NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Pregnancy and Infant Outcomes Following Exposure to PAXLOVID: A Post-Authorization Safety Study
Protocol number	C4671038
Protocol version identifier	V4.0
Date	20 NOV 2024
EU Post Authorization Study (PAS) register number	EUPAS106321
Active substance	Nirmatrelvir/ritonavir (ATC: J05AE30)
Medicinal product	PAXLOVID™
Research question and objectives	Research question: What is the risk of pregnancy outcomes of interest, and infant outcomes of interest, among pregnant women exposed to PAXLOVID, exposed to other coronavirus disease 2019 (COVID-19) therapies, and among pregnant women with COVID-19 unexposed to any therapies? Primary objective: To estimate the risk of major congenital malformation [MCM] among pregnant women exposed to PAXLOVID (and not other COVID-19 treatments) during pregnancy (Cohort 1), pregnant women not exposed to PAXLOVID but exposed to other COVID-19 treatments (Cohort 2), and pregnant women with COVID-19 not exposed to any COVID-19 treatments (Cohort 3). Secondary objectives:

	1. To estimate the risk of pregnancy outcomes (spontaneous abortion [SA], induced termination, stillbirth, livebirth) and the risk of infant outcomes (preterm birth, small for gestational age [SGA], postnatal growth deficiency and infant developmental delay) for livebirths among the 3 study cohorts. 2. Pending sufficient sample size, to compare the risk of pregnancy and infant outcomes in pregnant women in Cohort 1 compared to, separately, Cohort 2 and Cohort 3.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting-enzyme
AE	adverse event
AEM	adverse event monitoring
AMA	American Medical Association
ASD	atrial septal defect
ATT	average treatment effect among the treated
AVSD	atrioventricular septal defect
CHD	congenital heart disease
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
COVID-19	coronavirus disease 2019
CPT®	Current Procedural Terminology
DAPI	Dynamic Assessment of Pregnancies and Infants
DCT	data collection tool
ECD	estimated conception date
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
EU	European Union
EUA	Emergency Use Authorization
EUROCAT	European Surveillance of Congenital Malformations
FDA	US Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HIV	human immunodeficiency virus
ICD-10	International Classification of Diseases, 10th revision
IPTW	inverse probability of treatment weighted
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program

Abbreviation	Definition
MCM	major congenital malformation
NDC	National Drug Code
NIS	non-interventional study
ORD	Optum Research Database
PAS	post-authorization studies
PASS	post-authorization safety study
PDA	patent ductus arteriosus
PK	pharmacokinetic
PPV	positive predictive value
RR	relative risk
SA	spontaneous abortion
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standardized difference
SGA	small for gestational age
SOP	Standard Operating Procedure
TAPVR	total anomalous pulmonary venous return
UB	universal billing
US	United States
VSD	ventricular septal defect
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title

Pregnancy and Infant Outcomes Following Exposure to PAXLOVID: A Post-Authorization Safety Study

Version: V4.0

Date: 20 Nov 2024

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Rationale and background

On 22 December 2021, the United States (US) Food and Drug Administration (FDA) granted Pfizer's antiviral PAXLOVID™ (a combination of nirmatrelvir and ritonavir) emergency use authorization (EUA) for mild-to-moderate COVID-19 in patients aged 12 years or older who are at high risk for progression to severe COVID-19. On 25 May 2023, the US FDA granted full approval for PAXLOVID under the same indication in patients aged 18 years or older (FDA 2023). The safety of PAXLOVID in pregnant women and their offspring is unknown. In addition, there are currently no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

This protocol describes a study to evaluate the safety of PAXLOVID in pregnant women and their infants (up to 1 year of age) in a real-world setting. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the US FDA.

Research question and objectives

The research question for this study is: What is the risk of pregnancy outcomes of interest, and infant outcomes of interest, among pregnant women with COVID-19 exposed to PAXLOVID, and among pregnant women with COVID-19 unexposed to PAXLOVID?

The primary objective of this study is to estimate the risk of MCM among pregnant women who are exposed to PAXLOVID (and not other COVID-19 treatments) during pregnancy (Cohort 1), pregnant women not exposed to PAXLOVID but exposed to other COVID-19 treatments (Cohort 2), and pregnant women with COVID-19 not exposed to any COVID-19 treatments (Cohort 3).

