38384/1031778) among all women, and according to EUROCAT 2015, the prevalence of malformation outcome among all women in the EU is 2.6%. The anticipated sample sizes in study cohorts 1-6 are:

- Cohort 1: 294 (80% of 368) for MS pregnancies exposed only to IFN-β.
- Cohort 2: 368 (22% of 1671) for MS pregnancies exposed to IFN-β regardless of exposure to other MSDMDs.
- Cohort 3: 1270 (76% of 1671) for MS pregnancies unexposed to any MSDMD.
- Cohort 4: 1303 (78% of 1671) for MS pregnancies unexposed to IFN-β.
- Cohort 5: 33 (Cohort 4 size – Cohort 3 size = 1303 – 1270 = 33) for MS pregnancies exposed to MSDMDs except IFN-β or glatiramer acetate (Copaxone®) or dimethyl fumarate (Tecfidera®).
- Cohort 6: Approximately 2.9 Million pregnancies for women from the general population in FIN, SWE and NOR without MS diagnosis based on the based on the feasibility study (cf. Annex 1).

With these sample sizes and baseline outcome prevalence, the minimum detectable effect size between the MS women exposed to IFN-β only (cohort 1) vs. MS women unexposed to any MSDMDs (cohort 3) is 1.72 in terms of RR using 80% power and a 5% two-sided significance level. If the background prevalence calculated among MS pregnancies unexposed to any MSDMD's would be closer to that in the whole population, e.g. 6%, 5%, 4% or 3%, the respective minimum detectable effect sizes would be 1.81, 1.91, 2.04, and 2.23. Regarding the comparison of a composite serious adverse pregnancy outcome between women with MS exposed to IFN-β only (cohort 1) vs. unexposed to IFN-β regardless of exposure to other MSDMDs (cohort 4), the minimum detectable effect size (RR) is approximately 1.77. Regarding the comparison of the composite serious adverse pregnancy outcome between women with MS exposed to IFN-βs regardless of exposure to other MSDMDs (cohort 2) vs. unexposed to any MSDMD (cohort 3), the minimum detectable effect size (RR) is approximately 1.66.

The sample size calculations were performed using the bpower function of the R programming language (http://www.r-project.org).

Table 5: The estimated numbers of all MS pregnancies and MS pregnancies unexposed to IFN-βs available for the study during the study period by country.

Country and study period		ALL MS Pregnancies	MS Pregnancies unexposed to IFN-βs [4]
Country	Study period	Number of pregnancies	Number of pregnancies
Finland	1 Jan 1996 – 31 Dec 2014	777[1]	606[4]
Sweden	1 Jul 2005 – 31 Dec 2014	482[2]	376[4]
Norway	1 Jan 2004 – 31 Dec 2014	412[3]	321[4]
TOTAL		**1671**	**1303**[4]

1) Estimated as 433 from time period 1 Jan 1996 – 31 Dec 2010 plus 4*86 MS pregnancies from four additional years 2011 – 2014 where 86 denotes the number of MS pregnancies in 2010
2) Estimated as 329 MS births from Jul 2005 – 31 Dec 2011 plus (329 / 6.5) MS births from three additional years 2012 – 2014.
3) Estimated as 330 MS births from 1 Jan 2004 – 31 Dec 2014 divided by (1-0.2) where 0.2 denotes the estimated abortion prevalence
4) Estimated as the number of ALL MS PREGNANCIES x 78% where 78% denotes the estimated proportion of MS pregnancies unexposed to IFN-β regardless of exposure to other MSDMDs

9.6 Data management

R language (http://www.r-project.org) will be used for data management for creating the analysis database and in statistical analysis for creating tabulations and graphics as well as in all statistical modelling. R language is described in a detailed report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.r-project.org/doc/R-FDA.pdf). Full audit trail, starting from raw data obtained from register holders and ending with the creation of statistical tables and graphs in reports, will be maintained. Source code of data management and data analyses is kept for inspection for five years after publication of results. The study may be inspected by the sponsors' independent representative(s) or by competent authorities.

All study data and supporting documents will be retained for ten years after the completion of the study report. At the end of that period EPID Research shall request further instructions from the MAHs. EPID Research shall not destroy any relevant material related to the study without prior approval from all MAHs involved in the study. As the register holder of the study register EPID Research is in charge of archiving and deleting the data. Secure archives will be maintained for the orderly storage and retrieval of all study related material. An index shall be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorised personnel only. Access to the study data cannot be given to any third parties, and the study data cannot be used for other purposes than prescribed in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

9.7 Data analysis

The individual patient-level data from each country will be pooled into a single dataset and analyses will be done using the pooled dataset.

EPID Research will perform all statistical analyses by using the R programming language (http://www.r-project.org). Described below is the analysis strategy. A separate detailed statistical analysis plan will be written after approval of the study protocol.

