Protocol

Study ID: NN9536-4937

Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study: A Prospective Cohort Study to Investigate Safety Outcomes of Exposure to Wegovy during Pregnancy

Redacted protocol
Includes redaction of personal identifiable information only.

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PASS information

Title	Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study: A Prospective Cohort Study to Investigate Safety Outcomes of Exposure to Wegovy during Pregnancy
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Protocol version identifier	2.0
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Medicinal product	Wegovy®
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Procedure number	United States: Post Marketing Requirement (PMR) 4081-3 United Kingdom: Great Britain Product Licence (PLGB) 04668/0436-0440 and 04668/0429-0433
Marketing authorisation holder (MAH)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
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Research question and objectives	The aim of the Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study is to compare the maternal, foetal, and infant outcomes of pregnant women 15-50 years of age who are exposed to Wegovy during pregnancy with outcomes in an internal comparison cohort of pregnant women with obesity overweight with at least one weight-related comorbid condition at conception and who are not exposed to Wegovy or other glucagon-like peptide-1 receptor agonists during pregnancy. The primary objective is to compare the overall prevalence of major congenital malformations between cohorts.
Countries of study	Multi-country study in the United States, United Kingdom, and Spain

Marketing authorisation holder

Marketing authorisation holder (MAH)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	[redacted]

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2 List of abbreviations

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
AR	Adverse reaction
ART	Assisted reproductive technology
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
DOC	Date of conception
EDC	Electronic data capture
EDD	Estimated date of delivery
EMA	European Medicines Agency
EU	European Union
EUROCAT	European Registration of Congenital Anomalies and Twins
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
GLP-1 RA	GLP-1 receptor agonist
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HCP	Healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IEC	Independent Ethics Committee
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IPW	Inverse probability weighting
IRB	Institutional Review Board
LAR	Legally authorised representative
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorisation Holder
MCM	Major congenital malformation
NA	Not applicable

NIS	Non-interventional study
NVSS	National Vital Statistics System
PAS	Post-authorisation study
PASS	Post-authorisation safety study
RCC	Registry coordination centre
RR	Relative risk
SAB	Spontaneous abortion
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SGA	Small for gestational age
SOP	Standard operating procedure
TERIS	Teratogen Information System
UK	United Kingdom
US	United States
WHO	World Health Organization

3 Responsible parties

In this document, principal investigator refers to the individual responsible for the conduct of the non-interventional study.

Principal Investigator, United States: [redacted]

Medical Monitor: [redacted]

4 Abstract

Name of Sponsor:	Novo Nordisk A/S
Name of Product:	Wegovy® (semaglutide 2.4 mg)
Title of Study:	Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study: A Prospective Cohort Study to Investigate Safety Outcomes of Exposure to Wegovy during Pregnancy (PASS)
Protocol Version:	2.0
Date:	20 December 2022
Study Number:	NN9536-4937
Study Phase:	Postmarketing Observational Pregnancy Registry Study
Location:	United States, United Kingdom, Spain
Start of Data Collection:	March 2023
End of Data Collection:	31 August 2032
Final Report of Study Results:	31 August 2033

Objectives:

The aim of the Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study is to compare the maternal, foetal, and infant outcomes of pregnant women who are exposed to Wegovy during pregnancy for the treatment of obesity or overweight with at least one weight-related comorbid condition with outcomes in an internal comparison cohort of pregnant women with obesity or overweight with at least one weight-related comorbid condition at conception and who are not exposed to Wegovy or other glucagon-like peptide-1 receptor agonists (GLP-1 RAs) during pregnancy.

The primary objective is to compare the overall prevalence of major congenital malformations (MCMs) between cohorts.

The secondary objectives are to compare the prevalence of the following secondary outcomes between cohorts:

- Overall minor congenital malformations
- Pre-eclampsia
- Eclampsia
- Spontaneous abortion (SAB)
- Stillbirth
- Elective termination
- Preterm birth
- Small for gestational age (SGA)
- Postnatal growth deficiency
- Infant developmental delay

Methodology:

The Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study is a prospective, observational cohort study designed to evaluate the association between Wegovy exposure during pregnancy and subsequent maternal, foetal, and infant outcomes.

Pregnancy outcomes will be assessed throughout pregnancy, with data collection occurring at enrolment, the end of the second trimester, and pregnancy outcome. Infant outcomes will be assessed throughout the infant's first year of life, with active data collection for the registry occurring at 4 and 12 months after

delivery. Enrolled pregnant women and the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable, will serve as data reporters to the registry. The study is strictly observational; the schedule of office visits and all treatment regimens will be determined by the HCPs treating the pregnant women and their infants. No additional laboratory tests or HCP assessments will be required as part of this registry. This is a non-interventional post-authorisation safety study (PASS).

Number of participants (planned):

The registry aims to enrol a total of 728 pregnant women in the study population, with 364 women in each of the 2 pre-specified cohorts. This sample size will afford the study the ability to detect a 3-fold increase in the overall prevalence of the primary outcome, MCM, in the exposed cohort with meaningful confidence and precision.

Study population:

The study population will include pregnant women 15-50 years of age who provide consent to participate, as well as medical releases for their HCPs to provide data to the registry, and meet the criteria for inclusion into one of the following cohorts:

- Exposed cohort: pregnant women who are exposed to Wegovy at any time during pregnancy for the treatment of obesity or overweight with at least one weight-related comorbid condition
- Unexposed cohort: pregnant women who have overweight with at least one weight-related comorbid condition or who have obesity at conception and who are not exposed to Wegovy or other GLP-1 RAs at any time during pregnancy but who may be exposed to other products for weight management

Women will be eligible for enrolment but excluded from the main analysis population if the pregnancy outcome occurred prior to first contact with the registry, if they have been exposed to known teratogens and/or investigational medications during pregnancy, or if they are already included in the main analysis population for a prior pregnancy. However, these women will be included in supplementary analyses.

Duration of participation: For each pregnant woman, participation will begin at the time of providing informed consent and end either at pregnancy outcome (if foetal loss) or 12 months after pregnancy outcome (if live birth).

Statistical methods:

Analyses will be conducted in accordance with the study objectives, statistical analysis plan, table/listing shells, and applicable guidelines. Registry data will be summarised in tables and listings by study cohort, as appropriate. Comparisons of demographic and baseline characteristics and prevalence of the outcomes will be conducted between the study cohorts.

Demographic and baseline characteristics will be summarised with descriptive statistics, and balance between cohorts will be assessed using standardised differences. These data will be presented before and after the data are balanced with the inverse probability weighting (IPW) method. In addition, within each cohort, those included in the main analysis population will be compared with those excluded from the main analysis population for being lost to follow-up, retrospectively enrolled, exposed to teratogens or investigational medications during pregnancy, or having previously been included in the main analysis population for a prior pregnancy.

The prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge. For most outcomes, the analysis population (denominator) will be the number of pregnant women with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the specified time point, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted on the basis of certain relevant factors (e.g., SAB prevalence is restricted to women enrolled and, if applicable, exposed prior to 20 weeks of gestation).

Formal quantitative comparisons of prevalence of the outcomes will be conducted between the exposed and unexposed cohorts. For each outcome, if the number of events permits, results will be presented for both unadjusted and adjusted models. Summary statistics (relative risk or hazard ratio, as appropriate) will be reported along with their 95% confidence intervals and p-values. The IPW method will be used to

balance cohorts with regard to relevant, observable covariates. The adjusted comparison of the overall prevalence of MCMs observed in the exposed and unexposed cohorts will be considered the primary analysis. Prevalence of individual malformations will not be evaluated.

Where sample size permits, stratified/subgroup analyses of all outcomes will be conducted that consider the timing of exposure (earliest trimester of exposure), extent of exposure (cumulative dose during pregnancy or relevant exposure window), country, maternal body mass index at conception, and maternal age at conception. Supplementary analyses will be conducted that include pregnant women who were excluded from the main analysis population due to occurrence of the pregnancy outcome prior to enrolment (retrospectively enrolled participants), exposure to a known teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed participants), or inclusion of a prior pregnancy in the main analysis population (subsequent pregnancies). Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results.

5 Amendments and updates

Previous version 1.0 of protocol is updated to 2.0 in response of the FDA comments. Additionally, Protocol version 2.0 also includes minor text updates and edits.

6 Milestones

Milestone	Planned date
Start of data collection	March 2023
End of data collection	31 August 2032
Interim report 1	31 August 2023
Interim report 2	31 August 2024
Interim report 3	31 August 2025
Interim report 4	31 August 2026
Interim report 5	31 August 2027
Interim report 6	31 August 2028
Interim report 7	31 August 2029
Interim report 8	31 August 2030
Interim report 9	31 August 2031
Interim report 10	31 August 2032
Registration in the EU PAS Register	Study not yet registered
Final report of study results	31 August 2033

7 Rationale and background

7.1 Study rationale

The aim of this non-interventional study (NIS) is to compare maternal, foetal, and infant outcomes between women exposed to Wegovy during pregnancy and an unexposed reference population. This study is being conducted to satisfy a post-marketing requirement stipulated by the Food and Drug Administration (FDA) and the Medicines and Healthcare products Regulatory Agency (MHRA). The study is a post-authorisation safety study (PASS).

The Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study will add to the current body of knowledge regarding the safety of Wegovy exposure during pregnancy. Currently, there are no clinical studies of Wegovy in pregnant women, and available human data on Wegovy exposure during pregnancy are insufficient to inform risk analysis. Data from the registry will supplement data from animal toxicology studies and human exposure data. The registry will provide information on maternal, foetal, and infant outcomes following exposure to Wegovy during pregnancy so that participants and healthcare providers (HCPs) can make informed treatment decisions.

7.2 Semaglutide

Semaglutide (Wegovy®, Ozempic®, Rybelsus®) is a glucagon-like peptide-1 (GLP-1) analogue, classified as a glucagon-like peptide-1 receptor agonist (GLP-1 RA), and has a 94% homology to human GLP-1.[1] Both native GLP-1 and GLP-1 RAs reduce body weight by lowering energy intake via inducing feelings of satiety and fullness and lowering feelings of hunger. Subcutaneous semaglutide is based on the same acylation technology as liraglutide (Victoza®, Saxenda®) but with structural modifications to obtain a longer half-life of approximately 1 week, thus enabling once-weekly subcutaneous administration.[1]

The approved indication for Wegovy is as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition.

7.3 Potential risks associated with pregnancy exposure to semaglutide

7.3.1 Animal studies

The potential for semaglutide to affect fertility, embryo-foetal development, and pre- and postnatal development was investigated in rats, rabbits, and cynomolgus monkeys. Transfer of semaglutide across the placenta was observed in rats and rabbits.

In rats, a reduction in corpora lutea, and therefore litter size, was observed at higher doses. This effect was considered related to the reduced maternal food consumption and reduced weight gain. Semaglutide caused embryotoxicity in the rat, including embryo-foetal mortality and growth retardation, and major and minor visceral and skeletal foetal abnormalities. Based on a series of mechanistic studies, it was concluded that the effects on embryo-foetal development in the rat are caused by a GLP-1 receptor-mediated impaired function of the inverted yolk sac placenta.

Involvement of additional mechanisms leading to embryotoxicity in rats cannot be completely excluded.

In rabbits, early pregnancy losses and increased incidences of minor foetal abnormalities were observed. The foetal abnormalities in rabbits did not resemble the findings in rats. The observed effects in rabbits were possibly secondary to the marked effect on maternal body weight, as food restriction has been shown to cause increased pregnancy losses and foetal abnormalities in rabbits.

In cynomolgus monkeys, early pregnancy losses occurred at the high and intermediate dose levels in the pre- and postnatal study, but not in the two embryo-foetal development studies. A few sporadic foetal abnormalities were observed in the main embryo-foetal development study, whereas none were observed in the pre- and postnatal study. These abnormalities did not resemble the findings in rats, were unlikely to lead to early pregnancy losses, and coincided with a marked maternal weight loss. The lack of consistency between the monkey studies and the absence of commonality in nature of the foetal abnormalities supported that the findings could be either incidental or related to maternal stress and/or weight loss. In primates, the yolk sac does not invert to function as a placenta, as it does in rats, and the GLP-1 receptor is not expressed in the yolk sac membranes of cynomolgus monkeys. Accordingly, the GLP-1 receptor-related mechanism by which semaglutide causes embryotoxicity in the rat is unlikely to be of relevance to humans.

7.3.2 Clinical trial data

The clinical data available from exposure to semaglutide given subcutaneously (Ozempic®) and orally (Rybelsus®) during pregnancy do not suggest adverse effects on early pregnancy or embryo-foetal development. However, use of semaglutide has not as such been studied in pregnant or lactating women, and the potential risk of semaglutide treatment during pregnancy and lactation is unknown.

A total of 40 pregnancies were reported in the current weight management programme investigating subcutaneous semaglutide: 32 with Wegovy (24 of these were in the phase 3a pool) and 8 with placebo. In all cases, the female patient was exposed to trial product for a short time until the pregnancy was discovered and trial product discontinued. One child of a female patient exposed to Wegovy was born with a congenital anomaly of the external ear; investigators have reported that the child has recovered. Among the 32 pregnancies in the Wegovy group, 6 (18.8%) resulted in spontaneous abortion (SAB) and 0 (0.0%) resulted in stillbirth. Among the 8 pregnancies in the placebo group, 1 (12.5%) resulted in SAB and 1 (12.5%) resulted in stillbirth. None of the elective abortions were due to congenital anomalies. There were few adverse events (AEs) related to fertility and no differences between Wegovy and placebo.

As is noted in the label, women should stop using Wegovy 2 months prior to when they plan to become pregnant. Women who become pregnant while using Wegovy are instructed to stop as soon as the pregnancy is recognised.