The secondary objectives of this study are to:

1. Estimate the risk of pregnancy outcomes (SA, induced termination, stillbirth, livebirth) and the risk of infant outcomes (preterm birth, SGA, postnatal growth deficiency, and infant development delay) for livebirths among the 3 study cohorts.
2. Pending sufficient sample size (Section 9.5), to compare the risk of pregnancy and infant outcomes in Cohort 1 compared to, separately, Cohort 2 and Cohort 3.

Exposure (or lack thereof) to COVID-19 treatments will be assessed via the presence of pharmacy and/or medical claims in the Optum Research Database (ORD).

Study design

This is an observational cohort study using administrative healthcare claims data of commercially insured persons in the US (the ORD). Medical records will be retrieved for the adjudication of select outcomes from the subset of patients for whom access is available.

Population

The base population for this study will include pregnancies among women that began (based on the estimated conception date [ECD], equal to the date of last menstrual period [LMP] + 14 days) between 01 March 2021 and 01 December 2025. For the assessment of infant outcomes, pregnancies that begin on or before 01 April 2025 will be eligible for inclusion.

From the base population, each qualifying pregnancy will be classified according to the COVID-19 treatment received during the following relevant exposure windows:

- First trimester exposure window
- Pregnancy exposure window

Three mutually exclusive study exposure cohorts will be created based on received COVID-19 treatment during each exposure window (first trimester, full pregnancy) for a total of 6 study cohorts:

- Cohort 1 (PAXLOVID cohorts): at least 1 dispensing of PAXLOVID within the relevant exposure window, and no evidence of comparator medications within the relevant exposure window
- Cohort 2 (Treated Comparator Only cohorts): no evidence in the study database of a dispensing of PAXLOVID, and dispensing or administration of at least 1 of the following treatments indicated for the treatment of mild-to-moderate COVID-19 within the relevant exposure window:
  - Remdesivir
  - Bebtelovimab

- Cohort 3 (Untreated Comparator cohorts): no evidence in the study database of a dispensing or administration of any COVID-19 treatments within the relevant exposure window

The lists of approved and/or authorized COVID-19 therapies for the definition of the treated comparator will be periodically reviewed and updated in the statistical analysis plan (SAP) as necessary.

Variables

Exposures

Exposure to COVID-19 therapies used to define the study cohorts will be identified through the presence of National Drug Codes (NDCs) and/or drug administration codes.

Outcomes

Outcomes will be identified through the presence of corresponding codes on insurance claims.

Pregnancy outcomes:

- SA
- Induced termination
- Stillbirth
- Livebirth

Infant outcomes:

- MCM (primary outcome)
- SGA
- Preterm birth
- Postnatal growth deficiency
- Infant developmental delay

For the assessment of pregnancy outcomes, pregnancies will be followed from ECD until the earliest of: disenrollment from the health plan, pregnancy end, or 01 September 2026. For the assessment of infant outcomes, infants will be followed from the date of delivery until the earliest of: disenrollment or 1 year of age.

Covariates

Pregnancies will be described with respect to demographic, comorbidity, treatment history, proxies for COVID-19 severity (Garry et al. 2022), predictors of treatment choice, and co-medication indicators, as well as other potential confounders and risk factors. In this study, all covariates will be determined from claims data (without respect to outcome status).

Data sources

The patients included in this study will be drawn from the ORD containing eligibility, pharmacy claims, and medical claims data from a large, geographically diverse US health plan. For 2021, data are available for approximately 12.6 million individuals with medical and pharmacy coverage.

In the event that the accrual of PAXLOVID-exposed pregnancies is slower than expected, the addition of other data partners may be considered.

Study size

Detection of a relative risk (RR) of > 2.0 at 80% power requires a minimum of 127 PAXLOVID-exposed pregnancies for SA, 251 for SGA and preterm birth, and 2,212 for stillbirth (the rarest of the outcomes), with 1:2 matching. A minimum of 938 PAXLOVID-exposed pregnancies during the first trimester (the relevant etiologic window for MCMs) are required for the primary outcome of MCM. Fewer PAXLOVID-exposed pregnancies are required to detect an RR of > 2.5 at 80% power: 63 for SA, 127 for SGA and preterm birth, 1,142 for stillbirth, and 482 (exposed to PAXLOVID during first trimester) for MCM.