9.7.1 Population description

The study population consists of pregnant women with MS. A pregnancy event refers to terminations of pregnancy, spontaneous abortions, ectopic pregnancies, stillbirths and live births. The pregnancy event is considered as the experimental unit in this study. One woman may have several pregnancy events during the study period and all pregnancy events are included in the analysis.

The characteristics of all pregnancies are to be described with n, mean, median, standard deviation (SD), minimum, maximum and inter-quartile range for continuous variables and with n and percentage (%) for categorical variables. These population characteristics are to be presented for each study cohort separately and also for the whole study population. The following variables are to be included in the population description as available from the different countries:

- Country, university hospital district,
- Duration of MS treatment,
- Time since MS diagnosis,
- Year of pregnancy outcome,
- Maternal age at LMP,
- Pre-pregnancy maternal weight,
- Pre-pregnancy maternal BMI,
- Any chronic diseases during or before pregnancy,
- Exposure to any teratogenic medications (including steroids) during or before pregnancy,
- Number of previous pregnancies,
- Number of previous abortions,
- Smoking status during pregnancy and
- Number of foetuses in pregnancy (single, multiple).

Confounding factors and effect modifiers will be taken into account in the analyses according to availability and available time period from each register source.

9.7.2 Denominators used for different pregnancy outcomes

The denominator used for the calculation of the descriptive statistics and prevalence of specific pregnancy outcomes in each study cohort varies by pregnancy outcome. Table 6 below describes how the denominators are defined for each pregnancy outcome.

Table 6: Denominators used for calculation of the descriptive statistics and prevalence of pregnancy outcomes in each study cohort.

Pregnancy outcome	Denominator used in each study cohort
Serious adverse pregnancy outcome	Number of elective terminations + number of births (still or live)
Elective TOPFA or other reasons	Number of elective terminations + number of births (still or live)
Still births	Number of elective terminations + number of births (still or live)
Live births	Number of elective terminations + number of births (still or live)
MCA	Number of elective terminations + number of births (still or live)
MCA in live births	Number of live births
Mode of delivery (CS/vaginal)	Number of live births, separately for single and multiple pregnancies
Preterm birth	Number of live births, separately for single and multiple pregnancies
Birth weight, LBW and birth weight, head circumference for gestational age	Number of live births, separately for single and multiple pregnancies
Sex of the newborn	Number of live births, separately for single and multiple pregnancies
Head circumference, low head circumference	Number of full-term live births, separately for single and multiple pregnancies
Apgar scores	Number of full-term live births, separately for single and multiple pregnancies
Ectopic pregnancies	Number of all pregnancy events
Spontaneous abortions	Number of all pregnancy events
Defect cases	Number of elective terminations + number of births (still or live)

9.7.3 Analysis of primary objectives

With regard to objective #1, the descriptive statistics including the number of events (n) and prevalence (%) will be presented for each pregnancy outcome (i.e. serious adverse pregnancy outcome, elective TOPFA, MCA, stillbirth, and live birth) in each study cohort separately and also for the whole study population. Information on live births, stillbirths and TOPFAs will be included in the analyses of MCA, as approximately 10% of MCAs are detected in foetuses of TOPFA.

With regard to objective #2, the prevalence of the serious adverse pregnancy outcomes will be compared between the study cohorts using log-binomial regression. Two models, base and adjusted, will be used in these comparisons. The base model will be adjusted for the following design variables and *a priori* likely confounders: country, year of pregnancy outcome, maternal age at LMP, number of previous pregnancies, any chronic diseases, and exposure to any teratogenic medications including steroids.

The adjusted model will be built using a variable selection procedure (Bursac et al. 2008). Candidate covariates for the adjusted model will be those in the base model and the following additional ones: university hospital district, pre-pregnancy weight, pre-pregnancy BMI, number of previous abortions, smoking status during pregnancy, number of foetuses in pregnancy (single vs. multiple), time since MS diagnosis and duration of MS treatment as available in the data sources. Variable selection starts by applying first the unadjusted model and proceeds as follows:

1. Each candidate covariate will be considered a potential confounder if the univariate association between the covariate and the serious adverse pregnancy outcome, tested with the Wald test for logistic regression with *P*-value cut-point of 0.25.

2. All candidate covariates identified as potential confounders in step 1 will be added simultaneously to the model. After this, additional covariates not identified as potential confounders in step 1 will be added to the model one at a time and the model fit comparing each null vs alternative model will be assessed by the likelihood-ratio test. Variables in the alternate model will be retained at a likelihood ratio test of *P*-value <0.1.

3. An iterative process of reducing the model in step 2 will be performed by refitting and verifying model fit comparing null vs. alternative models by likelihood ratio test of *P*-value <0.1 to determine the main effects model.