7.4 Overweight and obesity

7.4.1 Description and epidemiology

Obesity is defined as abnormal or excessive fat accumulation that may impair health. According to the World Health Organization (WHO) classification system, overweight in adults is defined as a BMI of ≥25 kg/m^2, and obesity is classified as a BMI of ≥30 kg/m^2.[2]

Worldwide, obesity has tripled over the last 50 years, and in 2016, 1.9 billion adults (aged >18 years) worldwide were overweight; of these, over 650 million live with obesity.[2] Globally, obesity is now considered one of the most significant public health challenges.[3 4]

Women of childbearing age (15 to 44 years) are particularly vulnerable to weight gain, and weight gain during this time is strongly associated with adverse health outcomes later in life.[5 6 7 8] Pre-pregnancy obesity rates among women aged 15 to 44 are reported to be around 25% in the United States (US). However, there is significant variation by race/ethnicity. Pre-pregnancy obesity rates are higher for non-Hispanic black (36.2%) and Hispanic women (30.5%) compared to non-Hispanic white (24.8%) and Asian (18.6%) women.[9] Obesity during the childbearing years has been associated with adverse pregnancy outcomes for the mother (e.g., gestational diabetes, pre-eclampsia, gestational hypertension, antenatal anxiety, and postpartum depression), as well as for the babies (e.g., pre-term birth, and babies who are large for gestational age).[10 11]

7.4.2 Current standard of care

Although lifestyle modifications continue to be first-line treatment for obesity, most people with obesity struggle to achieve and maintain weight loss with diet and exercise alone. [12 13 14 15 16 17]

Surgical treatments offer an effective alternative for some people with severe obesity, but bariatric surgery carries a risk in connection with the procedure and is not without post-surgical complications. Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with obesity to achieve and sustain clinically relevant weight loss, improve comorbid conditions, and facilitate a healthier lifestyle. [12 14 17]

As of late 2021, only a limited number of pharmacological options are approved for weight management in the US and the European Union (EU), all with administrations between 1 and 3 times daily. All of these have shown effective weight loss, but generally only in the range of around 5%. STEP 1 (NN9536-4373) data demonstrated that treatment with Wegovy resulted in a weight loss of 14.9% compared with 2.4% in the placebo group (treatment policy estimand). [18]

Additionally, since Wegovy is administered once weekly, it offers a more convenient treatment option than existing weight-management drugs and may improve treatment adherence. [19 20 21] During pregnancy, lifestyle modifications are the primary tool for weight management. [22 23 24] Weight loss during pregnancy is generally discouraged and use of surgical and pharmacologic interventions are not recommended during, or immediately preceding, pregnancy due to known or suspected safety concerns as well as lack of data on safety of use during pregnancy.[25 26 27]

7.5 Pregnancy, foetal, and infant outcomes in women with overweight or obesity

Maternal obesity is associated with increased risk of adverse pregnancy outcomes, including SAB and stillbirth. [28 29 30] For stillbirth, the risk appears to increase in a stepwise fashion with each increase in BMI category (30.0–34.9, 35.0–39.9, 40+, 50+) and the relative risk in women with obesity versus women with non-obesity is higher in black women as compared to white women (hazard ratio [HR] for black women with obesity vs. black women without obesity: 1.9; HR for white women with obesity vs. white women with non-obesity: 1.4).[28 29] Maternal obesity is also associated with increased risk of adverse neonatal outcomes, including preterm birth, macrosomia, and a variety of birth defects. Studies have observed associations between maternal obesity and cardiovascular anomalies, limb reduction anomalies, orofacial anomalies, neural tube defects, and hydrocephaly.[31 32 33 34 35] In a recent population-based cohort study using Swedish national registries, compared with offspring of mothers with a weight in the normal range, the risk ratio of major congenital malformations (MCM) increased with maternal BMI: 1.05 in mothers with overweight (BMI, 25 to <30), 1.12 in mothers in obesity class I (BMI, 30 to <35), 1.23 in mothers in obesity class II (BMI, 35 to <40), and 1.37 in mothers in obesity class III (BMI ≥40).[36]

In terms of other medications for weight loss, a significant increase in MCM (cardiovascular defects) was reported with sibutramine exposure in early pregnancy (relative risk=1.81) and, among 12 infants exposed to rimonabant, a set of twins had malformations.[37] However, for medications similar to Wegovy, such as other GLP-1 RAs, the effects of medication use during pregnancy and on pregnancy, foetal, and infant outcomes are not well characterised.

8 Research question and objectives

The aim of the Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study is to compare the maternal, foetal, and infant outcomes of a cohort of pregnant women who are exposed to Wegovy during pregnancy for the treatment of obesity or overweight with at least one weight-related comorbid condition with outcomes in an internal comparison cohort of pregnant women who have overweight with at least one weight-related comorbid condition or have obesity at conception and who are unexposed to Wegovy or other GLP-1 RAs during pregnancy.

8.1 Primary objective

The primary objective is to compare the overall prevalence of major congenital malformations (MCM) between cohorts.

8.2 Secondary objectives

The secondary objectives are to compare the prevalence of the following secondary outcomes between cohorts:

- Overall minor congenital malformations
- Pre-eclampsia
- Eclampsia
- Spontaneous abortion (SAB)
- Stillbirth
- Elective termination
- Preterm birth
- Small for gestational age (SGA)
- Postnatal growth deficiency
- Infant developmental delay

9 Research methods

9.1 Study design

The Wegovy®(semaglutide 2.4 mg) Pregnancy Registry Study is a multi-country, prospective, observational cohort study designed to evaluate the association between Wegovy exposure during pregnancy and subsequent maternal, foetal, and infant outcomes. This is a PASS. The registry will be conducted in the US, the United Kingdom (UK), and Spain. Spain is included to increase sample size and expand on the geographic scope to cover an EU country in the registry. Participation in the registry is voluntary, and participants can withdraw their consent to participate at any time. Data will be collected from enrolled pregnant women and the HCPs involved in their care or the care of their infants, if applicable. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by HCPs. No additional laboratory tests or HCP assessments will be required as part of this registry. The design of this pregnancy registry follows current FDA guidance for designing and implementing pregnancy exposure registries.[38]

9.1.1 Endpoints

Endpoint Title	Time Frame	Unit
Major congenital malformation	From DOC to pregnancy outcome for foetal losses or 12 months of infant age for live births	Overall prevalence (percent)[a]
Minor congenital malformation	From DOC to pregnancy outcome for foetal losses or 12 months of infant age for live births	Overall prevalence (percent)[a]
Pre-eclampsia	From $20^{0/7}$ gestational weeks to 6 weeks postpartum[39]	Prevalence (percent)
Eclampsia	From $20^{0/7}$ gestational weeks to 6 weeks postpartum[39]	Prevalence (percent)
Spontaneous abortion	From DOC to $19^{6/7}$ gestational weeks	Prevalence (percent)
Stillbirth	From $20^{0/7}$ gestational weeks to pregnancy outcome	Prevalence (percent)
Elective termination	From DOC to pregnancy outcome	Prevalence (percent)
Preterm birth	From DOC to 37 gestational weeks	Prevalence (percent)
Small for gestational age	At delivery of live birth	Prevalence (percent)
Postnatal growth deficiency	At 4 and 12 months of infant age	Prevalence (percent)
Infant developmental delay	At 4 and 12 months of infant age	Prevalence (percent)

[a] Prevalence of individual malformations will not be evaluated.

DOC = date of conception.

9.1.1.1 Primary endpoint

The primary endpoint for the study is overall MCMs. The definition and ascertainment of this outcome are provided in Section 9.3.3.

9.1.1.2 Secondary endpoints

The secondary endpoints for the study include the following:

- Overall minor congenital malformations
- Pre-eclampsia
- Eclampsia

- SAB
- Stillbirth
- Elective termination
- Preterm birth
- SGA
- Postnatal growth deficiency
- Infant developmental delay

The definitions and ascertainment of these outcomes are provided in Section 9.3.3.

9.1.2 Treatment of participants

Participants in the exposed cohort will include women exposed to commercially available Wegovy during pregnancy for the treatment of obesity or overweight with at least one weight-related comorbid condition. These women will have been treated with Wegovy at the discretion of their treating HCPs, according to routine clinical practice; study participation will not impact participants' treatment. It is expected that most exposures during pregnancy will be inadvertent, as Wegovy is not indicated during pregnancy.

9.2 Setting

9.2.1 Study population

After regulatory authority (e.g., FDA) and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol, enrolment of women in the registry will begin. Data collection is planned for approximately 10 years, and a final report will be submitted to regulatory authorities by 31 August 2033. The enrolment period may be extended if the target sample size is not met or is shortened otherwise.

For each enrolled pregnant woman, participation will begin at the time of providing informed consent and end either at pregnancy outcome (if foetal loss – SAB, stillbirth, or elective termination) or 12 months after pregnancy outcome (if live birth). For each live born infant, participation will begin at birth and end at 12 months of age. Maternal and foetal outcomes will be assessed through the end of pregnancy, and infant outcomes will be assessed through 12 months of infant age.

The study population will include two cohorts of pregnant women: one cohort exposed to Wegovy for the treatment of obesity or overweight with at least one weight-related comorbid condition and one cohort of women who have overweight with at least one weight-related comorbid condition or have obesity at conception and who are unexposed to Wegovy or other GLP-1 RAs but who may be exposed to other products for weight management.

- Planned number of participants to be included: 728 (364 per cohort)
- Planned number of participants to complete the study: 692 (346 per cohort) (assumes a lost to follow-up rate of 5%, which is consistent with assumptions in the sample size section; see Section 9.5).
- Planned time period for the study: March 2023 to 31 August 2032 (last participant will be enrolled on or before 31 October 2030 to allow for full follow-up of mothers and infants)

9.2.2 Inclusion and exclusion criteria

For an eligible participant, all inclusion criteria must be answered 'yes', and all exclusion criteria must be answered 'no'. Table 9-1 summarises the inclusion and exclusion criteria for the cohorts.

Table 9-1 Study population[a]

Cohort	Inclusion Criteria	Exclusion Criteria	Exclusion Criteria for Main Analysis Population
Exposed cohort: pregnant women who are exposed to Wegovy at any time during pregnancy for the treatment of obesity or overweight with at least one weight-related comorbid condition	• Signed consent obtained before any study-related activities • Female 15–50 years of age at the time of signing consent • Currently or recently pregnant • Resident of country included in the study • Authorisation for her HCP(s) to provide data to the registry • *Exposure to at least one dose of Wegovy at any time during pregnancy[d] for the treatment of obesity[c] or overweight with at least one weight-related comorbid condition[b]*	• Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation	• Occurrence of pregnancy outcome prior to first contact with the RCC (retrospectively enrolled) • Exposure to known teratogens and/or investigational medications during pregnancy • Lost to follow-up[e] • Inclusion of a prior pregnancy in the main analysis population
Unexposed cohort: pregnant women who have overweight with at least one weight-related comorbid condition[b] or who have obesity[c] at conception and who are not exposed to Wegovy or other GLP-1 RAs at any time during pregnancy but who may be exposed to other products for weight management	• Signed consent obtained before any study-related activities • Female 15–50 years of age at the time of signing consent • Currently or recently pregnant • Resident of country included in the study • Authorisation for her HCP(s) to provide data to the registry • *Have obesity[c] or overweight with at least one weight-related comorbid condition[b] at conception*	• *Exposure to Wegovy or other GLP-1 RA at any time during pregnancy[d]* • Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation	• Occurrence of pregnancy outcome prior to first contact with the RCC (retrospectively enrolled) • Exposure to known teratogens and/or investigational medications during pregnancy • Lost to follow-up[e] • Inclusion of a prior pregnancy in the main analysis population

[a] Text italicised to highlight differences between cohorts. [b] Overweight defined as: BMI ≥27 kg/m^2 prior to conception and at least one weight-related comorbid condition.

[c] Obesity defined as: BMI ≥30 kg/m^2 prior to conception.

[d] Participants will be considered exposed to Wegovy or other GLP-1 RAs during pregnancy if a dose is taken up to 5 half-lives (5 weeks for Wegovy) prior to the DOC. Participants who are not exposed to Wegovy during pregnancy or within 5 weeks of the DOC but who are exposed prior to pregnancy, more than 5 weeks prior to DOC, may be eligible for enrolment into the unexposed cohort.

[e] A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant women without pregnancy outcome information will be considered lost to follow-up, and live-born infants without follow-up data after birth will be considered lost to follow-up

Abbreviations: BMI = body mass index; DOC = date of conception; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HCP = healthcare provider; RCC = registry coordination centre.

9.2.3 Exclusion criteria

Please refer to Table 9-1 for the exclusion criteria.

9.2.4 Rationale for selection criteria

The study aims to be inclusive of any woman 15-50 years of age who is exposed to Wegovy during pregnancy for the treatment of obesity or overweight with at least one weight-related comorbid condition or who has overweight with at least one comorbid condition or obesity at conception. Only inclusion criteria that are standard for observational studies are included, and there are minimal exclusion criteria for enrolment in the study. The study population is limited to women 15-50 years of age, because pregnancy complications are higher in women younger than 15 and older than 50 years of age. To address potential biases and confounding, the main analysis population for the study will be limited to women who are prospectively enrolled (prior to pregnancy outcome), not exposed to known teratogens and/or investigational medications during pregnancy, not lost to follow-up, and not already included in the main analysis population for a prior pregnancy.

9.2.5 Withdrawal criteria

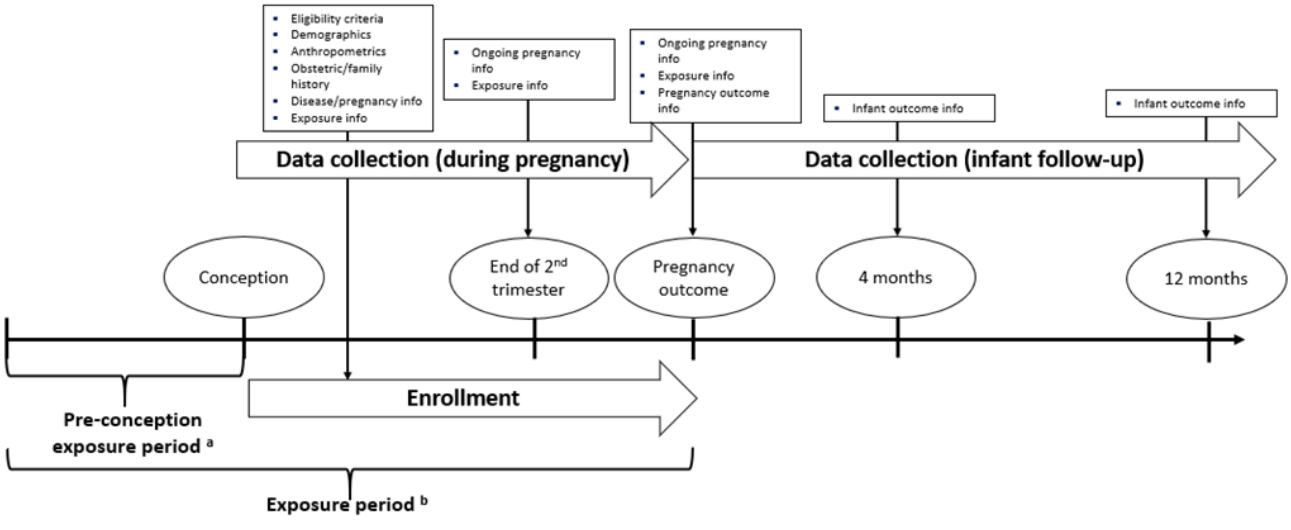
The participant or the legally authorised representative (LAR) may withdraw the consent to provide data to the registry at any time.

In case of withdrawal, the registry coordination centre (RCC) should attempt to collect any outstanding data. The primary reason for discontinuation should be specified in the data collection form.