Between 2020 and mid-2022, 35,303 of 460,062 pregnancies (7.7%) identified in the ORD had a COVID-19 diagnosis code. Of the 35,303 COVID-19 positive pregnancies, 409 (1.2%) pregnancies were exposed to bebtelovimab, while 382 (1.1%) were exposed to remdesivir. A total of 1,021 pregnancies were exposed to PAXLOVID, with roughly half of these also being diagnosed with COVID-19. Annual interim reports will provide information on the uptake of PAXLOVID and the ability to reach adequate sample size for the study outcomes. If needed, a data partner may be added to increase statistical power.

Data analysis

For the annual interim reports, Optum will identify the number of pregnancies accrued into each of the exposure cohorts by exposure window. Eligible pregnancies included in each of the study cohorts will be described with respect to demographic characteristics (age at the ECD, geographic region, etc.), year of cohort entry, and select comorbidities. Interim reports will also include a tabulation of claims-based outcomes, by cohort and exposure window. The number of claims-identified outcomes available for medical record request will also be indicated.

For the final analysis, descriptive summaries of baseline variables and prevalence of pregnancy and infant outcomes will be prepared for pregnancies in each cohort and exposure window. Adjudication results will be described including the number of medical records sought and retrieved. Pending sufficient sample size, comparative analyses will be undertaken for each of the pregnancy and infant outcomes, comparing the PAXLOVID-exposed pregnancy cohorts to the comparator pregnancy cohorts.

Propensity scores will be developed and used to account for potential covariate imbalance between the study cohorts via inverse probability of treatment weighted (IPTW) regression.

Sensitivity analyses will assess alternate exposure definitions and/or quantify the potential bias associated with unmeasured confounders or the occurrence of MCM leading to pregnancy loss.

Milestones

The first interim report will be submitted in March 2024 and prepared annually thereafter. Access to final study data, including outcome validation conducted for a subset of medical records, is expected by December 2027. The expected date of the final study report is planned for July 2028.

5. AMENDMENTS AND UPDATES

Amendment number; date	Section	Update	Rationale
1.0; 14 Feb 2024	Study information; Section 4; Section 8; Section 9.1; Figure 2; Section 9.3.1; Section 9.3.1.2; Section 9.7.2.2; Table 4	Postnatal growth deficiency and infant developmental delay added as secondary study outcomes.	Requested by FDA as the standard approach in pregnancy safety studies.
1.0; 14 Feb 2024	Section 4; Section 7	Date for full approval from US FDA added.	Reflect current approval status.
1.0; 14 Feb 2024	Section 6	Planned dates for the end of data collection and submission of interim reports revised.	Milestones reverted to previously planned dates for interim reports; end of data collection revised to meet reporting timeline requirements.
1.0; 14 Feb 2024	Section 9.3.3.1	Expanded description of baseline window definition.	Clarify the definition on the baseline period, depending on the timing of treatment initiation or COVID-19 diagnosis.
1.0; 14 Feb 2024	Section 9.3.3.2.1	Added covariates: • Calendar time of index date and duration (first COVID-19 treatment initiation or COVID-19 infection) • Duration between index date and ECD	Covariates to be included in the descriptive analyses and considered for inclusion in the comparative analysis, as calendar time of COVID-19 infection and timing of COVID-19 infection during pregnancy could both have impact on maternal and infant outcome.
1.0; 14 Feb 2024	Section 4; Section 9.5; Table 1, Table 2	Study size estimates updated using the Chi-square method.	The Chi-square approach for calculating sample sizes required for relative risk estimates was considered to be more appropriate that the Kelsey formula originally used, which the FDA considered better suited to test differences in proportion rather than relative risk.
1.0; 14 Feb 2024	Figure 1; Figure 2	Baseline window description updated.	Original figures 1 and 2 indicated ECD included in baseline period for all patients, which contradicts the updated definition in Section 9.3.3.1.
1.0; 14 Feb 2024	Annex 2	Operational definitions provided for Postnatal growth deficiency and infant developmental delay.	Consistency with information provided in Annex 2 for other study endpoints.