4. Model fit results and the effect of adding and removing variables in step 2 and step 3 will be reported at each step. If there are a low number of outcomes identified, the final adjusted model will be limited to a covariate-outcome ratio of 1 covariate: 10 outcomes to avoid over-adjustment. If the number of covariates is higher than the covariate-outcome ratio allows, then the covariates with least significant effect to the model fit will be omitted.

Comparisons will be made separately for different study cohorts: i) one comparison will be made between women with MS exposed to IFN-β only (cohort 1) vs. unexposed to any MSDMDs (cohort 3) and ii) another between women with MS exposed to IFN-β only (cohort 1) vs. unexposed to IFN-β regardless of exposure to other MSDMDs (cohort 4). The RR estimates with 95% CIs and associated p-values will be reported for these comparisons and for all relevant covariates used in the model.

9.7.4 Analysis of secondary objectives

With regard to objective #3, similarly as in the analysis of the primary objectives, the prevalence of the pregnancy outcomes (i.e. serious adverse pregnancy outcome, elective TOPFA, stillbirth, live birth and MCA) will be compared between the study cohorts specified in Section 8.

With regard to objective #4, the descriptive statistics including number (n) and prevalence (%) of ectopic pregnancies and spontaneous abortions will be presented in each study cohort separately. The prevalence of these pregnancy outcomes will be compared between the study cohorts specified in Section 8.

With regard to objective #5, the descriptive statistics (n and %) of the pregnancy outcomes (i.e. serious adverse pregnancy outcome, elective TOPFA, stillbirth, live birth and MCA) will be further described for study cohorts 1 – 4 stratified by country, year of pregnancy outcome, maternal age at LMP, any chronic diseases, exposure to any teratogenic medications including steroids, time since MS diagnosis, duration of MS treatment, gestational age and weight of the newborn as relevant for specific pregnancy outcomes and as the number of events allow.

9.7.5 Analysis of exploratory objectives

With regard to objective #6, only live births will be included in the analyses on birth health. The descriptive statistics given in Table 7 are to be presented for each additional pregnancy outcome in each study cohort 1 – 4 separately.

Table 7: Descriptive statistics calculation for each additional pregnancy outcome.

Pregnancy outcome	Descriptive statistics
Mode of delivery (CS/vaginal)	number (n), prevalence (%)
Preterm birth	number (n), prevalence (%)
Birth weight	mean, median, SD, minimum, maximum and inter-quartile range
LBW	number (n), prevalence (%)
Birth height	mean, median, SD, minimum, maximum and inter-quartile range
LBH	number (n), prevalence (%)
Weight adjusted for gestational age (SGA, AGA, LGA)	number (n), prevalence (%)
Sex of the newborn	number (n), prevalence (%)
Head circumference	mean, median, SD, minimum, maximum and inter-quartile range
Low head circumference	number of events (n), prevalence (%)
Apgar score (at 1 and 5 minutes)	mean, median, SD, minimum, maximum and inter-quartile range
Defect cases	number (n), prevalence (%)

With regard to objective #7, the pregnancy outcomes (n, %) of i) congenital malformations in live or still births, ii) ectopic pregnancies, iii) spontaneous abortions, and iv) live births in the general population without MS diagnosis in FIN, SWE and NOR (cohort 6) are to be estimated based on relevant official birth health statistics available from these countries. This is to be done by subtracting the prevalence attributable to MS-diagnosed women from the prevalence in the general population and dividing this by the proportion of pregnancies without an MS diagnosis. Thereafter, the observed numbers of pregnancy outcomes matched for age and country in cohort 3 will be compared to the numbers calculated for cohort 6. In these comparisons, the standardised prevalence ratio (ratio of the expected and observed prevalent cases) with 95% CI will be used.

9.7.6 Sensitivity analyses

- Lack of information on terminations of pregnancy due to foetal anomalies from SWE may yield underestimation of the prevalence of MCA in the study population. In FIN, 10.5% of total cases with MCAs were diagnosed and recorded in TOPFAs between 1993 and 2010. However, this may bias the study results on MCAs if the risk for TOPFA differs between women with different MSDMD exposures or MS exposure in SWE. Separate analyses will be performed on MCAs for the Norwegian and the Finnish data including pregnancy terminations, stillbirths and live births, and another analysis including live births only. The analyses will also be stratified by country as the follow-up times of the newborn babies for recording the malformations in MBRs or Malformation Register may vary between the countries.

- Information on pregnancy terminations is available from GW 12 onwards from the Norwegian data, and therefore, information on early pregnancy terminations conducted before GW 12 could result in incomplete data. Therefore separate analyses by trimesters on pregnancy terminations will be performed.