9.2.6 Visit procedures

9.2.6.1 Study flow chart

Figure 9-1 Study flow chart



[a] Time to product elimination (5 times terminal half-life); Wegovy half-life = 7 days; therefore, time to elimination = 35 days
[b] If a participant is exposed to the product during this time period, she will be considered exposed during pregnancy

9.2.6.2 Study visits

9.2.6.2.1 Data collection

Enrolled pregnant women and the HCPs involved in their care or the care of their infants, if applicable, will serve as data reporters to the registry. It is anticipated that the majority of obstetric data will be provided by the pregnant woman's obstetric HCP, defined as any HCP who provides care during pregnancy (e.g., obstetrician, family practitioner, general practitioner), and that the majority of paediatric data will be provided by the infant's paediatric HCP, defined as any HCP who provides paediatric care (e.g., paediatrician, family practitioner, general practitioner). PPD may also request data from other HCPs involved in the woman's or infant's care (e.g., prescriber, specialist) after appropriate medical release is obtained from the woman.

The data collection process for each participant will begin at enrolment, and cumulative data throughout the pregnancy will be collected at 3 time points: at enrolment, at the end of the second trimester (approximately 26 gestational weeks), and at pregnancy outcome (live birth or foetal loss). For live-born infants, data from paediatric visits at 4 and 12 months of age will be collected at 2 time points: 4 months and 12 months after delivery. Data collection efforts will be identical for all enrolled pregnant women regardless of their exposures and study cohort assignment.

At enrolment, once consent, registration information (including eligibility criteria), reporter contact information, and medical releases have been provided by the pregnant woman, maternal demographic characteristics and pre-pregnancy anthropometrics will be collected from the pregnant woman. These data will be collected on the ***Registration Form for Participants***. Registration information, including eligibility criteria, will be confirmed by HCP(s), as appropriate. The HCP(s) will additionally provide maternal pre-pregnancy anthropometrics, maternal obstetrical history, family history of congenital malformations, disease information, pregnancy information, and maternal exposures during pregnancy. All of these data will be collected on the ***Registration Form for Healthcare Providers*** and ***Pregnancy Information Form***. At approximately the end of the second trimester, the HCP(s) will be asked to complete another ***Pregnancy Information Form***, which will collect any updates to pregnancy information and maternal exposures during pregnancy. Around or after the estimated date of delivery (EDD) or after a known pregnancy outcome, the HCP(s) will be asked to complete another ***Pregnancy Information Form*** as well as the ***Pregnancy Outcome Form***, which will collect pregnancy outcome information. For each live-born infant, the paediatric HCP will be asked to complete an ***Infant Outcomes Form***, which will collect infant information, including infant growth and development data, at 2 time points: at approximately 4 and 12 months after delivery. These visits align with the recommended infant well-child visit (health visitor check) schedules in the study countries. [40 41]

If a congenital malformation (major or minor) or other event of interest is reported, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form*** to properly characterise the event. The date each data collection form is completed will also be collected.

Table 9-2 provides a summary of the data collection process, including the forms that will be used to collect the data, the timing for completion of each form, the potential reporters or sources of the data, and the types of data that will be collected. Section 9.4 provides additional details regarding the data collected.

Table 9-2 Summary of data collection process

Data Collection Form	Data Sources/Reporters	Timing of Completion	Data Collected
Registration Form for Participants	Participant	Enrolment	Registration information, including eligibility criteria Maternal demographic characteristics Maternal pre-pregnancy anthropometrics
Registration Form for HCPs	Obstetric HCP and prescriber, if needed	Enrolment	Registration information, including eligibility criteria Maternal pre-pregnancy anthropometrics Maternal obstetrical history Family history of congenital malformations Disease information Baseline pregnancy information
Pregnancy Information Form	Obstetric HCP and prescriber, if needed	Enrolment, end of 2nd trimester[a], and EDD/pregnancy outcome[a]	Ongoing pregnancy information Maternal exposures during pregnancy
Pregnancy Outcome Form	Obstetric HCP and paediatric HCP, if needed	EDD/pregnancy outcome	Pregnancy outcome information
Infant Outcomes Form	Paediatric HCP	4 and 12 months after delivery	Infant outcome information at 4 and 12 months
Targeted Follow-up Form	Obstetric, paediatric, or other HCP	Any time after pregnancy outcome	Targeted follow-up information

[a] Obtain updated information since the previous contact.

Abbreviations: EDD = estimated date of delivery; HCP = healthcare provider.

9.2.6.2.2 Attempts to obtain follow-up information

In the month that the follow-up is due, the HCP will be contacted by PPD and asked to provide follow-up information. If needed, 3 subsequent attempts will be made approximately every 2 weeks via various modes of communication. If no response is received from the HCP, additional attempts may occur at the next planned data collection time point (e.g., at pregnancy outcome). When appropriate, the participant will be asked to encourage her HCP to provide the missing data. A final communication to obtain follow-up data will be sent via certified mail indicating that the participant will be considered lost to follow-up if no further data are received. If, at any point in the follow-up process, the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (e.g., no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

9.2.6.2.3 Follow-up process for clarification for information

For critical data points (e.g., exposure and outcome data), if there are outstanding questions, discrepancies between forms, or missing data, the appropriate HCP will be contacted for clarification. If needed, 3 subsequent attempts will be made at intervals of approximately 2 weeks. If no further information is obtained, qualified registry staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

9.2.6.3 Awareness and retention

9.2.6.3.1 Awareness strategy

An active, targeted, multi-pronged awareness campaign will be employed to recruit participants for the registry. The campaign will focus on:

- Pregnant women
- Patients who have overweight with at least one weight-related comorbid condition or who have obesity
- Patients using Wegovy or other products for weight management
- Obstetric HCPs
- HCPs who are likely to treat patients who have overweight or who have obesity or weight-related comorbid conditions
- HCPs who are likely to prescribe Wegovy

As described in Section 7.4.1, non-Hispanic black and Hispanic women are at increased risk of pre-pregnancy obesity compared to non-Hispanic white and Asian women; therefore, Novo Nordisk will make efforts to improve enrolment of participants from underrepresented racial and ethnic populations in this study.

Obstetric HCPs and HCPs who are likely to treat patients with obesity may be identified via HCP directories and/or professional associations. Pregnant women, patients who have overweight or obesity, and patients using Wegovy may be identified through patient support groups and external data sources, such as pharmacy/medical claims or electronic medical records. The sponsor's existing infrastructure for distributing Wegovy and supporting stakeholders (e.g., Medical Information, the Novo Nordisk Call Center, pharmacies that dispense Wegovy, and the Patient Support and Marketing Research programs) may be leveraged to identify HCPs who are known to prescribe Wegovy and pregnant women who have been exposed to Wegovy.

To start, the primary aim of the registry's awareness strategy will be to recruit women exposed to Wegovy during pregnancy. Once the characteristics of a portion of the Wegovy-exposed participants are understood, the awareness campaign for the unexposed cohort will be tailored to increase comparability of the cohorts. In addition, women who were exposed to Wegovy before (>35 days prior to date of conception [DOC]) but not during pregnancy (≤35 days prior to DOC to pregnancy outcome) will be targeted for enrolment into the unexposed cohort.

A multi-modal approach will be used to deliver registry education and awareness materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach as well as online and print advertising directed to both HCPs and patients. In addition, stakeholders may be identified and provided with information regarding the registry via telephone through the Medical Information Contact Centre and/or the patient assistance program.

Direct-to-HCP outreach

Direct-to-HCP outreach will be achieved by delivering awareness materials to targeted HCPs via email, fax, and/or hardcopy mail. In addition, the sponsor's representatives may provide registry education and recruitment materials to HCPs in person. HCPs will be asked to identify potential

registry participants and encourage their participation by speaking to them about the registry and providing them with the patient-directed registry recruitment materials.

Digital advertising

Information regarding the registry and the registry recruitment materials will also be available online. A registry-specific website will be developed, where all recruitment materials will be available for download. This website will be accessible through the Wegovy product website and discoverable in any internet browser by performing a search related to pregnancy and Wegovy, semaglutide, and/or weight management. Information regarding the registry and/or a link to the registry website also will be available on the following websites:

- FDA listing of pregnancy registries on FDA website
- Clinical trials database website
- Society for Maternal-Fetal Medicine listing of registries
- PPD website

A web-based interface compatible with both computers and mobile devices will also be developed to improve information accessibility and enable broader participation. As deemed necessary, online advertisements on social media sites or other relevant websites (e.g., professional association websites or websites commonly visited by pregnant women) may be used to direct potential participants to the registry website. Targeted advertisements on web-based applications frequented by pregnant women will be strategically implemented to drive registry awareness.

Print advertising

Various print materials will also be used to provide information related to the registry and to facilitate recruitment. The Wegovy prescribing information provides registry information, including contact information (US requirement only). Information related to the registry also may be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the registry, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics, weight-loss centres).

Awareness materials

In addition to the registry information in the product label, educational materials designed to elicit interest in registry participation will be developed. All messaging will be aligned with the product label and will be balanced to ensure that it does not unintentionally promote use of Wegovy during pregnancy. Materials may include the following:

- An information sheet and/or brochure that will briefly describe the registry purpose and procedures, including the incentives for participation
- Information on how to access the registry web-based/mobile application
- Registration form and sample participant consent form
- Prescribing information
- Participant consent-to-contact card (this card enables the RCC to contact the potential participant and provide additional information about the registry)

9.2.6.3.2 Retention strategy

A retention strategy, facilitated by engaging both the participant and HCP, will seek to minimise the reporting burden on these groups to the extent possible.

The registry staff will serve as the first and single point of communication for both registry participants and HCPs. The specialised staff, many of whom are obstetric nurses, have experience collecting data for observational studies from both patients and research-naive HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow-up. To promote HCP engagement, status updates may be shared with HCPs through various means (i.e., email, newsletters, and the registry website). Materials provided will emphasise the mission of the registry to promote participant engagement and point participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on specified endpoints to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (e.g., phone, fax, mail, email, website, web-based/mobile application) and a flexible follow-up schedule to enhance retention and maximise data reporting. The registry will also attempt to collect contact information of family members or friends in case the participant cannot be reached, which can further promote retention. Finally, in countries where local guidelines permit, the registry will provide stipends to participants (at enrolment and at the end of data collection) and their HCPs who serve as data reporters (once all data have been collected and all queries have been resolved).

Assessment of recruitment and retention

Participant recruitment and retention are the greatest challenges experienced with pregnancy registries. Recruitment largely depends on a strong awareness campaign and product use or uptake in the market. It is important to note that low recruitment/enrolment in pregnancy registries may be due to limited use of the product, especially when the product is new to the market. Pregnancy registries typically enrol only a small fraction of all exposed pregnancies, regardless of awareness strategies employed.

To maximise recruitment and retention, the registry's recruitment and retention strategies will be flexible and will be continuously assessed. The registry will assess recruitment and retention by collecting information from reporters (i.e., HCPs and participating women) on the sources from which they received information about the registry (recruitment) and the reasons for which they ceased participation or were lost to follow-up (retention). Based on these assessments, the registry's recruitment and retention strategies will be adjusted to maximise registry participation. The registry's Scientific Advisory Committee (SAC) will also be consulted regarding recruitment and retention strategies.

9.2.6.4 Participant registration

Pregnant women who are interested in providing data to the registry and participate in the registry study will self-enrol in the registry through the web-based/mobile application or by calling the RCC. To enrol, each woman will answer a series of screening questions to assess her eligibility, and, if eligible, she will be asked to provide informed consent, her primary contact information, alternate contact information for a family member or friend, contact information for HCPs who

are/will be involved in her care or the care of her infant, and medical releases to allow these HCPs to provide data to the registry. To allow for full follow-up on all enrolled pregnant women and their infants prior to study end, the last participant will be enrolled on or before 31 October 2030.

9.2.7 Assessments for safety

The registry is strictly observational; office visits and all treatment regimens will be determined by HCPs.. No additional laboratory tests or HCP assessments will be required as part of this registry. Refer to Section 11 for reporting of adverse events and other safety information.

9.2.8 Other assessments

Not applicable.

9.3 Variables

9.3.1 Exposure definitions and ascertainment

Exposure to Wegovy is a condition for inclusion into the exposed cohort. Exposure is defined as bodily uptake of any dose of Wegovy at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time period based on the product's half-life). Due to the half-life of Wegovy (approximately 7 days), Wegovy is likely to be eliminated from the body within 5 half-lives (35 days or 5 weeks).

Detailed information on dose, route, frequency, dates/duration of exposure, and indication/reason for use will be collected, and exposure will be further categorised by earliest trimester of exposure. Section 9.3.5 provides information on the methods used to determine gestational age and trimester of exposure.

Exposure information will be updated at each pregnancy follow-up and changing exposures will be accounted for in the analysis. For example, if a pregnant woman was enrolled into the unexposed cohort but later in pregnancy became exposed to Wegovy, for the analysis she would be included in the exposed cohort.

9.3.2 Disease definitions and ascertainment

Having overweight with at least one weight-related comorbid condition or having obesity is a condition for inclusion into the unexposed cohort. Disease information, including date of diagnosis, height and weight (used to derive BMI) at different time points, and weight-related comorbid conditions will be collected from HCPs.

9.3.3 Outcome definitions and ascertainment

Table 9-3 presents the definitions of the outcomes. For outcomes not simply reported by the HCP, additional information on outcome ascertainment is provided.

Table 9-3 Outcome definitions and ascertainment

Outcome	Definition	Ascertainment
Major congenital malformation (MCM)	An abnormality of body structure or function that is present at birth; is of prenatal origin (i.e., birth defect); has significant medical, social, or cosmetic consequences for the affected individual; and typically requires medical intervention [42]	The registry defines and codes MCMs with criteria specified by CDC MACDP.[43] When participants who reside in Europe are enrolled, MCMs will also be defined and coded using the criteria specified by EUROCAT [44] (Appendix B). Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not known to be associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple foetuses), will not be considered MCMs in the statistical analyses [45] . Adjudication process: A panel of 2–3 independent experts in clinical genetics and neonatology, blinded to exposure, will review all malformations reported to the registry and classify them using the CDC's MACDP system (and EUROCAT, if applicable). Additionally, the birth defect evaluators will provide the organ system involved, aetiology of the defect (e.g., chromosomal abnormality, prematurity), and approximate timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators will request additional information using the targeted follow-up process outlined in Section 9.2.6.2. These assessments will be recorded in the database. If there is a discrepancy, a third expert will independently review and code the case serving as tie breaker. These reviews will occur soon after the malformation is reported. Additional reviews will occur if new information is received for the case. The SAC that will not be blinded to exposure will assess the possible temporal association between exposure (to Wegovy) and the development of observed defects. Additionally, the SAC will review all malformation cases reported to the registry and reach consensus on the coding of each case. The sponsor will not be involved in any activities related to case review or adjudication.
Minor congenital malformation	An anomaly or abnormality of body structure that is present at birth, is of prenatal origin (i.e., birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual [42]	The registry defines and codes minor congenital malformations with criteria specified as defined by CDC.[46] The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.
Pre-eclampsia	High blood pressure and signs of liver or kidney damage occurring at > 20 gestational weeks through 6 weeks postpartum[39]	-
Eclampsia	Seizures or coma in a woman with pre-eclampsia during pregnancy through 6 weeks postpartum	-

Outcome	Definition	Ascertainment
Spontaneous abortion (SAB)	An involuntary foetal loss or the expulsion of the products of conception occurring at <20 gestational weeks	Section 9.3.5 provides information on the methods used to calculate gestational age.
Stillbirth	As defined by the ACOG, an involuntary foetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a foetus weighing ≥350 g [47]	Section 9.3.5 provides information on the methods used to calculate gestational age.
Elective termination	A voluntary foetal loss or interruption of pregnancy that occurs for any reason, including but not limited to for the preservation of maternal health or due to foetal abnormalities	-
Preterm birth	A live birth occurring at <37 gestational weeks	Section 9.3.5 provides information on the methods used to calculate gestational age.
Small for gestational age (SGA)	Birth weight <10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants [48]	For the determination of SGA, the registry will utilise the sex-specific international growth reference standards from the INTERGROWTH-21st for those born between 24$^{0/7}$ and 42$^{6/7}$ gestational weeks.[49 50] The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multi-ethnic, diverse population, and have been specifically developed for modern research.
Postnatal growth deficiency	Weight, length, or head circumference in <10th percentile for sex and age using standard growth charts	Postnatal growth deficiency will be evaluated at 4 and 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilise the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age.[51]
Infant developmental delay	Failure to achieve the developmental milestones for age, as defined by the CDC [52]	Infant developmental delay will be evaluated at 4 and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development), separately. HCPs will indicate on the data collection forms whether infants are meeting CDC-defined milestones (yes/no) for each category and age. Infants who are failing to achieve at least one milestone in any category will be considered developmentally delayed in that category.