Amendment number; date	Section	Update	Rationale
2.0; 22 Jul 2024	Section 4, Section 8	Primary objective wording updated to align with cover page summary and research question	Internal consistency of protocol
2.0; 22 Jul 2024	Section 6; Section 12; Annex 2	References to EU PAS Register replaced with HMA-EMA Catalogues of RWD Studies (note, references to 'EU PAS Register Number' remain	Administrative update to reflect changes implemented to EU PAS registration system subsequent to V 2.0 C4671038 study protocol
2.0; 22 Jul 2024	Abstract; Section 9.1; Figure 2; Section 9.2.7.	Revision of eligibility window for pregnancy exposure to end on 01 Apr 2025 instead of 01 Dec 2025, in order to allow follow-up period for infants of up to 1 year of age	Per protocol version 1.0, pregnancy exposures were based on ECD from March 2, 2021 to December 1, 2025; therefore, those with ECD on December 1, 2025 would not have infant follow-up for 1 year after birth by the end of the study period (November 30, 2026).
2.0; 22 Jul 2024	Section 9.2.6.3; Section 9.3.3.1	The index date for Cohort 3 has been specified as the date of COVID-19 diagnosis plus the treatment interval (the median interval between COVID-19 diagnosis and treatment in Cohort 1;	Use of COVID-19 diagnosis date for cohort 3 may lead to underestimated risk of outcomes related to early pregnancy termination; addition of median interval between COVID-19 diagnosis and treatment in cohort 1 will reduce the risk of this bias.
2.0; 22 Jul 2024	Section 9.3.3.1	Definition of index date for all cohorts added to section 9.3.3.1	Consistency across cohorts following updated index date definition for cohort 3.
2.0; 22 Jul 2024	Section 9.3.3.2.1	Time since most recent COVID-19 vaccination added as a baseline covariate.	Characterize baseline risk factors across cohorts
2.0; 22 Jul 2024	Section 9.5	Specify that the addition of data partners would be considered to increase statistical power for the comparative analysis of MCM.	Clarification of the endpoint for which additional data partners would be considered.
2.0; 22 Jul 2024	Section 9.5	Specified that the number of PAXLOVID-exposed pregnancies required	For the MCM outcome, exposure during first trimester is more biologically relevant than exposure at any time during pregnancy.

Amendment number; date	Section	Update	Rationale
		for the primary outcome of major congenital malformations (MCMs) will be limited to first trimester exposure	
2.0; 22 Jul 2024	Section 9.7.1	Content of interim reports 2 -4 expanded to include information on all pre-specified covariates, and estimates of effective sample size using ATT weights.	Per regulatory request.
2.0; 22 Jul 2024	Section 9.7.2	Added specification that all baseline characteristics will be initially included in the propensity score models; and if there are too many covariates, LASSO regression will be used and coefficients that are penalized to zero will be dropped.	Per regulatory request.
2.0; 22 Jul 2024	Section 9.7.2.2; Table 4; Section 9.7.2.3; Section 9.7.4.6	Clarified that Poisson regression would be the primary method used for comparative safety analysis, with log-binomial analysis as sensitivity.	To avoid potential challenges in the interpretation of the log-binomial analysis, which can yield values outside of the range of 0 to 1.
3.0; 20 Nov 2024	Figure 1, Figure 2 (Section 9.1)	Figures revised to list start of study period as 01Jan2016	To reflect the earliest date of data available for the analysis
3.0; 20 Nov 2024	Section 9.2.4; Section 9.3.3.2; Section 9.7.2.3; Section 9.7.4.7.	Removed references to ‘stratified’ analysis and replace them with ‘subgroup’ analysis.	Per regulatory requestion, to avoid confusion given that the term stratified analysis usually refers to analyses that give a common estimate while accounting for different strata, for example, the stratified Cox proportional hazard model.

Amendment number; date	Section	Update	Rationale
3.0; 20 Nov 2024	Section 9.2.6.2	Replaced 1 day with 6 days	Correction of a typo
3.0; 20 Nov 2024	Section 9.2.6.3	Specified inclusion criteria of at least 1 COVID-19 diagnosis 'in an outpatient, inpatient, or emergency room setting'; clarified that the list of COVID-19 therapies to be reviewed and updated pertains to the exclusion criteria	To improve comparability with Cohorts 1 and 2; and clarity on the scope for potential future revisions to the exclusion criteria for Cohort 3
3.0; 20 Nov 2024	Section 9.3.3.1; Section 9.3.3.2.1	Simplified language to refer to cohort index dates rather than re-defining the index date, and specifying the pre-pregnancy lookback period from Jan 2016 onward	To improve the clarity of the description of the study time periods
3.0; 20 Nov 2024	Section 9.3.3.2.1	Addition of ', and the subset with evidence of treatment (for select comorbidities)' to the baseline variable pertaining to increased risk for evolution to severe COVID-19	Per regulatory request, as treatment may be a proxy for the severity of underlying disease.
3.0; 20 Nov 2024	Section 9.3.3.2.1	Addition of drugs with established or potentially significant interactions with PAXLOVID as a baseline covariate	Per regulatory request, to include a broader list of medications included in the covariate list (in addition to contraindicated drugs).
3.0; 20 Nov 2024	Section 9.3.3.2.1	Deleted 'outpatient' from site of diagnosis for COVID-19 diagnosis	This characteristic was included in the protocol prior to the requirement of outpatient visits for cohort 1 and 2, and outpatient/inpatient/emergency room diagnosis dates for cohort 3.