- In additional sensitivity analyses on MCAs, outcomes will be assessed where exposure occurred prior to pregnancy and through to the end of the first trimester of pregnancy. Also, an analysis of MCA outcomes from live births only will be performed.

- As there is a geographical variation in MS prevalence not only between countries but also within countries, descriptive statistics will be conducted by country and university hospital district level. Country and region will also be included in the multivariate analyses.

- Possible changes in diagnostic criteria and developments in examination and treatment throughout time, as well as trends in obstetric care may influence the estimated prevalence. The study periods also vary between the countries, which may reflect the deviation in the results. Therefore the year of pregnancy outcome will be taken into account in the descriptive statistics and analyses. By taking into account the data from 1 Jan 2005 to 31 Dec 2014 from each country (time period in which the data is available i.e. overlaps for all 3 countries), a separate sensitivity analysis of the primary objective will be provided as well.

- New MS immunomodulatory therapies (e.g. cladribine, mitoxantrone and teriflunomide) can have long-term side effects. The proportion of pregnancies in different study cohorts that are using these treatments with respective treatment duration and duration of unexposed period at LMP will be reported. In addition, two separate sensitivity analyses are to be performed: 1) analysis further adjusting for a variable never vs. ever exposed to cladribine, mitoxantrone or teriflunomide as a covariate and 2) analysis adjusting for the duration of cladribine, mitoxantrone or teriflunomide treatment prior to LMP as a covariate.

- Regarding the identification of cohort 1, exposure to IFN-β without exposure to any other MSDMD is based on drug purchase data. It is possible that individuals in this cohort have received other MSDMDs in a hospital. In addition, steroids may be given by infusion in a hospital. To account for this possibility, a sensitivity analysis will be done for primary objective #2 using only those individuals from cohort 1 who are unexposed to the proxy MSDMD/steroid hospital exposure during the pregnancy period. To do this, a proxy for the MSDMD /steroid infusion hospital exposure will be defined for cohort 1, based on diagnoses (ICD-10 codes) and all operations codes (Nomesco classification of surgical procedures (NCSP) based classification) recorded pertaining to any hospital visits during the pregnancy period.

- To investigate if cohort 5 could be a proxy for the severity of disease with impact on the pregnancy outcomes, the descriptive statistics (n, %) will be presented for each pregnancy outcome (i.e. serious pregnancy outcome, elective TOPFA, stillbirth, live birth and MCA) in women with MS exposed to other MSDMDs but not to IFN-β or glatiramer acetate (Copaxone®) or dimethyl fumarate (Tecfidera®) before or during pregnancy. The impact of disease severity will be assessed by presenting the prevalence of the outcomes for cohort 5 versus cohort 3.

9.7.7 Missing data

For study variables, if a variable is totally missing from a database, it will be excluded from the analysis. If a variable is missing for only some of the patients a missing data category will be added and used in the analysis. In addition, to investigate the robustness of the variable selection procedure (section 9.7.3) to missing data, if a candidate covariate is missing from over one quarter of patients, missing values will be imputed multiple times and the variable selection re-performed using each of the complete (imputed) data sets (Wood et al. 2008). Results for models including predictors that appear in i) any, ii) at least half, and iii) all models selected using the imputed data sets will be reported as part of the sensitivity analyses (Wood et al. 2008 section 2.4.3).

9.7.8 Multiplicity adjustment

No formal adjustments for multiple comparisons will be performed. It should be noted that several comparisons will be made and some of the significant results may be due to chance although this is a population-based study which collects information from all MS pregnancies in FIN, SWE and NOR during the specified follow-up period.

9.8 Quality control

The study will be conducted as specified in this protocol. The principal investigator, the co-investigators and the sponsors of the study must approve all revisions to the protocol. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to relevant ethics committees and register holders.

The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, 2014). The protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (www.pharmacoepi.org/resources/guidelines_08027.cfm).

EPID Research, the principal investigator, co-investigators, the sponsors and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study protocol will be registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp). Study results will also be published in the ENCePP E-register.

For information on storage of records, archiving of the statistical programming performed to generate the results and possible audits, see section 9.6. Due to the study type (register study using administrative databases) on-site monitoring will not be performed.

9.9 Limitations of the research methods

Exposure information

Information on patient-level data on MSDMD used in hospitals and other institutions is not included in the data from prescription databases in FIN, SWE or NOR (Furu et al 2009). This creates observation gaps and therefore there may be some cases classed as MSDMD unexposed, who are actually treated in hospitals. Some drugs are dispensed only through outpatient clinics (for example, antiretroviral drugs), and some new drug groups including some biological drugs (for example, infliximab) are mainly administered in hospitals, and are therefore not usually included in the prescription databases. Nonetheless, in FIN information on patients who have a special reimbursement for i.e. intramuscular injection, and who want to be injected by a professional instead of themselves, is included in the prescription register as the patient buys the medicine from pharmacy (personal communication with Leena Saastamoinen, SII on Finland Jan 5, 2015). In similar situation with infusion, the medicine is always obtained from the hospital pharmacy, and therefore information is not included in the Prescription Register.