Abbreviations: ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; EUROCAT = European Registration of Congenital Anomalies and Twins; HCP = healthcare provider; INTERGROWTH-21st = International Fetal and Newborn Growth Consortium for the 21st Century; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; SAB = spontaneous abortion; SAC = Scientific Advisory Committee; SGA = small for gestational age; US = United States; WHO = World Health Organization.

9.3.4 Potential covariates and confounders

In accordance with FDA and the Agency for Healthcare Research and Quality (AHRQ) guidance,[38,53] the following variables may be considered potential covariates and confounders, as appropriate:

- Geographic region
- Maternal age at conception
- Calendar year at conception
- Maternal race
- Maternal ethnicity
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Maternal pre-pregnancy BMI, calculated from pre-pregnancy weight and height
- Gestational age at registry enrolment
- Method of conception
- Number of foetuses
- Concurrent maternal medical conditions, including thyroid abnormalities, infectious diseases (including coronavirus disease 2019 [COVID-19]), asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders, hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, preterm labour, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, molar pregnancy
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, elective termination, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, SGA)
- Previous foetus/infant with congenital malformations (major and minor)
- Family history of congenital malformations (major and minor)
- Disease characteristics, including duration, BMI, and weight-related comorbid conditions
- Maternal exposure to other drugs or biological products, including prescription and non-prescription drugs, dietary supplements (including folic acid and prenatal vitamins), and vaccines (including COVID-19), during pregnancy and gestational age at exposure
- Maternal exposure to tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and timing of exposure
- Maternal weight change prior to pregnancy
- Maternal weight change during pregnancy
- Labour type (induced vs. spontaneous)
- Delivery method and complications

9.3.5 Other variable definitions and ascertainment

Per the American College of Obstetricians and Gynecologists (ACOG), gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the last

menstrual period (LMP), first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or foetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from assisted reproductive technology (ART), the obstetric HCP should use ART-derived gestational age (e.g., based on age of embryo and date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes.[54]

Based on ACOG's recommendations, the registry will collect the EDD from the obstetric HCP, and the HCP will report whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, whether the ultrasound was performed before $14^{0/7}$, before $22^{0/7}$, or at $22^{0/7}$ gestational weeks or later will also be recorded. EDD data will be collected on each data collection form throughout pregnancy. If the HCP reports a corrected EDD on subsequent forms that is different from the EDD initially reported, the registry will evaluate whether a correction is appropriate, based on the timing of the correction and the methods used to determine the corrected EDD, and follow-up with the HCP, if needed.

The registry will conform to ACOG recommendations for determining the 'best' EDD, and EDD will be used to calculate gestational age. Based on EDD, the following will be calculated:

- First day of LMP, defined as $0^{0/7}$ gestational week, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
  - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester
  - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
  - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester
- DOC, defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks)

If EDD is not reported by the HCP but LMP data are available, the registry will use first day of LMP to calculate EDD, gestational age, and DOC.

Women will be considered exposed during pregnancy if the exposure occurs any time from 35 days prior to the DOC to the pregnancy outcome. For the analysis of MCM, first trimester exposure will be defined as exposure from 35 days prior to the DOC to $13^{6/7}$ gestational weeks.

9.4 Data sources

An overview of the data collection process and forms can be found in Section 9.2.6.2.

Registration Information

Collected from participant at enrolment

- Date of first contact with registry
- Date of consent (enrolment)
- Recruitment source(s)

- Minimum data for assignment to a study cohort, including:
  - Country of residence
  - Pregnancy status
  - Diagnosis information
  - Exposure information
  - Prior enrolment status

Collected from HCP(s) – obstetric and prescriber, if needed, – at enrolment

- Minimum data for assignment to a study cohort, including:
  - Pregnancy status
  - Diagnosis information
  - Exposure information

Maternal Demographic Characteristics

Collected from participant at enrolment

- Date of birth
- Country of residence
- Ethnicity
- Race
- Education
- Employment status
- Household income

Maternal Pre-Pregnancy Anthropometrics

Collected from participant at enrolment

- Pre-pregnancy anthropometrics (weight and height) just prior to pregnancy, weight at approximately 12 months prior to pregnancy, and weight prior to starting prescription weight-loss medication (e.g., Wegovy)

Collected from HCP at enrolment

- Pre-pregnancy anthropometrics (weight and height) just prior to pregnancy, weight at approximately 12 months prior to pregnancy, and weight prior to starting prescription weight-loss medication (e.g., Wegovy)

Maternal Obstetrical History

Collected from obstetric HCP at enrolment; if not available from HCP, can be collected from participant

- Number of previous pregnancies, including multiple gestations
- Outcomes of previous pregnancies (SAB, stillbirth, elective termination, live birth)
- Complications of previous pregnancies (e.g., pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, preterm labour, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, molar pregnancy)

- Characteristics of previous live births (preterm, SGA)
- Number of previous foetuses/infants with congenital malformations (major and minor) and contributing factors

Family History of Congenital Malformations

Collected from obstetric HCP at enrolment; if not available from HCP, can be collected from participant

- Maternal and paternal family history of congenital malformations (major and minor), including specific malformation and relation of family member to mother or father

Disease Information

Collected from HCP(s) – obstetric and prescriber, if needed – at enrolment

- Maternal history of having overweight or obesity, including date of diagnosis
- Maternal pre-pregnancy anthropometrics (weight and height) just prior to pregnancy, weight 12 months prior to pregnancy, and additionally for Wegovy-exposed participants, weight at the time of first Wegovy prescription
- Weight-related comorbid conditions

Baseline Pregnancy Information

Collected from obstetric HCP at enrolment only

- First day of LMP
- Method of conception
- History of fertility treatment
- Relevant maternal and paternal risk factors (medical history and exposures) for adverse pregnancy outcomes (e.g., genetic disorders, consanguinity, occupation, past chemotherapy or exposure to teratogens)

Ongoing Pregnancy Information

Collected from obstetric HCP at enrolment, end of 2nd trimester, and pregnancy outcome; at the end of the 2nd trimester and pregnancy outcome, HCPs are asked only for updates to the data previously reported

- Number of foetuses
- EDD and method of determination (i.e., LMP, ultrasound, or ART data); if ultrasound-determined, timing of ultrasound (before $14^{0/7}$, before $22^{0/7}$, or at or after $22^{0/7}$ gestational weeks)
- Prenatal tests (e.g., ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling) performed, including type of test (diagnostic or screening), date of test, and results/findings (e.g., congenital malformations)
- Relevant maternal medical conditions, including, but not limited to
  - Inheritable diseases
  - Thyroid abnormalities

- Infectious diseases (e.g., COVID-19, toxoplasmosis, cytomegalovirus, rubella, parvovirus)
- Asthma
- Diabetes
- Hypertension
- Seizure disorder
- Autoimmune diseases
- Anaemia
- Depression and other psychiatric disorders
- Hepatitis
- Sexually transmitted diseases
- Uterine or cervical abnormalities, including congenital uterine abnormalities

- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including
  - Pregnancy-induced hypertension
  - Pre-eclampsia
  - Eclampsia
  - Gestational diabetes
  - Preterm labour
  - Placenta previa
  - Placental abruption
  - Incompetent cervix
  - Ectopic pregnancy
  - Molar pregnancy

Maternal Exposures during Pregnancy

Collected from HCP(s) – obstetric and prescriber, if needed – at enrolment, end of 2nd trimester, and pregnancy outcome; at the end of the 2nd trimester and pregnancy outcome, HCPs are asked only for updates to the data previously reported

- Exposure to Wegovy, including indication/reason for use (approved according to label in country of residence), dose, route, frequency, and dates/duration of exposure, if available
- Exposure to other drugs or biological products (including prescription and non-prescription drugs, dietary/herbal supplements (including folic acid and prenatal vitamins), vaccines (including COVID-19), known teratogens (see Section 9.7.1.1.3), and investigational medications), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

Pregnancy Outcome Information

Collected from HCP(s) – obstetric and paediatric, if needed – at or after pregnancy outcome

- Pregnancy outcome (for each foetus, classified in one of the following mutually exclusive categories: SAB, stillbirth, elective termination, and live birth)
- Date of pregnancy outcome

- Gestational age at pregnancy outcome
- Foetal/infant sex
- Foetal/infant weight, length, and head circumference at pregnancy outcome
- Labour type (spontaneous or induced)
- Route of delivery (i.e., vaginal delivery, assisted vaginal delivery, planned caesarean delivery, or emergency caesarean delivery)
- Delivery complications
- 1-, 5-, and 10-minute Apgar scores
- Congenital malformations (major and minor) and assessment of potential contributing factors
- Maternal weight at (just prior to) pregnancy outcome
- For live births, prolonged hospitalisation after delivery and reason
- For a non-induced foetal loss (SAB, stillbirth), factors that may have had an impact on the foetal loss and attribution
- For elective termination, reason (e.g., finding on prenatal test, risk to mother's health, undesired pregnancy)

Infant Outcome Information

Collected from paediatric HCP at 4 and 12 months post-delivery

- Infant weight, length, and head circumference at birth (if not provided at pregnancy outcome) and at 4 and 12 months of age
- Achievement of the developmental milestones in each Centers for Disease Control and Prevention (CDC)-defined category (social/emotional, language/communication, cognitive, and movement/physical development) at 4 and 12 months of age
- Congenital malformations (major and minor) and assessment of potential contributing factors
- Infant death, including date and cause of death
- Infant illnesses (e.g., neonatal hypoglycaemia), infections, and hospitalisations
- Breastfeeding information, including breastfeeding start/stop dates and maternal medicinal and recreational exposures during breastfeeding

Targeted Follow-up Information

Collected from HCP(s) – obstetric and/or paediatric – at any time after pregnancy outcome

- Details of congenital malformations (major or minor) or other conditions
- Aetiology
- Exposures that may have had an impact on the outcome
- Additional factors that may have had an impact on the outcome
- Specific questions requested by the sponsor and/or the birth defect evaluator

9.5 Study sample size

Table 9-4 presents by outcome the sample size (number of live births or pregnant women, depending on the outcome) required in each cohort to detect a range of relative risks, from 1.5 to 5.5. Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) for the outcomes using the Fisher's exact conditional test with Walters

normal approximation method, and assuming a power of 80%, a 2-sided α level of 0.05, an equal number of women in each cohort (although other sampling ratios were considered), and observed prevalence of the outcomes in the unexposed cohort equivalent to reference comparator rates in the general population. These general population rates were obtained for most (but not all) of the outcomes from various sources, including the Metropolitan Atlanta Congenital Defects Program (MACDP), the National Vital Statistics System (NVSS), and published literature.

Although the registry aims to examine a variety of maternal, foetal, and infant outcomes, the target sample size for the registry is based on the primary endpoint, overall prevalence of MCM, which also is the outcome with the most restrictive denominators and one of the lowest prevalence in the general population.

As shown in Table 9-4, 265 live births in the main analysis population of each cohort are needed to detect a 3-fold increase in the overall prevalence of MCM between cohorts, or a relative risk of 3.

To estimate the number of pregnant women who will need to be enrolled to result in 265 live births, several factors were considered, including the expected registry live birth rate, the proportion of enrolled women expected to be exposed to Wegovy in the first trimester, and the proportion of enrolled women expected to be excluded from the main analysis population. It was assumed that 90% of enrolled women would be exposed in the first trimester, 90% of enrolled pregnancies would result in a live birth,[55,56] and 10% of enrolled women would be excluded from the main analysis population due to the occurrence of pregnancy outcome prior to enrolment (retrospectively enrolled participants), exposure to a known teratogen or an investigational medication during pregnancy (teratogen/investigational medication-exposed participants), lack of pregnancy outcome data (participants lost to follow-up; assumed to constitute 5%), or inclusion of a prior pregnancy in the main analysis population (subsequent pregnancies).

Given these assumptions, to attain 265 live births per cohort, 364 (=265/0.9/0.9/0.9) pregnant women would need to be enrolled in each of the 2 cohorts of the study population, and a total of 728 women would need to be enrolled in the registry. This sample size will afford the study the ability to detect a 3-fold increase in the overall prevalence of the primary outcome, MCM, in the Wegovy-exposed cohort, with meaningful confidence (95% confidence level). Additionally, Table 9-5 shows that, without any adjustments for multiple comparisons, the proposed sample size will afford the study >80% power to detect a 3-fold increase in all other outcomes except eclampsia and stillbirth (for which the study will have 5.9% and 21.4% power to detect a 3-fold increase, respectively).

Although the sample size calculations were based on general population rates of the outcomes, the overall prevalence of MCM is higher among women with obesity (BMI >30 kg/m^2; 3.9%; Persson 2017) than that of the general population (3%).[57] However, because it is difficult to estimate the proportion of enrolled women who will have obesity at the time of conception (as some will have lost weight prior to conception due to weight management treatment), the more conservative approach assuming an overall prevalence of 3% has been chosen. Had the higher rate (3.9%) been used, the total sample size for the registry would have been substantially lower (551 vs. 728). These assumptions may be re-evaluated after interim analyses have been conducted.