Amendment number; date	Section	Update	Rationale
3.0; 20 Nov 2024	Section 9.3.3.2.2	Removed bullet point on specific therapies used during COVID-19 therapies, and revised last bullet point on medication use to clarify that this is specific to treatment during the COVID-19 episode	Combine separate covariates that were overlapping
3.0; 20 Nov 2024	Section 9.3.3.2.2	Removed 'gestational age at the start of COVID-19 episode'	Data already captured by variable on duration between first COVID-19 treatment initiation or COVID-19 infection and ECD, plus age at ECD
3.0; 20 Nov 2024	Section 9.3.3.2.2	Simplified the list of diagnoses associated with pregnancy outcomes	The list of diagnoses associated with pregnancy outcomes has been restricted to only characteristics which are likely to change between the baseline (section 9.3.3.2.1) and post-baseline periods
3.0; 20 Nov 2024	Section 9.7.1	Definition of second MCM definition, to be applied as an additional measure in the interim and final reports	Highly sensitive primary definition likely to be capturing both minor and major congenital malformations

6. MILESTONES

Milestone	Planned date
Registration in the HMA-EMA Catalogues of RWD Studies	To be registered before the start of data collection
Start of data collection	01 January 2024
End of data collection	31 August 2027
Interim report 1	30 March 2024
Interim report 2	30 March 2025
Interim report 3	30 March 2026
Interim report 4	30 March 2027
Final study report	31 July 2028

7. RATIONALE AND BACKGROUND

On 22 December 2021, the US FDA granted Pfizer's antiviral PAXLOVID™ EUA for mild-to-moderate COVID-19 in patients aged 12 years or older who are at high risk for progression to severe COVID-19. On 25 May 2023, the US FDA granted full approval for PAXLOVID under the same indication among patients aged 18 years or older (FDA 2023). Pregnant patients are considered at high risk for progression to severe COVID-19 (CDC 2022).

PAXLOVID, the first FDA-authorized oral COVID-19 antiviral (FDA 2021), is a combination of 300 mg nirmatrelvir (two 150 mg tablets) and 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days (Pfizer 2022). Nirmatrelvir is the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3-chymotrypsin–like (3CL) cysteine protease (also known as Mpro) inhibitor. Ritonavir is co-administered at a low dose as a pharmacokinetic (PK) enhancer, to inhibit the CYP3A metabolism of nirmatrelvir and increase plasma concentrations to allow for twice daily dosing (Pfizer 2022). Ritonavir was approved in the US in 1996 for human immunodeficiency virus (HIV) (Schouten et al. 1996).

The Phase 2/3 trial, Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients ("EPIC-HR"), examined PAXLOVID safety and efficacy among non-hospitalized COVID-19 patients. Interim analyses observed an 89% lower risk of hospitalization or death compared to placebo when PAXLOVID was initiated within 3 days of symptom onset (Pfizer 2021).

There is limited data on the safety of PAXLOVID in pregnant women and their offspring (Garneau et al. 2022, Loza et al. 2022). In addition, there are currently no available human data on the use of nirmatrelvir during pregnancy to evaluate a drug-associated risk of major

birth defects, miscarriage, or other adverse maternal or fetal outcomes (Pfizer 2022). Published observational studies on ritonavir use in pregnant women did not identify an increase in the risk of major birth defects (APRSC 2012, Pasley et al. 2013).

Other approved or authorized outpatient therapies for treatment of mild-to-moderate COVID-19 in patients aged 12 years or older who are at high risk of progression to severe COVID-19 include the antivirals remdesivir and molnupiravir, several monoclonal antibodies (bebtelovimab, sotrovimab, casirivimab-imdevimab, and bamlanivimab-etesevimab), and convalescent plasma (FDA 2022a). Of the antivirals, remdesivir is preferred over molnupiravir in pregnant women due to molnupiravir's mechanism of action (HHS 2022). Of the monoclonal antibodies, bebtelovimab is currently the only authorized therapy whose availability has substantially overlapped in time with PAXLOVID availability, due to its greater efficacy against circulating COVID-19 variants in 2022; however, approval for bebtelovimab was rescinded in November 2022 (FDA 2022e). High quality epidemiologic safety data in pregnancy are lacking for both remdesivir and bebtelovimab (FDA 2022b, FDA 2022c).