In FIN, most of the MSDMDs are included in the prescription databases and are included in the study database. In FIN, SWE or NOR, IFN-β natural (L03AB02) is not on market. Furthermore, human normal immunoglobulin (J06BA02), cyclophosphamide (L01AA01), some products of methotrexate (L01BA01, L04AX03), cladribine (L01BB04), mitoxantrone (L01DB07), alemtuzumab (L01XC04) and natalizumab (L04AA23) are on market, but they are not under the special reimbursement and are given in hospitals. Information on glatiramer acetate (Copaxone®) (L03AX13) is available since 2004, when the product was approved in EU and in NOR.

Study power

The primary comparisons in this study will be performed between MS patients exposed to IFN-β only vs. unexposed to any MSDMDs and also between women with MS exposed to IFN-β only vs. unexposed to IFN-β (regardless of exposure to other MSDMDs) and the study has been powered for these comparisons. The secondary objectives will also include comparisons between women with MS exposed to IFN-β regardless of exposure to other MSDMDs vs. unexposed to any MSDMDs which will also be sufficiently powered. However, the study is not powered for comparisons made using individual pregnancy outcomes or for comparisons that only employ a subset of the cohorts in the primary comparisons.

In the power calculations, the anticipated background prevalence of serious adverse pregnancy outcomes was based on the Finnish feasibility data. Because the availability of data regarding the serious adverse pregnancy outcome varies between countries (mainly, elective termination not available in Sweden), the observed overall prevalence of serious adverse pregnancy outcomes in all of the Nordic countries might be smaller than anticipated. However, as presented in the power calculations, if the prevalence of the serious adverse pregnancy outcome is above 3%, the minimum detectable effect size is still below 2.5 (RR).

In addition, to remove any bias from Sweden, a sensitivity analysis is being done on MCAs for the Norwegian and the Finnish data including pregnancy terminations, stillbirths and live births, and another analysis including live births only.

Variation in MSDMD use between countries

There is variation between the countries regarding MSDMDs on market. Some of the products are not on market and some of the products are new on market. For example, teriflunomide was licensed in the European Union in 2013. New MS immunomodulatory therapies (e.g. cladribine, mitoxantrone and teriflunomide) can have long-term side effects. Although we are not able to evaluate the long-term effects of these newer MSDMDs in this study, we are reporting the proportion of pregnancies in different groups that are using these treatments with respective treatment duration and duration of unexposed period at LMP. We will also perform separate sensitivity analyses that adjust for exposure of these treatments and their duration.

Information on MS disease

It is known that there are regional and international differences in prevalence and incidence of MS. As for information on age at MS onset, disease status, and disease severity are not available from all MS data sources of these countries, the effect of MS and MSDMDs on these pregnancy outcomes in patients with different types of MS cannot be distinguished in this study. Therefore, confounding by indication is possible.

MS is more prevalent in Northern European countries than in southern part of Europe. It is unlikely that drug-related effects are due to the prevalence of the disease, but the large study population increases the likelihood of observed rare adverse outcomes. Information on country and region will be included in the descriptive, multivariate, as well as sensitivity analyses in this study.

Information on elective terminations, spontaneous abortions and stillbirths

Information on elective TOPFA is not available from SWE, while in NOR information on pregnancy terminations is available only from GW 12 onwards. Furthermore, Information on spontaneous abortions is incomplete in this study, as only women treated in hospitals due to spontaneous abortions are included in the data. Usually spontaneous abortions are in the early pregnancy and women may not even know yet about the pregnancy. Therefore estimates based on hospital records lead to underestimation of the actual number of spontaneous abortions. However, it is expected, but not certain, that the underestimation of spontaneous abortions would be comparable across cohorts. Therefore, any differences observed between cohorts are likely to be due to the differences in cohort exposure. As noted in section 9.7.2, the denominator for the prevalence of MCAs includes the number of elective terminations and the number of births (still or live). Because data on elective terminations are not available in SWE, the prevalence of MCAs will be calculated first in the data from FIN and NOR. The prevalence of MCAs will then be re-calculated to include MCAs identified from SWE. However, the denominator for this prevalence will exclude the elective TOPFAs identified from FIN and NOR.

Because information on elective pregnancy terminations is not available from SWE, analyses on MCAs will be calculated including TOPFA with Finnish and Norwegian data and for births without TOPFA including data from all three countries.