Table 9-4 Sample size calculations

Outcomes[a]	Reference Prevalence in Unexposed Group	Reference	Denominator of Reference	Sampling Ratio (Exposed: Unexposed)	Sample Size Needed per Cohort to Detect Specific RR (Exposed: Unexposed)								
					RR= 1.5	RR= 2.0	RR= 2.5	RR= 3.0	RR= 3.5	RR= 4.0	RR= 4.5	RR= 5.0	RR= 5.5
MCM	3.0%	CDC 2008 [57]	Live births	1:1	2,627	796	413	265	190	146	117	97	82
Pre-eclampsia	3.8%	Ananth 2013 [58]	Pregnant women	1:1	2054	622	322	206	148	113	91	75	64
Eclampsia	0.281%	Butwick 2020 [59]	Live births	1:1	28973	8824	4600	2961	2130	1640	1322	1101	940
SAB	11.8%	Wu 2019 [60]	Pregnant women	1:1	596	177	90	57	40	30	24	19	16
Stillbirth	0.596%	MacDorman 2015 [61]	Live births and stillbirths	1:1	13610	4142	2159	1389	999	769	619	516	440
Elective termination	18.6%	Jatlaoui 2019 [62]	Live births	1:1	343	100	50	31	21	15	12	9	NA[b]
Preterm birth	8.47%	Martin 2021 [63]	Singleton live births	1:1	868	260	134	85	60	46	36	30	25
SGA	10.0%	By definition	Live births	1:1	721	215	110	70	49	37	29	24	20
Postnatal growth deficiency	10.0%	By definition	Live births	1:1	721	215	110	70	49	37	29	24	20

Sample size calculations were performed in SAS (version 9.4) for the outcomes using Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80% and a 2-sided α level of 0.05.

[a] Only outcomes with published reference rates in the general population are included in the table.

[b] For elective termination, an RR of 5.5 with a reference rate of 18.6% in the unexposed cohort would result in a rate above 100% in the exposed cohort.

Abbreviations: MCM = major congenital malformation; NA = not available; reference prevalence = prevalence of outcome in general population for pregnant women of any age; RR = relative risk; SAB = spontaneous abortion; SGA = small for gestational age.

Table 9-5 Power to detect a 3-fold increase, by study outcome

Outcomes	Power Estimate
MCM	80%
Pre-eclampsia	>80%
Eclampsia	5.9%
SAB	>80%
Stillbirth	21.4%
Elective termination	>80%
Preterm birth	>80%
SGA	>80%
Postnatal growth deficiency	>80%

Note: No adjustments for multiple comparisons were made.

Abbreviations: MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age.

To assess the feasibility of this study, data-based assumptions regarding the prevalence of obesity, pregnancy, and Wegovy uptake were made to estimate the number of women who will potentially be exposed to Wegovy during pregnancy. The prevalence of obesity among women in the US, Spain, and the UK was assumed to be 39.7%, 31.3%, and 27.2%, respectively [64 65] and the proportion receiving pharmacotherapy for obesity was assumed to be 0.8%.[66] It was further assumed that 15% of those receiving pharmacotherapy for obesity would be treated with Wegovy. These assumptions were applied to the population of women of childbearing potential (aged 15–49 years) in the US, Spain, and UK (approximately 74.4 million, 10.4 million, and 14.7 million, respectively), which yielded an estimated 44,192 women of childbearing potential who will potentially receive Wegovy. After application of the live birth rates (average annual number of births during a year per 1,000 persons in the population; US: 12.33/1000; Spain: 11.77/1000; UK: 8.05/1000) and the rate of pharmacotherapy discontinuation during pregnancy among women with obesity (95% assumed rate of discontinuation due to contraindication during pregnancy), it was estimated that 261 women in the US, UK, and Spain may potentially be exposed to Wegovy during pregnancy over a 10-year period.

This estimate is less than the target sample size for the exposed cohort (364 enrolled women); however, this is considered a conservative estimate for several reasons. First, it is anticipated that the proportion of women exposed to Wegovy for its approved indications will increase over the duration of the study. Furthermore, the feasibility calculations were based on the prevalence of obesity alone, since reliable statistics regarding the prevalence of overweight and weight-related comorbidities are not available. Therefore, the estimated number of women with the indication is an underestimate. Novo Nordisk will perform ongoing monitoring of enrolment and will continue to assess the feasibility of the study to achieve its target sample size.

9.6 Data management

Paper/electronic data collection forms will be used to capture study-specific participant data. Instructions for completion and correction of data collection forms will be provided.

Appropriate measures such as encryption or deletion must be enforced to protect the identity of participants when transmitting data, in all presentations and publications as required by local/regional/national requirements.

For electronic case report forms: The system for electronic data capture (EDC) and support services for the system will be supplied by CISIV. The activities of CISIV will be under the direction and supervision of PPD and Novo Nordisk.

An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry, and the corrected entry.

9.7 Data analysis

Analyses will be conducted by PPD in accordance with the study objectives, statistical analysis plan (SAP), table/listing shells, and applicable guidelines. Data analyses will be performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC). Additional details will be provided in the SAP.

To minimise the potential impact of bias, adjusted analyses (Section 9.7.2.4), stratified analyses (Section 9.7.2.5), supplementary analyses (Section 9.7.2.6), and sensitivity analyses (Section 9.7.2.7) will be performed.

9.7.1 Definition of analysis sets

9.7.1.1 Main analysis population

The main analysis population will include participants who:

- Are valid (Section 9.7.1.1.1)
- Are prospectively enrolled (Section 9.7.1.1.2)
- Are not exposed to teratogens or investigational medications during pregnancy (Section 9.7.1.1.3)
- Are not considered lost to follow-up (Section 9.7.1.1.4)
- Are not already included in the main analysis population for a prior pregnancy (Section 9.7.1.1.5)

For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple gestation pregnancies will be excluded from the main analysis population.

9.7.1.1.1 Valid versus invalid participants

A valid participant is defined as a pregnant woman with sufficient data, submitted or confirmed by an HCP, for determining inclusion/exclusion into one of the study population cohorts (Section 9.2.2). Participants who lack the minimum data required for determining inclusion/exclusion into one of the study cohorts or who lack confirmation from an HCP will be considered invalid. Invalid participants will be enumerated in each registry report but will not be included in statistical analyses.

9.7.1.1.2 Prospectively enrolled versus retrospectively enrolled participants

The registry will encourage prospective registration; however, retrospective enrolment in the registry will be permitted. A prospectively enrolled participant is defined as a pregnant woman who enrols or makes initial contact with the registry prior to pregnancy outcome. A retrospectively

enrolled participant is defined as a pregnant woman who enrols or makes initial contact with the registry after the pregnancy outcome has occurred.

Retrospectively enrolled participants can introduce bias toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. Therefore, retrospectively enrolled participants will be excluded from the main analysis population but will be included in supplementary analyses.

Diagnostic prenatal tests (e.g., ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a foetus has a structural or chromosomal abnormality. Therefore, inclusion of women who have had diagnostic prenatal testing in the main analysis population may introduce bias. To examine this potential bias, a sensitivity analysis that applies a stricter definition of prospective enrolment will be conducted. For this analysis, women who enrol or make initial contact with the registry prior to diagnostic prenatal testing (and pregnancy outcome) will be considered prospectively enrolled, and women who enrol or make initial contact with the registry after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled in addition to women who enrol after pregnancy outcome. The outcomes of women who enrol prior to diagnostic prenatal testing will be compared with those of women who enrolled after diagnostic prenatal testing.

9.7.1.1.3 Participants exposed to teratogens or investigational medications

Participants will be considered exposed to teratogens or investigational medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time period based on the product's half-life). If the teratogen or investigational medication has a relatively short half-life (<3 days), participants will be considered exposed during pregnancy if a dose is taken during the period of time just prior to conception, between the first day of the LMP and the DOC. If the teratogen or investigational medication has a longer half-life, participants will be considered exposed during pregnancy if a dose is taken prior to conception within a time period equivalent to 5 times the product's half-life. A list of teratogens has been developed (Appendix C) and will be continually updated based on the data available in the Teratogen Information System (TERIS) database of teratogenic agents and recent publications.[67 68 69 70] Participants exposed to teratogens or investigational medications during pregnancy will be excluded from the main analysis population but will be included in supplementary analyses.

9.7.1.1.4 Participants lost to follow-up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant women without pregnancy outcome information will be considered lost to follow-up, and live-born infants without follow-up data after birth will be considered lost to follow-up. Section 9.2.6.2 provides more information on the circumstances under which participants will be considered lost to follow-up. Information from these participants (e.g., baseline characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarised in each registry report, but these participants will be excluded from the main analysis population.

9.7.1.1.5 Subsequent pregnancies

Women who have previously enrolled in the registry with a prior pregnancy will be eligible to enrol in the registry, but any subsequent pregnancy will be excluded from the main analysis population if a prior pregnancy is included. Subsequent pregnancies will be included in supplementary analyses.

9.7.1.1.6 Multiple gestation pregnancies

Multiple gestation pregnancies will be enrolled in the registry and included in the main analysis population; however, for the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple gestation pregnancies will be excluded from the main analysis population due to the higher risk of these outcomes in twins and higher order multiples.

9.7.2 Statistical methods

Registry data will be summarised in tables and listings by study cohort, as appropriate. These data include maternal demographic characteristics and pre-pregnancy anthropometrics, pregnancy information, maternal obstetrical history, family history of congenital malformations, disease information, maternal exposures during pregnancy, pregnancy outcome information (including gestational age of outcome), and infant outcome information.

For each continuous variable, the number of observations, median, mean, standard deviation, minimum, and maximum will be reported. For each categorical variable, the frequency and percentage in each category will be reported. The frequency and percentage of participants with missing data for each data point will be presented. Results will be rounded to one decimal place; therefore, percentages may not always add up to 100.

Comparisons of demographic and baseline characteristics and prevalence of the outcomes will be conducted between the study cohorts. For the main analysis, participants from all countries will be pooled. Comparisons will be conducted using the methods described below, and p-values and 95% confidence intervals will be reported, as appropriate, to reflect statistical uncertainty. All outcomes will be analysed as binary variables; in addition, if information on gestational age allows, SAB and preterm birth may be analysed as time-to-event outcomes. The study is not powered for multiple comparisons; thus, p-values associated with secondary or exploratory outcomes will be nominal.

In addition, the prevalence of the outcomes in the general population and/or populations of women with overweight or obesity will be used to put the registry-observed outcome prevalences into context.

9.7.2.1 Analysis of primary endpoint

Prevalence of the primary outcome will be calculated according to the conventions described in Table 9-6. In general, prevalence will be calculated by dividing the number of cases with an MCM by the appropriate denominator. Prevalence is preferred over incidence when examining pregnancy outcomes, such as congenital malformations, because incidence cannot be reliably estimated given the complexities in the reproductive process.[71]

For MCM, prevalence in the exposed cohort will be calculated among the subset of women who are exposed during the first trimester. For the primary analysis, prevalence will be calculated among

live births, and a secondary analysis will be conducted among live births and foetal losses (Table 9-6).

Exact methods will be used to calculate a crude (unadjusted) relative risk of MCM. Adjusted methods will incorporate weights estimated using the inverse probability weighting (IPW) method to balance the cohorts with regard to observable covariates. A weighted generalised linear model using a binomial family and a log (relative risk) link will be employed to estimate an adjusted relative risk.

The adjusted comparison of the overall prevalence of MCM observed in the exposed and unexposed cohorts will be considered the primary analysis. A p-value <0.05 will be considered statistically significant.

Table 9-6 Calculation of primary outcome prevalence

Outcome	Numerator	Denominator
Primary analysis: among live births	Live births with confirmed MCMs (excluding MCMs not known to be associated with medication exposure[a]) among women with pregnancy outcome data and, if applicable, exposure during 1st trimester	Live births among women with pregnancy outcome data and, if applicable[b], exposure during 1st trimester
Secondary analysis: among all pregnancy outcomes	Live births and foetal losses[c] with confirmed MCMs (excluding MCMs not known to be associated with medication exposure[a]) among women with pregnancy outcome data and, if applicable, exposure during 1st trimester	Live births and foetal losses[c] among women with pregnancy outcome data and, if applicable, exposure during 1st trimester

[a] To avoid misattribution of the malformation to the medication, MCMs not known to be associated with medication exposure such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple foetuses) will not be considered MCMs in the statistical analyses comparing MCM prevalence between the internal cohorts [45].

[b] Exposure during first trimester applicable only for exposed cohort.

[c] Foetal losses include stillbirths, SABs, and elective terminations.

Abbreviations: MCM = major congenital malformation.

9.7.2.2 Analysis of secondary endpoints

Prevalence of the secondary outcomes will be calculated according to the conventions described in Table 9-7. In general, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge.

Table 9-7 Calculation of secondary outcome prevalence

Outcome	Numerator	Denominator
Minor congenital malformations	Live births with minor congenital malformations among women with pregnancy outcome data	Live births among women with pregnancy outcome data
Pre-eclampsia	Pre-eclampsia among women with pregnancy outcome data	Women with pregnancy outcome data

Outcome	Numerator	Denominator
Eclampsia	Eclampsia among women with pregnancy outcome data	Women with pregnancy outcome data
SAB	SABs among women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks	Women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks
Stillbirth	Stillbirths among women with pregnancy outcome data	Women with pregnancy outcome data
Elective termination	Elective terminations among women with pregnancy outcome data	Women with pregnancy outcome data
Preterm birth	Singleton preterm live births without MCMs among women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks	Singleton live births without MCMs among women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks
SGA	Singleton live births without MCMs who are SGA among women with pregnancy outcome data	Singleton live births without MCMs with weight data among women with pregnancy outcome data
Postnatal growth deficiency (at 4 and 12 months)	Singleton infants without MCMs who were not born preterm or SGA with postnatal growth deficiency based on weight/length/head circumference among infants with weight/length/head circumference data at the time point	Singleton infants without MCMs who were not born preterm or SGA with weight/length/head circumference data at the time point
Infant developmental delay (at 4 and 12 months)	Infants without MCMs who were not born preterm with developmental delay in a particular category among infants with developmental milestone data for the category at the time point	Infants without MCMs who were not born preterm with developmental milestone data for the category at the time point

Abbreviations: MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age.

For most outcomes, the analysis population (denominator) will be the number of pregnant women with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the specified time points, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted based on certain relevant factors:

- For preterm birth, SGA, and postnatal growth deficiency, prevalence will be calculated among singleton live births due to the higher risk of these outcomes in twins and higher order multiples.
- For live birth and infant outcomes (i.e., preterm birth, SGA, postnatal growth deficiency, and infant developmental delay), prevalence will be calculated among live births/infants without MCMs due to the higher risk of these outcomes among infants with MCM.
- For postnatal growth deficiency, infants born preterm, or SGA will be excluded from the analysis population (denominator).
- For infant developmental delay, infants born preterm will be excluded from the analysis population (denominator).
- For SAB and preterm birth, prevalence will be calculated among the subset of women who are enrolled in the registry prior to 20 and 37 gestational weeks, respectively. Additionally, for these time-to-event outcomes, data will be censored at appropriate time points: 20 gestational weeks for SAB and 37 gestational weeks for preterm birth.