This protocol describes a study to evaluate the safety of PAXLOVID in pregnant women and their infants (up to 1 year of age) in a real-world setting. This non-interventional study is designated as a PASS and is a commitment to the US FDA.

8. RESEARCH QUESTION AND OBJECTIVES

The research question for this study is: What is the risk of pregnancy outcomes of interest, and infant outcomes of interest, among pregnant women exposed to PAXLOVID, exposed to other COVID-19 therapies, and among pregnant women with COVID-19 unexposed to any therapies?

The primary objective of this study is to estimate the risk of MCM among pregnant women who are exposed to PAXLOVID (and not other COVID-19 treatments) during pregnancy (Cohort 1) , pregnant women not exposed to PAXLOVID but exposed to other COVID-19 treatments (Cohort 2), and pregnant women with COVID-19 not exposed to any COVID-19 treatments (Cohort 3).

The secondary objectives of this study are to:

1. Estimate the risk of pregnancy outcomes (SA, induced termination, stillbirth, livebirth) and the risk of infant outcomes (SGA, preterm birth, postnatal growth deficiency, and infant developmental delay) for livebirths among the 3 study cohorts.
2. Pending sufficient sample size (Section 9.5), to compare the risk of pregnancy and infant outcomes in Cohort 1 compared to Cohort 2, and Cohort 3, separately.

9. RESEARCH METHODS

9.1. Study design

This 5-year observational cohort study will use administrative healthcare claims data (the ORD) to assess PAXLOVID exposure and pregnancy and infant outcomes including SA, induced termination, stillbirth, livebirth, SGA, preterm birth, postnatal growth deficiency, and infant developmental delay and MCM. The primary outcome is MCM, which will be confirmed via medical record review. Pregnancies that begin (based on the ECD, equal to LMP + 14 days) between 01 March 2021 and 01 December 2025 will be identified. For the assessment of infant outcomes, pregnancies that begin on or before 01 April 2025 will be eligible for inclusion. Pregnancies that began in March 2021 are the earliest eligible PAXLOVID-exposed pregnancies in the US (ie, potentially exposed to PAXLOVID close to delivery in December 2021).

All qualifying pregnancies per woman will be included in the study and classified according to the COVID-19 treatments received during 2 relevant exposure windows:

- First trimester exposure window
- Full pregnancy exposure window

These 2 windows provide the flexibility to assess the timing of exposure during pregnancy, as the relevant etiologic period may be the first trimester for MCM whereas the full pregnancy may be the relevant exposure period for pregnancy or other infant outcomes. Given that COVID-19 treatment is typically administered shortly after COVID-19 diagnosis, these exposure windows will account for timing of COVID-19 during pregnancy as well.