Information on pregnancy terminations is available from GW 12 onwards from the Norwegian data, and therefore, information on early pregnancy terminations conducted before GW 12 could result in incomplete in the data. Therefore we will conduct separate analyses by trimesters on pregnancy terminations.

Information on stillbirths is available from GW 28 onwards from the Swedish data. Country-specific prevalence rates will be estimated for outcomes, where stillbirths are included as nominator, or denominator.

Information on maternal age at LMP

LMP is available from the registers if the pregnancy outcome is live birth, stillbirth or elective termination of pregnancy. If the pregnancy outcome is either spontaneous abortion or ectopic pregnancy, then the date of diagnosis but not the date of LMP will be available. In the latter two cases, in which maternal age is not available at LMP, the average time from LMP to the date of diagnosis will be subtracted from maternal age at diagnosis to approximate maternal age at LMP. For the average time from LMP to spontaneous abortion or to ectopic pregnancy, same estimates as in Nybo-Andersen et al 2000 will be used (spontaneous abortion: 9 and ectopic pregnancy: 8 weeks). These average estimates can be further justified based on previous studies and current care guidelines (spontaneous abortion: Cramer and Wise 2000, Tong et al 2008; ectopic pregnancy: Saxon et al 1997, Association of Finland Medical Society Working Group (2014) Current care guidelines, Ectopic pregnancies (in Finnish)).

Information on alcohol use and other abuse substances

Information on maternal alcohol use or other substance abuse is not available in this study, but it is a potential confounding factor. Heavy alcohol use may affect the risk for spontaneous abortion, and also other pregnancy outcomes. However, it is not expected that the relative risks in relation to IFN-β exposure would differ by substance abuse.

Information on pregnancy family history

Information on family history on pregnancies is not available in MBRs. Therefore, for example, heredity in multiple pregnancies cannot be evaluated in this study.

Variation in follow-up period

The follow-up periods vary between the three Nordic countries: In FIN the follow-up period for the registration of MCA is 12 months after birth, in SWE 6 months. In NOR malformations are registered in the MBR and the newborns are followed until the end of the stay at the birth clinic (usually at least 4 days). To address this, analyses will be done with stratification by country.

Relevance of results to the European IFN-β Pregnancy Registry

Results of this retrospective cohort study are not directly comparable with the information derived from the European IFN-β Pregnancy Registry. Available information on disease severity and other confounding factors differs between the health registers and the European IFN-β Pregnancy Registry and in some cases is missing, such that the rates cannot be adjusted to be comparable. In addition, the pregnancy cases included in the Nordic health registers are population-wide and are not based on a sample, whereas the European IFN-β Pregnancy Registry is based on spontaneous reports.

Furthermore, study and exposure periods differ between the countries in this study and follow-up periods in the European IFN-β Pregnancy Registry. Also, it is known that there are regional and international differences in MSDMD treatment practices, MSDMDs on market and prevalence of MS. With the available data in this study we aim to partially control for some of these variations by stratification and adjustment for country, hospital district, year of pregnancy outcome, maternal age at LMP, time since MS diagnosis and duration of IFN-β treatment.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

EPID Research will receive unidentifiable data including SIDs only. Patient data handled by the researchers do not include PINs or other identification numbers, which ensures the data protection of the patients. EPID Research employees have undertaken professional secrecy agreements. The study databases will further be constructed and data will be handled according to the national data protection requirements.

The protocol will be subjected to relevant ethical committees in each country for review and approval. Register notifications of the forming study registers will be sent to the relevant data protection offices in each country.

11 Management and reporting of adverse events/adverse reactions

According to Good Pharmacovigilance Practice, non-interventional post-authorisation studies based on secondary use of data, such as this study, do not require reporting of suspected adverse reactions in the form of Individual Case Safety Reports. All reports of adverse events/reactions will be summarised in the final study report.

12 Plans for disseminating and communicating study results

The principal investigator together with the co-investigators will write a study report. This report will be delivered to the sponsors. After study report, the principal investigator and co-investigators with co-authors will prepare (a) scientific manuscript(s) for academic publication. The principal investigator will ensure that authorship for all publications complies with the criteria defined by the International Committee of Medical Journal Editors. Each author should have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

A summary of the main results of the study, whether positive or negative and including results from prematurely terminated studies, will always be made available to the public. The principal investigator and co-investigators will be responsible of publication of the results. An abstract of the study findings will be provided through the ENCePP e-register of studies within three months following the final study report. The principal investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period pending response to peer-review comments. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests. The study Sponsors are entitled to view the final results and interpretations thereof at least 30 days prior to submission for publication and to comment in advance of submission and without unjustifiably delaying the publication.

The final study report may be used for the discussions with the competent authorities as required.