- For some outcomes, prevalence will be calculated at multiple time points. For example, postnatal growth deficiency and infant developmental delay will be assessed at 4 and 12 months of infant age. At each time point, prevalence will be calculated among infants with data available for the particular outcome at that time point.

Exact methods will be used to calculate crude (unadjusted) relative risks for all outcomes. Adjusted methods will incorporate weights estimated using the IPW method to balance the cohorts with regard to observable covariates (Section 9.7.2.4). A weighted generalised linear model using a binomial family and a log (relative risk) link will be employed to estimate an adjusted relative risk. Additionally, for time-to-event outcomes, including SAB and preterm birth, a secondary analysis may be conducted that estimates crude (unadjusted) and adjusted HRs using Cox proportional hazards modelling.

9.7.2.3 Demographic and baseline characteristics

Demographic and baseline characteristics will be summarised with descriptive statistics, and balance between cohorts will be assessed using standardised differences. These data will be presented before and after balancing using the IPW method (Section 9.7.2.4). In addition, within each cohort, those included in the main analysis population will be compared with those excluded from the main analysis population for being lost to follow-up, retrospectively enrolled, exposed to teratogens or investigational medications during pregnancy, or having already been included in the main analysis population for a prior pregnancy.

9.7.2.4 Adjustment for covariates and confounders

Because of the real-world nature of the study, there is a high potential for imbalance between the cohorts with regard to observed covariates. To address this imbalance, adjusted analyses that employ the IPW method will be conducted. The IPW method is widely used in observational studies, and, unlike propensity score matching, the IPW method does not require a 1:1 match between participants in the two cohorts being compared.[72 73 74] The IPW approach assigns a weight to each participant based on observed covariates; the weight is equivalent to the inverse probability of the participant belonging in her assigned cohort (inverse propensity score). Weights will be estimated for each participant using logistic regression, then the weights will be incorporated into a regression model to balance the cohorts. When cohorts are far from being balanced, extreme weights can have an impact on the results. If extreme weights are observed in the IPW analysis, stabilised weights will be applied. Weights will be stabilised by using the marginal probability of 'treatment' in the numerator instead of 1. [75] Standardised differences for the covariates will be examined after applying weights. If the standardised differences for most of the covariates are greater than 10% after applying weights, the propensity model will be revisited (e.g., by including interaction terms or non-linear terms). If some (stabilised) weights are extreme, it may indicate that few patients have a very high or low probability of being exposed and may have a disproportionate influence on the analysis. If this is the case, these individuals will be investigated, and weights may be trimmed for instance at the 1st and 99th percentile.

The final selection of covariates (see Section 9.3.4 for a list of potential covariates and confounders) will depend primarily on data availability, clinical importance, and observed imbalances in the model. The list of covariates and confounders will be considered for each outcome separately. As the expected frequency of outcomes in the study is small, the number of potential covariates

included in the model could be limited. Priority will be given to covariates that are possibly associated with the exposure and outcomes. In addition, a high rate of missing data for a covariate could make application of the IPW method more challenging, as weights can be estimated only for participants with known values. If there is a high degree of missing covariate data and multiple imputation is applied, the imputed values will be used for weight estimation (see Section 9.7.2.8).

9.7.2.5 Stratified analyses

Where sample size permits, stratified/subgroup analyses of all outcomes will be conducted that consider the timing of exposure (earliest trimester of exposure), extent of exposure (cumulative dose during pregnancy or relevant exposure window), country, BMI at conception, and maternal age group at conception15–18 years, 18–34 years, and 35–50years).

9.7.2.6 Supplementary analyses

Supplementary analyses of all outcomes will be conducted that include pregnant women who were excluded from the main analysis population due to:

- Occurrence of the pregnancy outcome prior to enrolment (retrospectively enrolled participants)
- Exposure to a known teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed participants)
- Inclusion of a prior pregnancy in the main analysis population (subsequent pregnancies)

9.7.2.7 Sensitivity analyses

Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results. The following sensitivity analyses are planned:

- As described in Section 9.7.1.1.2, a sensitivity analysis will be conducted that applies a stricter definition of prospective enrolment. For this analysis, women who enrol or make initial contact with the registry prior to diagnostic prenatal testing (and prior to pregnancy outcome) will be considered prospectively enrolled, and women who enrol or make initial contact with the registry after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled in addition to women who enrol after pregnancy outcome. The outcomes of women who enrol prior to diagnostic prenatal testing will be compared with those of women who enrolled after diagnostic prenatal testing.
- To test the robustness of the IPW method, a sensitivity analysis will be conducted that includes the propensity score and a variable for treatment in an unweighted generalised linear model using a binomial family and a log (relative risk) link.
- A sensitivity analysis will be conducted that limits the unexposed cohort to women unexposed to any weight loss medications during pregnancy.
- Separate sensitivity analyses may also be conducted to assess the potential impact of missing data.

9.7.2.8 Missing data

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. As is described in Section 9.2.6.2, the registry will make multiple attempts to obtain

missing data for critical data points. The frequency and percentage of participants with missing data for each data point will be presented.

For start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month. Listings will continue to present the day as missing.

If there is a high degree of missing covariate data, further imputation may be considered to minimise the loss of observations in the analysis.

9.7.3 Interim analysis

The registry will produce interim progress reports in August of each year beginning in 2023. These reports will be submitted to the appropriate regulatory authorities. Reports will include a presentation of the registry design, methodology, and results to date. Until enough data have accumulated to warrant a full comparative analysis, reports will be abbreviated and include only results of descriptive analyses.

9.8 Quality control

Ensuring that the data obtained and delivered to the sponsor are of high quality will be an ongoing, multistep process involving programming of edit checks for critical data variables in the electronic data capture system and visual review for completeness, logic, consistency, and accuracy. As is recommended in regulatory guidance documents, data collection forms have been carefully designed to ensure data quality and integrity. Participant-reported data may be verified by the appropriate HCP. PPD will follow their standard operating procedures (SOPs) as they relate to training of personnel, data handling, and processing, complying with 21 Code of Federal Regulations (CFR) Part II and Good Pharmacoepidemiology Practice (GPP).

9.8.1 Monitoring procedures

During the course of the study, monitoring should be performed to ensure that the protocol has been adhered to.

9.8.2 Critical documents

Before the study is started (which is when informed consent is obtained from the first participant), the following documents must be available to Novo Nordisk and PPD:

- Regulatory approval and/or notification as required
- Documentation of the principal investigator's qualifications (for instance a short curriculum vitae or authorisation)
- Signed and dated agreement on the final protocol
- Approval/favourable opinion from IRB/IEC (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol including version, participant information/informed consent form and any other written information to be provided to the participant, participant enrolment procedures
- Copy of IRB/IEC approved participant information/informed consent form/any other written information/advertisement (or waiver by IRB/IEC of documentation of informed consent)

- Non-interventional study agreement
- Source document agreement

9.8.3 Retention of study documentation

Novo Nordisk and PPD will comply with GPP and relevant national legislation related to archiving of study documentation.

The central registry site must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The central registry site should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

9.9 Limitations of the research methods

As this is an NIS, potential confounding factors cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data and its interpretation.

The general limitations of pregnancy registries with voluntary participation are well known, and these will apply to this study as well. One key limitation of the study is the limited size of the population of pregnant women expected to be exposed to Wegovy during pregnancy.

Another key limitation of the registry, due to the voluntary nature of participation, relates to representativeness. Since participation in the registry is voluntary, the pregnant women who voluntarily enrol in the registry may not be representative of the overall population of pregnant women. This could introduce selection bias and affect the generalisability of the results. To minimise the potential for selection bias, a multi-faceted awareness strategy will be employed.

Because the registry will enrol women only after recognition of pregnancy and in some cases much later in pregnancy, there will be left truncation of the enrolled population. That is, the enrolled population of pregnant women will include women with a shortened period at risk of the outcomes and exclude women who have already had certain outcomes (e.g., SAB, elective termination). To minimise the impact of this potential bias, statistical methods may be used to address left truncation, and the registry's awareness strategy will encourage enrolment of participants as early in pregnancy as possible.

Additionally, women in the exposed cohort may differ from those in the unexposed cohort in important factors that could impact pregnancy outcomes (e.g., access to healthcare and medications, socioeconomic status, disease severity, etc.). To minimise the impact of potential confounders, the registry will record the characteristics of women in both cohorts and use statistical methods to examine and account for any differences between cohorts in the analysis. The registry will employ identical data collection and follow-up procedures across the registry cohorts to minimise any potential bias. Although statistical methods will be used to account for confounding or mediating variables, it may not be possible to control for all variables (e.g., unknown) that could influence the

results of the study. Therefore, some important confounders (either measured or not) could still be unbalanced.

As described in Section 9.7.2, comparisons of prevalence of the outcomes will be conducted between the exposed and unexposed cohorts. The adjusted comparison of the prevalence of MCM observed in the exposed and unexposed cohorts will be considered the primary analysis. Because participants who seek and receive pharmacotherapy for weight management may have greater disease severity, confounding by indication (also known as channelling bias) will need to be carefully considered for the comparison. Confounding by indication can occur when participant characteristics, such as disease severity, affect prescribing patterns. If not accounted for in the analysis, such confounding could result in an apparent increased risk of the outcomes associated with medication use. As is described in Section 9.7.2, this study will employ the IPW method to address the imbalance between cohorts; however, if the cohorts vary greatly in terms of disease severity, this comparison may nonetheless fail to produce meaningful results.

Since the registry is focused on prospective enrolment, misclassification of drug exposure is non-differential with regard to outcome. However, outcome misclassification could occur, especially with regard to minor congenital malformations that may be overlooked or unreported. Although some MCMs may not be easily visible at birth, most will be apparent by 12 months of age, so misclassification of these outcomes is expected to be minimal in this registry, which aims to follow infants through 12 months of age.

It is possible that outcomes among pregnant women and infants lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases from the losses to follow-up may have on the analyses. However, the characteristics of those participants considered lost to follow-up will be descriptively compared with those in the main analysis population in an attempt to address this potential source of bias.

Pregnancies that result in foetal losses (stillbirths, SABs, and elective terminations) without reported MCMs may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting HCP may not know the condition of the lost foetus.

Each source of potential bias will be evaluated descriptively and discussed in the report.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

The sponsor respects the participants' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations. Each participant's identity will be known only to the third-party contractor (i.e., PPD), the central registry site (principal investigator, medical monitor, and RCC), and the enrolling/participating individual (i.e., participant or HCP). At no time during the operation of the registry will the sponsor have access to personal identifier information for any woman or any infant who has been enrolled in the registry, with the exception of date of birth for safety reporting purposes. The registry will assign all women and infants identification numbers, which will be used to identify registry participants and their infant offspring. The dataset used in each analysis of data from the registry will contain coded registry participant identifiers only for both the pregnant women and infants.

Each employee in the RCC is fully trained in the protection of human subjects and data privacy and follows established SOPs that outline specifically how to maintain confidentially of and data protection for all registry participants. These SOPs also establish procedures should privacy be compromised in any way. The RCC staff must train and test on these privacy SOPs annually.

Exemption of Health Insurance Portability and Accountability Act Authorisation

As a post-marketing safety reporting activity, this registry meets the following criteria and is therefore exempt from the US Health Insurance Portability and Accountability Act (HIPAA) authorisation.

The CFR, in 45 CFR 164.512, states:

> (iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:
>
> a. To collect or report adverse events (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labelling of a product), or biological product deviations;
>
> b. To track FDA-regulated products;
>
> c. To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
>
> d. To conduct post marketing surveillance

To further clarify this issue, an article published by the Pregnancy Labelling Task Force, US FDA, states:

> The HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as HCPs or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting adverse events, tracking FDA-regulated products and

conducting post-marketing surveillance to comply with requirements or at the direction of the FDA.[76]

Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with GPP,[77] with applicable local regulations and with the ethical principles established in the Declaration of Helsinki. The protocol will be submitted to the applicable regulatory authorities and IRBs/IECs for approval prior to registry implementation. The protocol, informed consent forms, and waiver of documentation of informed consent will be reviewed and approved by IRBs/IECs before study implementation. A signed and dated statement that the protocol and waiver have been approved by the IRBs/IECs will be given to the sponsor before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

10.1 Informed consent form for study participants

Informed consent will be obtained for each registry participant. Where allowed by local laws and regulations (currently only in US), adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent or signed informed consent through the web-based/mobile application or via courier. For the registry, adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various countries and US states.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various countries and US states. The definitions of a minor and an emancipated minor vary by country and state within the US. This registry will follow applicable laws for the country/state in which the participant resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian through the web-based/mobile application or via courier. Written consent from both parent(s) or both guardian(s) will be obtained in the countries/states in which this is required by local laws and regulations.

At the initial screening with potential participants, the registry web-based/mobile application or registry associate will obtain consent to collect basic information about the individual, such as age and country/state of residence, to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

Additional safeguards for children in clinical investigations

Although this registry involves the collection of information on infants after birth, the registry protocol will be conducted in full consideration of 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research) and applicable regulations in other countries. This registry will ascertain maternal and infant information only via maternal and paediatric HCPs, and no clinical specimens will be collected from the infants; therefore, data collected on infants of women in this pregnancy registry involves no greater than minimal risk to the infants. Although the infants will be too young to provide assent,

the registry protocol will require permission from the mothers, and they will be asked to provide authorisation for release of medical information from their infants' HCPs.

Electronic informed consent process

The website will contain information about the registry and will provide access to the study web-based/mobile application. Via the web-based/mobile application, the woman will register with her computer or mobile device using credentials (i.e., name, email address, and password).

Once the woman has registered, the application will automatically start the consent process. The application will present the contents of the consent in a scrollable window. The woman will review the document, and the application will present the following options: 'Hold', 'Disagree', and 'Sign and Publish'.

If the woman has questions during the consent process, she will be encouraged to stop the consenting process on the application via the 'Hold' button and call the RCC, where study specialists will assist with any questions. The woman can resume completion of the consent process at any time. If the woman does not wish to provide consent, she will be directed to choose the 'Disagree' option, and the process will stop. If the woman wishes to provide consent, she will be directed to choose 'Sign and Publish'.

The application will provide an option for the woman to view or email her completed consent form(s).

After the informed consent, the woman will complete the medical release form(s) and answer some basic medical information questions.

Waiver of documentation of informed consent

The following US regulations indicate that waiver of documentation of informed consent is appropriate for this registry.

As is stated in US CFR, 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorised representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

The research involves no more than minimal risk to the participants. This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in

place to prevent any such breach of confidentiality. Extensive safeguards are in place to ensure that participants' privacy is protected:

a. An adequate plan is provided to protect the identifiers from improper use and disclosure.
b. An adequate plan is provided to remove the identifiers at the earliest opportunity.
c. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research involves no procedures for which written consent is normally required outside the research context. Enrolment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time. The schedule of participant visits and all treatment regimens will be at the discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the participant's medical record.