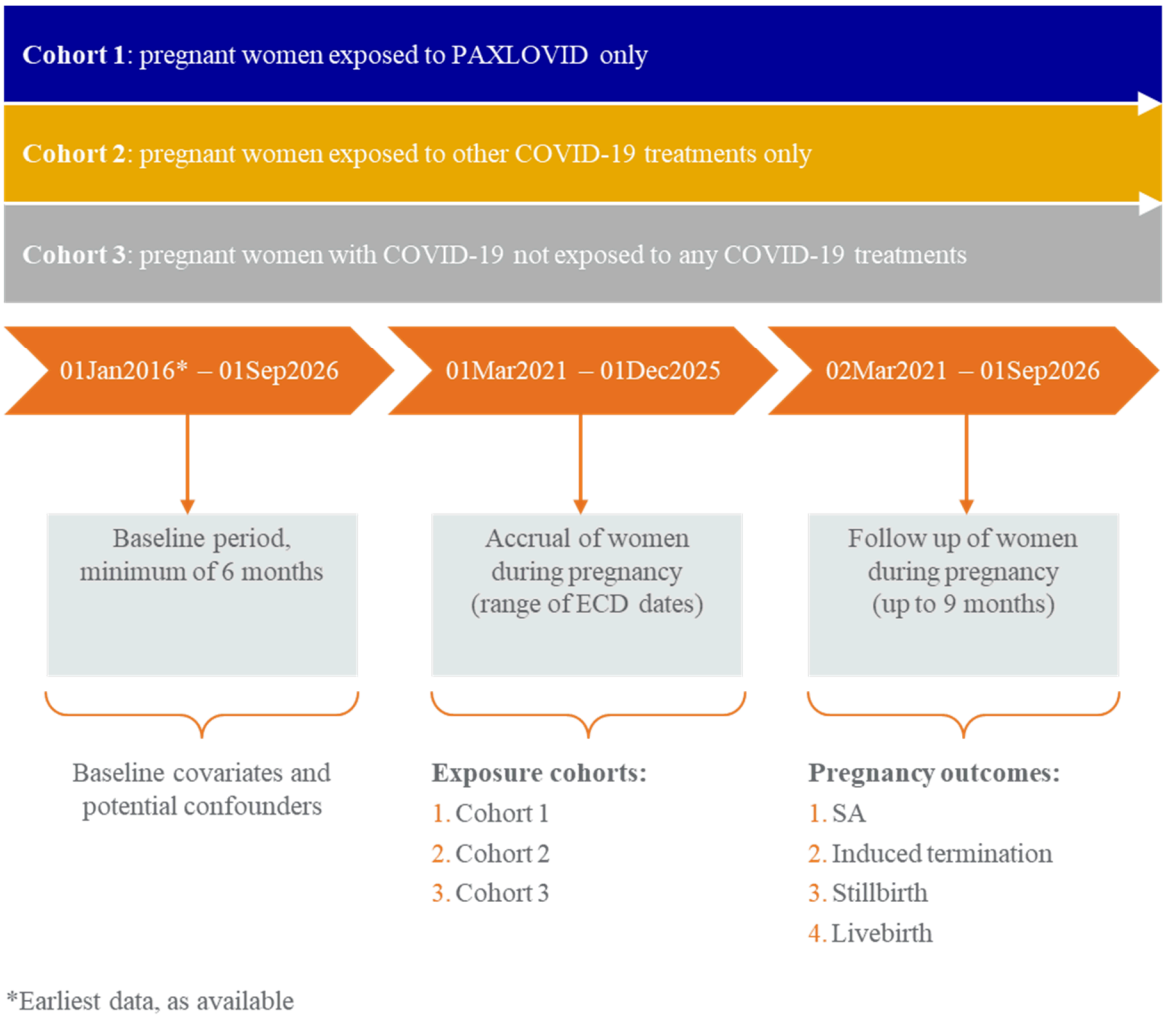
Based on received COVID-19 treatments during each of 2 exposure windows (first trimester, pregnancy), the pregnancies will be classified into the following exposure cohorts (for a total of 6 cohorts):

- Cohort 1 (PAXLOVID cohorts): at least 1 dispensing of PAXLOVID within the relevant exposure window, and no evidence of comparator medications within the relevant exposure window
- Cohort 2 (Treated Comparator Only cohorts): no evidence in the study database of a dispensing of PAXLOVID, and dispensing or administration of at least 1 of the following treatments indicated for the treatment of mild-to-moderate COVID-19 within the relevant exposure window:
  - Remdesivir
  - Bebtelovimab
- Cohort 3 (Untreated Comparator cohorts): no evidence in the study database of a dispensing or administration of any COVID-19 treatments within the relevant exposure window

The exposure cohorts will be defined separately for each exposure window, so that each pregnancy will be assigned an exposure cohort based on the first trimester window, and an exposure cohort based on the full pregnancy window. Women who receive PAXLOVID plus another COVID-19 treatment during pregnancy will be excluded. As some women may receive multiple COVID-19 treatments during pregnancy, the number of pregnancy episodes excluded due to exposure to more than 1 type of medication (eg, PAXLOVID followed by remdesivir) will be reported. Presence of COVID-19 and exposure to COVID-19 treatments will be identified through reimbursement of medical or pharmacy services. Exposure during relevant windows will be determined by pharmacy dispensings (or drug administrations) of the corresponding COVID-19 treatments and the days' supply (or recommended administration schedule), in addition to time to nondetectable concentration of the COVID-19 treatments based on 5x the clearance half-life.

For the assessment of pregnancy outcomes (ie, SA, induced termination, stillbirth, livebirth), pregnancies that begin on or before 01 December 2025 (the final day of accrual) will be followed through the end of pregnancy, as data allow (Figure 1).