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1.	Feasibility study report	11 Dec 2013, Version 1.0	Pregnancy outcomes in an unexposed Multiple Sclerosis population in the Nordic countries

Annex 2. ENCePP checklist for study protocols

A copy of the ENCePP Checklist for Study protocols available at

http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2. The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

Annex 3. Potentially or clearly harmful drugs during pregnancy

Definitions for the risk categories in the Swedish Catalogue of Approved Drugs during pregnancy (FASS, 1993) classification system are given below. This classification comprises 4 separate categories (A, B, C, D): A includes the safest drugs; B is divided into 3 subgroups (B1, B2, B3); and C and D categories are used for drugs which may have different risks for the foetus depending on the evidence on which the risk is based.

Risk category	Description
A	Medicinal products which may be assumed to have been used by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect effects on the foetus. This category comprises: drugs that have been available for many years; those that have been used by many pregnant women and women of child-bearing age and; drugs for which satisfactory retrospective studies in pregnant women are considered to have been carried out.
B	Medicinal products which may be assumed to have been used only by a limited number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the foetus. As experience of effects of medicinal products in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of 3 subgroups B1, B2 or B3 according to the following definitions: **B1**: Reproduction toxicity studies have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproductive process. **B2**: Reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of foetal damage or other deleterious effects on the reproductive process. **B3**: Reproduction toxicity studies in animals have revealed an increased incidence of foetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans.
C	Medicinal products, which by their pharmacological effects have caused or must be suspected of causing, disturbances in the reproductive process that may involve risk to the foetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of foetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.
D	Medicinal products, which have caused an increased incidence of foetal malformations or other permanent damage in humans or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects that may directly or indirectly have a harmful effect on the foetus.

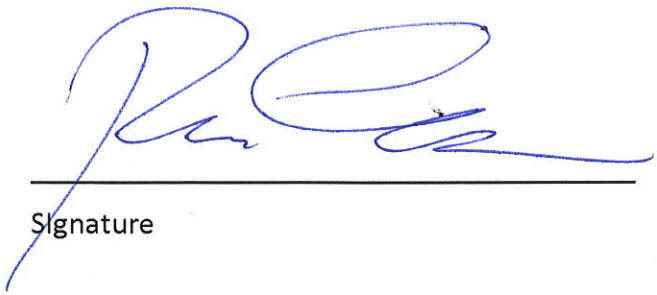
In this study, the following drugs (ATC codes) from categories C and D will be included in this study as potentially teratogenic drugs or teratogenic drugs.

	ATC codes						
Potentially teratogenic drugs – risk category C	A01AB11	A01AC01	A02BC02	A03AB02	A03FA01	A04AA03	A04AD12
	A05AA02	A07DA03	A07EA02	A07EA06	A10BB01	A10BB07	A10BB12
	A10BG02	A10BG03	A10BH01	A10BX02	A10BX03	A11HA30	B01AC06
	B01AC11	B01AC30	B01AD02	B01AD07	B01AD11	B01AE07	B03XA01
	C01BC03	C01BC04	C01BD01	C01BD05	C01CA04	C01CX08	C01EA01
	C02AC05	C03AA03	C03BA11	C03CA01	C03EA01	C04AD03	C07AA03
	C07AA05	C07AA07	C07AB02	C07AB03	C07AB05	C07AB07	C07AB09
	C07AG01	C07AG02	C07FB02	C08CA01	C08CA02	C08CA03	C08CA05
	C08CA06	C08CA07	C08CA13	C08DA01	C08DB01	C08DB01	C10AA03
	C10AA04	C10AA07	C10AB02	C07AB09	C07AG01	C07AG02	C10AB04
	C10AB05	D01AA02	D01AC07	D01AC08	D01AE16	D05AX03	D05AX52
	D06BB03	D06BB04	D07AB01	D07AB02	D07AB08	D07AC01	D07AC03
	D07AC13	D07AD01	D07BC01	D07CC01	D07XC01	D08AG02	D10AD01
	D10AD03	D11AH01	D11AX01	D11AX18	G01AF08	G02AB01	G02BB01
	G02CB03	G03AA11	G03AA12	G03AA13	G03AB03	G03AB05	G03AB06
	G03AC01	G03AC03	G03AC08	G03AC09	G03CX01	G03DA02	G03FA01
	G03FA12	G03FA17	G03FB05	G03FB06	G03GA01	G03AA07	G03AA09
	G03AA10	G03GA01	G03GB02	G03HB01	H01CA02	H01CB02	H01CB03
	H01CC02	H02AA02	H02AB01	H02AB02	H02AB04	H02AB06	H02AB07
	H02AB08	H03BB01	H05AA02	J01CA08	J01EA01	J01EE01	J01EE02
	J01FA09	J01FA15	J01GB01	J01MA01	J01MA02	J01MA06	J01MA12
	J01MA14	J01XC01	J01XE01	J01XX08	J02AB02	J02AC01	J02AC02
	J02AC03	J02AX04	J04AB02	J04AB04	J05AB01	J05AB11	J05AE02
	J05AE03	J05AE07	J05AF01	J05AF05	J05AF06	J05AF08	J05AR01
	J07BA02	J07BK01	L01XE01	L01XE06	L01XX19	L01XX23	L02AB01
	L02AE01	L02AE02	L02AE03	L02AE04	L02BA02	L02BG03	L02BG04
	L02BG06	L03AA02	L03AA10	L03AA13	L03AB05	L03AB10	L03AB11
	L04AA10	L04AB02	L04AB04	L04AD02	M01AB01	M01AB05	M01AB08
	M01AB15	M01AB51	M01AB55	M01AC06	M01AE01	M01AE02	M01AE03
	M01AE51	M01AG01	M01AH01	M01AH04	M01AH05	M01AX01	M01CB03
	M01CB03	M02AA07	M02AA10	M02AA15	M02AC	M03AB01	M03AX01
	M03BX02	M05BA03	M05BA04	M05BA06	M05BA07	M05BA08	M05BC01
	N01AB07	N01AH01	N01AH02	N01AH06	N01AX01	N01AX10	N01BB10
	N01BB58	N02AA01	N02AA05	N02AA59	N02AB03	N02AE01	N02AX02