10.2 Data handling

If the participant (or the participant's LAR) withdraws the previously given informed consent, the participant's data will be handled as follows:

- Data collected will be used as part of the statistical analysis
- Safety events will be reported to Global Safety, Novo Nordisk/health authorities

Data will be collected and handled in accordance with local law and IRB/IEC procedures.

10.3 Institutional Review Boards/Independent Ethics Committee, health authorities, and premature termination of the study

Study-specific documentation (for example, study protocol, Participant Information/Informed Consent Form, participant materials) must be submitted to the relevant national bodies as required by national regulation and procedures in the participating countries.

The study must be approved by the IRB/IEC for each participating country.

In accordance with regulatory requirements, including Good Pharmacovigilance Practices (GVP), the sponsor will inform the health authorities of Wegovy-related AEs.

10.4 Premature termination of the study

The sponsor may decide, in agreement with regulatory authorities, to stop the study or part of the study at any time.

Prior to making a final decision regarding the premature termination of the study, information will be provided to the relevant regulatory authorities.

10.5 Responsibilities

Sponsor

Novo Nordisk A/S, the sponsor, will provide financial support, general oversight, and decision-making for the registry. The sponsor may transfer any or all of its study-related

responsibilities to a contract research organisation and other third parties; however, the sponsor retains overall accountability for these activities.

Principal investigator

The principal investigator is responsible for providing oversight of the registry and all submissions (protocol, amendments) to the IRBs/IECs. The principal investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable regulations. The principal investigator will be available to the sponsor and the SAC for ongoing consultations regarding the review, analysis, and conduct of the registry.

Registry coordination centre

The RCC is responsible for assisting the principal investigator in all aspects of participant recruitment, informed consent, data collection, and management. As is noted in Section 10, the RCC staff is fully trained on and compliant with SOPs regarding the protection of human subjects and data privacy.

11 Management and reporting of adverse events/adverse reactions

Active solicitation of safety information for the registry will be limited to specific maternal, foetal, and infant outcomes (Section 9.1.1) that may be classified as AEs or serious adverse events (SAEs). If the central site (PPD) is made aware of any other safety information than the actively solicited, then these events will also be reported to Novo Nordisk's pharmacovigilance department. Full details on how AEs/SAEs are defined, handled, and reported will be included in the safety and medical management plan.

11.1 Collection of adverse events and other safety information

Safety definitions and a guideline for evaluation of outcome, severity, and causality can be found in Appendix A.

All AEs, including all fatal outcomes that are reported after informed consent is obtained and until the end of study, must be collected and reported by PPD to Novo Nordisk. PPD will contact HCPs to remind them to report t data at certain timepoints throughout the study, at which safety information will be collected.

In addition, if PPD becomes aware of events of overdose, abuse, misuse, medication errors, or occupational exposure related to the study product treatment with or without an associated suspected adverse reaction (AR), this should be reported on the Adverse Event Form. These events will be summarised in the interim and final study reports.

11.2 Reporting of adverse events

AE information will be reported by the HCPs either via phone contact with PPD or by filling in an Adverse Event Form.

The HCP should be encouraged to record/provide the diagnosis, if available. If no diagnosis is available each sign and symptom should be recorded as an individual adverse event. When a diagnosis becomes available, the diagnosis should be reported, and the signs and symptoms covered by the diagnosis should be described.

The central site (PPD) must report AEs (non-serious and serious) to Novo Nordisk within 1 (SAE) or 2 (AE) business day(s) of its knowledge of the event. AEs must be reported using the Adverse Event Form.

The HCP must complete the Adverse Event Form. The form may be completed via telephone with a remote study specialist from PPD, or on paper and forwarded by fax, mail, or electronically in an encrypted manner. Outside of the US, the principal investigator in each country may also complete the form via the EDC application.

11.3 Follow-up on safety information

All SAEs and non-serious ARs must be followed until the outcome of the event or reaction is 'recovered', 'recovered with sequelae', or 'fatal' and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse reactions (SARs), SAEs, or non-serious ARs ongoing at the time of death (that is, the participant dies from another SAE) can be closed with the outcome of

'recovering' or 'not recovered'. Cases can be closed with an outcome of 'recovering' when the participant has completed the study and is expected by the HCP to recover.

All other non-serious AEs must be followed until the outcome of the event is 'recovering', 'recovered', or 'recovered with sequelae' or until the end of study, whichever comes first, and until all queries related to these AEs have been resolved. AEs ongoing at time of death (that is, participant dies from another AE) can be closed with an outcome of 'recovering' or 'not recovered'.

Follow-up information concerning previously reported AEs must be reported by the central site (PPD) on the Adverse Event Form **within 1 (SAE) or 2 (AE) business day(s) of** its knowledge of the follow-up information, but no later than three calendar days (SAE) if the information is received during a weekend or on a public holiday.

If follow-up to previously reported adverse events or other safety information is requested by Novo Nordisk, PPD will be responsible for contacting the reporting HCP for more information. PPD must make and document (electronically or in handwriting) at least two attempts to obtain the required follow up information within 60 days of receiving the request from Novo Nordisk.

PPD must ensure that the worst-case severity and seriousness is kept consistent through the series of forms used for safety reporting. The follow-up information collected from the HCP should only include new (update and/or additional) information that reflects the situation at the time of the HCP's signature. The information provided by PPD to Novo Nordisk will include all information related to the event, with updated information highlighted.

11.4 Regulatory reporting requirements for adverse events

Sponsor's assessment of expectedness of AEs is done according to the Company Core data sheet for Novo Nordisk product(s).

In addition, local expectedness assessment of AEs is done according to local reference safety information document for reporting to national health authorities where required by local legislation.

11.5 Collection and reporting of technical complaints

Technical complaints on Novo Nordisk product, Wegovy, that occur from the first time of usage of the product(s) until the last time of usage of the product(s), and that are considered related to and according to study collected AE/SAE or AR/SAR must be reported to Novo Nordisk along with safety information on the Adverse Event Form within the timelines given for reporting of the AE/SAE or AR/SAR, as described in Section 11.2.

Technical complaints on Wegovy not related to an AE/SAE or AR/SAR may be reported to Novo Nordisk affiliate via the spontaneous reporting system.

11.6 Collection, storage and shipment of technical complaint samples

PPD must collect the technical complaint sample, coordinate initiation of the shipment to Novo Nordisk, and ensure that the sample is sent in accordance with local regulations as soon as possible

to Novo Nordisk. A copy of the Adverse Event Form describing the complaint must be sent with the sample, if available.

PPD must ensure that the technical complaint sample contains the batch or lot number. Storage and shipment of the technical complaint sample should be done in accordance with the conditions prescribed for the product.

11.7 Reporting of pregnancies in female participants and adverse events in pregnant participants, foetuses, or new-born infants

Female participants taking Wegovy:

Pregnancy must be reported by PPD to Novo Nordisk **within 2 business days** of the central site (PPD)'s first knowledge of the pregnancy.

Elective termination of the pregnancy or any AEs or pregnancy complications experienced by the pregnant female should be reported by PPD to Novo Nordisk as AEs or SAEs within the timelines specified in Section 11.2 for reporting of AEs/SAEs. Elective terminations and SABs will always be considered SAEs and should be reported as such.

The outcome of the pregnancy and follow-up information on the new-born, including medication during lactation, should be reported by PPD to Novo Nordisk **within 2 business days** of PPD's first knowledge of the pregnancy outcome and follow-up information.

In case of abnormal pregnancy outcome, AEs experienced by the foetus or new-born infant, or ARs in an infant exposed via breast milk, then an Adverse Event Form should also be completed using the infant identification number, which is equivalent to the mother's identification numbers plus a letter (e.g., A, B, C) at the end. The timelines for reporting from PPD to Novo Nordisk are the same as the ones specified in Section 11.2 for reporting AEs/SAEs.

11.8 Precautions/Over-dosage

SAEs have been observed in some populations and include risk of thyroid c-cell tumours, acute pancreatitis, acute gallbladder disease, hypoglycaemia, acute kidney injury, hypersensitivity, diabetic retinopathy complications, heart rate increase, and suicidal behaviour and ideation. Further details can be found in the product insert.[78]

Overdoses have been reported with other GLP-1 RAs. Effects have included severe nausea, severe vomiting, and severe hypoglycaemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, considering the long half-life of Wegovy of approximately 1 week.

11.9 Novo Nordisk safety committee

Novo Nordisk has an internal Semaglutide Obesity and non-alcoholic steatohepatitis (NASH) safety committee that performs ongoing safety surveillance of the study product.

11.10 External safety committee

11.10.1 Scientific Advisory Committee

The SAC is responsible for overseeing the scientific affairs of the registry, including its ongoing monitoring. The SAC is an independent (not associated with the Sponsor) group of recognised experts in the fields of teratology, epidemiology, maternal and foetal medicine, and therapeutic areas from academia and private practice. They will meet twice prior to the finalisation of each annual summary report: first, to review and classify reported MCMs (as described in Section 9.3.3) prior to annual analyses, and again after analyses to review the accumulated body of data from the registry and to carry out any actions required, including review and interpretation of interim data analyses, reports, and publications of registry data. The SAC may meet on ad hoc occasions if indicated to address potential signals or other issues that arise during the course of the registry.

A critical function of the SAC is to detect potential signals or patterns, to evaluate them, and to determine the necessary course of action if a signal is generated. To aid in this function, the registry has adopted a plan used by other registries, which applies the 'Rule of Three' for detecting a potential signal and the 'threshold' strategy for determining the appropriate course of action [79]. The 'Rule of Three' convention specifies that once 3 like MCMs have accumulated with any specific exposure, these cases are flagged for immediate review. For a specific defect that occurs at a rate of <1/700 in the general population, the likelihood of 3 defects occurring in a cohort of up to 600 live births by chance alone is <5%. To ensure prompt, responsible, and appropriate action in the event of a potential signal, the registry will employ the strategy of 'threshold' based on the Council of International Organizations for the Medical Sciences.[80] The threshold for action will be determined by the extent of certainty about the cases and tempered by the specifics of the cases. Novo Nordisk will be notified within 2 working days upon identification of a new safety signal by the SAC.

In addition to the above activities, the SAC will design and implement strategies to heighten awareness of the registry. The responsibilities of the SAC will be described in a charter to which each SAC member will agree.

11.10.2 Birth defect evaluators

As described in Section 9.3.3, a panel of 3 evaluators, with appropriate training and credentials and blinded to exposure, will adjudicate congenital anomalies for the registry. Two evaluators will independently review all congenital anomalies reported to the registry and classify them using the CDC's MACDP (and European Registration of Congenital Anomalies and Twins). If there is a discrepancy, a third evaluator will independently review and code the case, serving as tie breaker. Additionally, the birth defect evaluators will provide their opinions regarding the timing of the development of observed defects. These reviews will occur soon after the MCM is reported. Additional reviews will occur if new information is received on the case. Novo Nordisk will not be involved in any activities related to case review or adjudication.

12 Plans for disseminating and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of Wegovy. All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other HCPs who are conducting other studies with the study product, if deemed necessary by Novo Nordisk.

12.1 Registration of study information

In accordance with Novo Nordisk's commitment to transparency in clinical activities, this study will be registered on ClinicalTrials.gov and www.novonordisk-trials.com and added to the FDA's listing of pregnancy registries on www.fda.gov no later than at enrolment of the first study participant. At least one study site per participating country will be included in the study registration.

For studies that include data collected also retrospectively, the study is to be registered prior to the first capture of data.

This non-interventional PASS will be registered in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register®) maintained by the European Medicines Agency (EMA) and accessible through the EMA's web portal.

12.2 Communication and publication

Novo Nordisk commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means.

At the end of the study, one or more publication(s) may be prepared in collaboration with Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property and reserves the right not to release interim results or data until a study report is available. The results of this study will be subject to public disclosure on external websites according to international regulations, as reflected in the Novo Nordisk Commitment to share information about clinical studies.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the investigator from each site will be named in the acknowledgement.

The investigator must ensure submission of the results of the study (either abstracts or full study report) to IRB/IEC (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In all cases, the study results must be reported in an objective, accurate, balanced, and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the HCPs' and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

Novo Nordisk maintains the right to be informed of any plans for publication and to review any scientific paper, presentation, communication, or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within 4 weeks from receipt of the planned communication. For PASS studies in Europe, an advance agreement on publication policy between Novo Nordisk and investigator allows the latter to independently prepare publications based on the study results. Also PASS studies in Europe require Novo Nordisk to communicate to the EMA and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication. This is to allow national competent authorities to review in advance the results and interpretations to be published.

12.3 Healthcare provider's access to data and review of results

As owners of the study database, Novo Nordisk has discretion to determine who will have access to the database.

Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same disease and/or product studied in this study.

13 References

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Appendix A Safety definition and evaluation of outcome, severity and causality

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects

Adverse Event (AE)

Any untoward medical occurrence in a participant or clinical investigation participant administered/using a product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not it is considered to be related to the product. An AE may be associated with the use of a drug, a medical device or both.

Adverse reaction (AR)

An Adverse reaction (AR) is a response to a medicinal product which is noxious and unintended. This includes AR which arises from:

- The use of a product within the terms of the marketing authorisation
- The use of a product outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors.
- Occupational exposure

An AR may be associated with the use of a drug, a medical device or both. An AR is an AE for which the causal relationship between the product and the AE is suspected; that is judged to be possible or probable by either Novo Nordisk or the reporter.

Causality assessment

Probable: good reason and sufficient documentation to assume a causal relationship

Possible: a causal relationship is conceivable and cannot be dismissed

Unlikely: the event is most likely related to an aetiology other than Wegovy

Hospitalisation

When a participant stays at the hospital for treatment or observation for more than 24 hours. However, medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation.

Medication error

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the participant. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failure.

Medication errors can therefore be:

- Associated with an AR
- Not associated with an AR
- An intercepted medication error ('near miss') is when an intervention caused a break in the chain of events in the treatment process before reaching the participant which would have resulted in a 'potential' adverse drug reaction. This intervention has prevented actual harm being caused to the participant; for example, a wrongly prepared medicine was actually not administered to the participant because the error was noticed by the nurse.
- A potential medication error which is recognition of circumstances that could lead to a medication error and may or may not involve a participant. The term potential medication error refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process. An example is a pharmacist who noticed that the names of two medicines are similar and could clearly lead to product name confusion, but no participant was actually involved or has taken the medicine.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used in a manner not in accordance with the authorised product information.

Non-serious

An AE or AR that does not fulfil the requirement for being an SAE or SAR.

Occupational Exposure

An exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release of a finished product.

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation. Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of participants (for example, a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used.

Outcome categories and definitions

- Recovered/resolved – The participant has fully recovered from the condition, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the participant has signed the informed consent.
- Recovering/resolving – The condition is improving, and the participant is expected to recover from the event. This term is only applicable if the participant has completed the study or has died from another AE.

- Note: Non-serious AEs can be closed with the outcome recovering/resolving at any time during the study.