	N02BA01	N02BA51	N02BG08	N02CA01	N02CA52	N02CC07	N03AE01
	N03AG06	N03AX09	N03AX11	N03AX12	N03AX14	N03AX15	N03AX16
	N05AA01	N05AB02	N05AB03	N05AB04	N05AD01	N05AD03	N05AE03
	N05AE04	N05AF01	N05AF03	N05AF05	N05AH03	N05AX08	N05AX12
	N05BA01	N05BA02	N05BA04	N05BA06	N05BA09	N05BA12	N05BB01
	N05CD02	N05CD05	N05CD07	N05CD08	N05CF01	N05CF02	N05CF03
	N06AA04	N06AA06	N06AA09	N06AA10	N06AA12	N06AB03	N06AB04
	N06AB05	N06AB06	N06AB10	N06AX03	N06AX05	N06AX11	N06AX16
	N06AX18	N06AX21	N06BA04	N06CA01	N06DA03	N06DA04	N06DX01
	N07AA02	N07AA51	N07AX01	N07BA01	N07BB04	N07BC02	N07XX02
	P01BA01	P01BA02	P01BB51	P01BC02	P02CA01	R01AC02	R01AC03
	R01AD01	R01AD08	R01AD09	R01AD11	R01AD12	R03AC13	R03AK06
	R03AK07	R03BA01	R03BA05	R03BB04	R05	R05DA20	R06A
	S01AD03	S01AX11	S01AX19	S01BA01	S01BA13	S01BC03	S01EC01
	S01ED51	S01EE01	S01EE03	S01EE04	S01GX06	S01JA01	S01LA04
	ATC codes						
Teratogenic drugs – risk category D	A02BB01	A16AX03	B01AA03	C01BA01	C02KX01	C09AA01	C09AA02
	C09AA03	C09AA04	C09AA05	C09AA06	C09BA02	C09BA03	C09BA05
	C09BA06	C09BA15	C09CA01	C09CA02	C09CA03	C09CA06	C09CA07
	C09CA08	C09DA01	C09DA02	C09DA03	C09DA06	C09DA07	C09DB01
	C10AA01	C10AA02	C10AA05	D05BB02	D06AX04	D10AD04	D10BA01
	D11AX10	G03BA03	G03DC02	G03DC03	G03FA14	G03FB08	G03GA06
	G03HA01	G03XB01	G03XC01	G04CB01	L01BC02	L01BC05	L01BC06
	L01CA04	L01CB01	L01CD01	L01CD02	L01DB01	L01DB03	L01DB06
	L01DC01	L01DC03	L01XA01	L01XA02	L01XC07	L01XX05	L01XX11
	L01XX14	L01XX17	L01XX32	L02BA01	L02BA03	L02BB03	L03AB07
	L03AB08	L04AA13	L04AX01	L04AX02	L04AX03	N03AB02	N03AB05
	N03AF01	N03AF02	N03AG01	N03AG04	N05AN01		

APPROVAL

I have reviewed this study protocol (version 2.0, dated 18 August 2015) and approve it with my signature.



Signature

8.4.2016

Date

Principal Investigator

Pasi Korhonen, PhD

EPID Research, Research Director

Adjunct professor of biostatistics

This study protocol has been approved by the Committee for Medicinal Products for Human Use of the European Medicines Agency.