- Recovered/resolved with sequelae – The participant has recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If a sequela meets a SAE criterion, the AE must be reported as a SAE.
- Not recovered/not resolved – The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known.
- Fatal – (only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AE in a participant before he/she died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae', or 'not recovered/not resolved'. An AE with fatal outcome must be reported as an SAE.
- Unknown – This term should only be used in cases where the participant is lost to follow-up.

Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

Serious Adverse Event (SAE)

An SAE is an experience that at any dose results in any of the following:

- Death
- Life-threatening experience (actual risk not hypothetically)
- Inpatient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity or is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalisation may be considered an SAE, when based upon appropriate medical judgement - they may jeopardise the participant or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Suspicion of transmission of infectious agents must always be considered an SAE.

Note: Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE

Serious Adverse Reaction (SAR)

Is an AE that fulfils the criteria for both a SAE and an AR

Severity assessment definitions

Mild – No or transient symptoms, no interference with the participant's daily activities.

Moderate – Marked symptoms, moderate interference with the participant's daily activities.

Severe – Considerable interference with the participant's daily activities, unacceptable.

Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an adverse event, but does not concern the adverse event itself.

Appendix B Congenital Malformation Coding References

MACDP Birth Defects Code List:

https://www.cdc.gov/ncbddd/birthdefects/documents/bpa-codes-rev2021-508c.xlsx

CDC List of Minor Congenital Anomalies:

https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html

EUROCAT Coding and Classification:

https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/JRC-EUROCAT-Full%20Guide%201%204%20version%2022-Nov-2021.pdf

Appendix C List of Teratogens

Table 13-1 provides a list of known teratogens. This list has been developed and will be continually updated based on the data available in the TERIS database of teratogenic agents and recent publications.[67 68 69 70]

Participants will be considered exposed to teratogens or investigational medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time period based on the product's half-life). If the teratogen or investigational medication has a relatively short half-life (<3 days), participants will be considered exposed during pregnancy if a dose is taken during the period of time just prior to conception, between the first day of the LMP and the DOC. If the teratogen or investigational medication has a longer half-life, participants will be considered exposed during pregnancy if a dose is taken prior to conception within a time period equivalent to 5 times the product's half-life.

Table 13-1 Known Teratogens

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
Androgen	Methyltestosterone	2.5 to 3.5 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Testosterone	Per Google: Plasma half-life of testosterone ranges from 10 to 100 min. The cypionate and enanthate esters of testosterone have longer durations of action than testosterone. Cypionate half-life is about 8 days.	Variable	1st, 2nd, and 3rd trimesters
	Mesterolone	12 to 13 h	LMP to DOC	Not in TERIS
	Nandrolone	144 to 288 h	2 months prior to DOC to DOC	Not in TERIS
	Oxandrolone	13.3 h	LMP to DOC	Not in TERIS
	Prasterone	216 h	45 days prior to DOC to DOC	Not in TERIS
Angiotensin II receptor antagonist	Candesartan	9 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Eprosaratan	5 to 9 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Irbesartan	11 to 15 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Losartan	2 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Olmesartan	13 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Tasosartan	Not available, but half-life of	LMP to DOC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
		angiotensin II receptor antagonists range from 1 to 3 days		
	Telmisartan	24 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Valsartan	6 h	LMP to DOC	1st, 2nd, and 3rd trimesters
Angiotensin-converting enzyme inhibitors	Benazepril	10 to 11 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Captopril	2 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Cilazapril	9 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Enalapril	11 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Fosinopril	11.5 to 14 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Lisinopril	12.6 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Moexipril	2 to 9 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Perindopril	0.8 to 1 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Quinapril	3 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Ramipril	13 to 17 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Trandolapril	6 h	LMP to DOC	1st, 2nd, and 3rd trimesters
Antiarrhythmic	Amiodarone	61 days	10 months prior to DOC to DOC	1st, 2nd, and 3rd trimesters
Antibiotic	Sulfamethoxazole/ Trimethoprim	8 to 10 h	3 months prior to DOC to DOC	3 months prior to conception and 1st trimester for MCMs and 2nd trimester for preterm birth and low birth weight
Anticoagulant	Acenocoumarol	8 to 11 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Dicumarol	5 to 28 h	LMP to DOC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Phenprocoumon	4 to 6 days	1 month prior to DOC to DOC	1st, 2nd, and 3rd trimesters
	Warfarin	40 h	LMP to DOC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Fenprocoumon	0.75 h	LMP to DOC	1st trimester
Anticonvulsant	Lamotrigine	Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy)	LMP to DOC	1st, 2nd, and 3rd trimesters
	Trimethadione/ Paramethadione	Paramethadione—12 to 24 h Trimethadione—11 to 16 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Valproic Acid/Valproate	4 to 16 h	LMP to DOC	Primarily 1st trimester, but MCMs have been associated with 2nd and 3rd trimester exposures.
	Carbamazepine	18 to 65 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Ethotoin	3 to 9 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Phenytoin/Fosphenytoin	15 min	LMP to DOC	1st, 2nd, and 3rd trimesters
	Primidone	10 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Topiramate	21 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Ethosuximide	17 to 56 h	LMP to DOC	Unknown
	Oxcarbazepine	Oxcarbazepine: immediate-release formulations, about 2 h; extended-release tablet, 7 to 11 h Active metabolite, 10–monohydroxy: 9 to 11 h	LMP to DOC	Unknown
	Sultiam	24 h	LMP to DOC	Not in TERIS
	Vigabatrin	10.5 h	LMP to DOC	Unknown
	Phenobarbital	70 to 140 h	1 month prior to DOC to DOC	1st, 2nd, and 3rd trimesters
	Methylfenobarbital	34 h	LMP to DOC	Not in TERIS
Antifungal	Fluconazole[b]	30 h	LMP to DOC	2 weeks before conception and 1st trimester
Antineoplastic	Aminopterin	12 to 24 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Methotrexate[c]	55 h	6 months prior to DOC to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cytarabine	1 to 3 h	LMP to DOC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Daunorubicin	Per Google: The plasma half-life of daunorubicin averages 45 min in the initial phase and 18.5 h in the terminal phase. By 1 h after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has as average terminal plasma half-life of 26.7 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Mechlorethamine	11 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Mercaptopurine[c]	47 min	LMP to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures 'during pregnancy'
	Vinblastine	24.8 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Cyclophosphamide	3 to 12 h	LMP to DOC	1st trimester
	Altretamine	4.7 to10.2 h	LMP to DOC	Unknown
	Amsacrine	5 h	LMP to DOC	Unknown
	Bevacizumab	480 h	100 days prior to DOC to DOC	Unknown
	Bleomycin	2 h	LMP to DOC	Unknown
	Bortezomib	40 to 193 h	40 days prior to DOC to DOC	Unknown
	Busulfan	2.3 to 3.4 h	LMP to DOC	Not in TERIS
	Capecitabine	0.75 h	LMP to DOC	Unknown
	Carboplatin	24 h	LMP to DOC	Not in TERIS
	Carmustine	IV, 22 min, 1.4 min (1st phase), 17.8 min (2nd phase)	LMP to DOC	Unknown
	Cetuximab	112 h	24 days prior to DOC to DOC	Unknown
	Chlorambucil	1.5 h	LMP to DOC	Not in TERIS
	Cisplatin	120 h	25 days prior to DOC to DOC	Not in TERIS
	Cladribine	5.4 h	LMP to DOC	Not in TERIS
	Clofarabine	5.2 h	LMP to DOC	Unknown
	Dacarbazine	5 h	LMP to DOC	Unknown
	Dactinomycin	36 h	LMP to DOC	Not in TERIS

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Dasatinib	3 to 5 h	LMP to DOC	Unknown
	Docetaxel	11.1 h	LMP to DOC	Unknown
	Doxorubicin	20 to 48 h	LMP to DOC	Unknown
	Epirubicin	31.1 h ± 6 h to 35.3 h ± 9 h	LMP to DOC	Not in TERIS
	Erlotinib	36.2 h	LMP to DOC	Unknown
	Estramustine	10 to 20 h	LMP to DOC	Not in TERIS
	Etoposide	4 to 11 h	LMP to DOC	Unknown
	Fludarabine	20 h	LMP to DOC	Unknown
	Fluorouracil	8 to 20 min	LMP to DOC	Unknown
	Gemcitabine	1.7 to 19.4 h	LMP to DOC	Not in TERIS
	Hydroxycarbamide	2 to 4.5 h	LMP to DOC	Unknown
	Idarubicin	20 to 22 h	LMP to DOC	Not in TERIS
	Ifosfamide	15 h	LMP to DOC	Unknown
	Imatinib	18 h	LMP to DOC	Unknown
	Irinotecan	6 to 12 h	LMP to DOC	Unknown
	Lapatinib	24 h	LMP to DOC	Unknown
	Lomustine	16 to 48 h	LMP to DOC	Unknown
	Melphalan	10 to 75 min	LMP to DOC	Unknown
	Mitomycine	46 min	LMP to DOC	Not in TERIS
	Mitoxantrone	23 to 215 h	45 days prior to DOC to DOC	Not in TERIS
	Nelarabine	Adults: prodrug: 30 min; ara-G: 3 h	LMP to DOC	Unknown
	Oxaliplatin	392 h	3 months prior to DOC to DOC	Unknown
	Paclitaxel	13 to 52 h	LMP to DOC	Not in TERIS
	Pemetrexed	3.5 h	LMP to DOC	Unknown
	Pentostatin	5.7 h	LMP to DOC	Not in TERIS
	Procarbazine	(IV), approximately 10 min	LMP to DOC	Not in TERIS
	Raltitrexed	260 h	2 months prior to DOC to DOC	Not in TERIS
	Sorafenib	25 to 48 h	LMP to DOC	Unknown
	Streptozotocin	Systemic: 35 min unchanged drug; 40 h metabolites	LMP to DOC	Not in TERIS
	Sunitinib	40 to 60 h	LMP to DOC	Unknown
	Tegafur	6.7 to 11.3 h	LMP to DOC	Not in TERIS
	Temozolomide	1.8 h	LMP to DOC	Unknown
	Teniposide	5 h	LMP to DOC	Not in TERIS
	Thioguanine	80 min	LMP to DOC	Not in TERIS
	Thiotepa	1.4 to 3.7 h	LMP to DOC	Not in TERIS
	Topotecan	2 to 3 h	LMP to DOC	Unknown

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Vincristine	85 h	18 days prior to DOC to DOC	Unknown
	Vindesine	2.9 h	LMP to DOC	Not in TERIS
	Vinorelbine	27.7 to 43.6 h	LMP to DOC	Not in TERIS
	Lenalidomide	3 h	LMP to DOC	Not in TERIS
Antithyroid	Propylthiouracil	1 to 2 h	LMP to DOC	1st and 2nd trimesters
	Methimazole	4.9 to 5.7 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Radioiodine (I-131)	192 h	40 days prior to DOC to DOC	Unknown
Antiviral	Ribavirin	120 to 170 h	36 days prior to DOC to DOC	1st, 2nd, and 3rd trimesters
Oestrogen	Diethylstilbesterol	Per Google: Once in the human body, DES reaches peak concentration within 20 to 40 min, having a primary half-life of 3 to 6 h. It has a terminal half-life of 2 to 3 days due to entero-hepatic circulation, and is primarily excreted in urine	LMP to DOC	1st, 2nd, and 3rd trimesters
Immunomodulatory agent	Mycophenolate mofetil	16 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Thalidomide	5 to 7 h	1 month prior to DOC to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Penicillamine	2 to 4 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Azathioprine[c]	5 h	LMP to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures 'during pregnancy'
	Leflunomide	432 to 456 h	3 months prior to DOC to DOC	Unknown
	Mycophenolic acid	8 to 16 h	LMP to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures 'during pregnancy'
Mood stabiliser	Lithium	24 h	LMP to DOC	1st, 2nd, and 3rd trimesters
Prostaglandins analogue	Misoprostol	20 to 40 min	LMP to DOC	1 month prior to conception and 1st,

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
				2nd, and 3rd trimesters
Retinoid	Alitretinoin	1 to 3 h	LMP to DOC	Unknown
	Tretinoin	0.5 to 2 h	LMP to DOC	Unknown
	Vitamin A	TERIS only notes 'long half-life'; 75 days per Google search	12 months prior to DOC to DOC	1st, 2nd, and 3rd trimesters
	Acitretin	50 to 60 h	2 years prior to DOC to DOC	2 years prior to stopping treatment and throughout pregnancy, especially 1st trimester
	Etretinate	120 days to 3 years	10 years prior to DOC to DOC	10 years prior to stopping treatment and throughout pregnancy, especially 1st trimester
	Isotretinoin	10 to 12 h	1 month prior to DOC to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tazarotene	18 h	LMP to DOC	Unknown
	Retinol	2 to 9 h	12 months prior to DOC to DOC	12 months prior to conception and 1st trimester
Steroid	Danazol	9.7 to 23.7 h	LMP to DOC	1st, 2nd, and 3rd trimesters
Tetracycline antibiotic	Demeclocycline	10 to 17 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Oxytetracycline	6 to 11 h	LMP to DOC	1st, 2nd, and 3rd trimesters
	Tetracycline	6 to 11 h	LMP to DOC	2nd and 3rd trimesters; limited data for 1st trimester exposure
	Chlortetracycline	5.6 h	LMP to DOC	Unknown
	Doxycycline	18 to 22 h	LMP to DOC	Unknown
	Methacycline	14 to 22 h	LMP to DOC	Unknown
	Minocycline	11 to 24.31 h	LMP to DOC	Unknown
	Tigecycline	42.4 h	LMP to DOC	Unknown

[a]A woman will be considered exposed during the 1st trimester, if a dose is taken during this pre-conception exposure window. [b] Only applies to ≥2 doses during pregnancy. [c]Teratogenic risk is low; however, exposure during pregnancy may be associated with other adverse outcomes, including preterm birth and intrauterine growth restriction.

Abbreviations: ara-G = guanine nucleoside analogue; DES = diethylstilbesterol; IV = intravenous; MCM = major congenital malformation; TERIS = Teratogen Information System

ANNEX 1 List of Standalone Documents

Not applicable.

ANNEX 2 ENCePP Checklist (Revision 4) for Study Protocols

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Wegovy® (semaglutide 2.4 mg) Pregnancy Registry Study: A Prospective Cohort Study to Investigate Safety Outcomes of Exposure to Wegovy During Pregnancy

EU PAS Register® number: Study not yet registered
Study reference number (if applicable): NN9536-4937

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[a]	☒	☐	☐	6
1.1.2 End of data collection[b]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6; 9.7.3
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[a] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[b] Date from which the analytical dataset is completely available.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.1
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8; 9.2.1
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7.2.5
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	N/A

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.2; 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.2; 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.2; 9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.4; 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.4; 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	Will be addressed in SAP
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	Will be addressed in SAP

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☐	☒	☐	Will be addressed in SAP
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	N/A

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2.5
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9.9 – misclassification expected to be minimal
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6; 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11.10.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	9.6; 10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	6; 9.7.3
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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