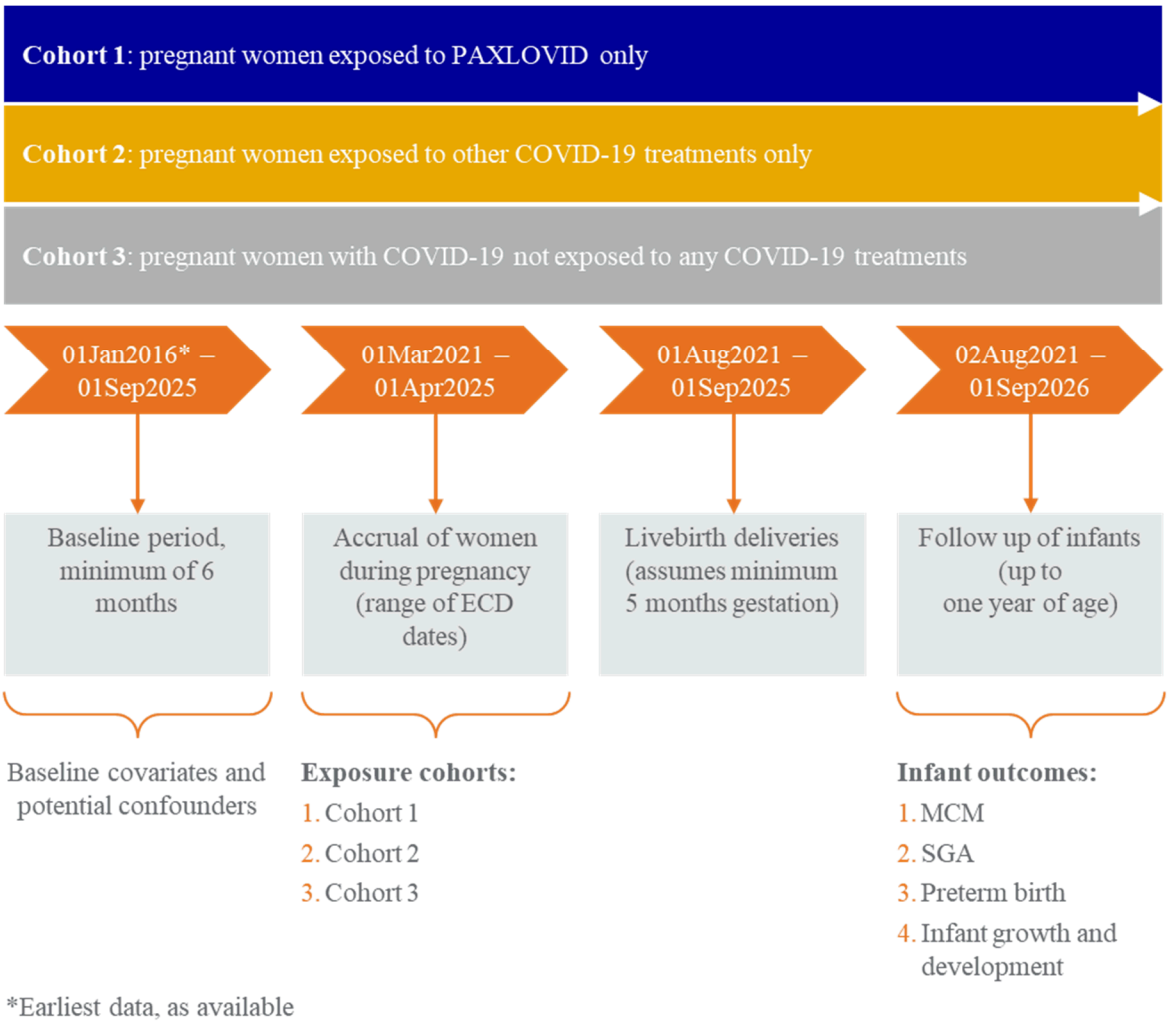
Figure 1. Study Overview for Pregnancy Outcomes



*Earliest data, as available

For the assessment of infant outcomes, pregnancies that begin on or before 01 April 2025 will be eligible for inclusion. Infant follow-up will occur through the first year of an infant's life (Figure 2). To assess infant outcomes, the subset of women whose pregnancy results in livebirth(s) will be linked to their infants' available data.

Figure 2. Study Overview for Infant Outcomes



During the accrual period, pregnancies that qualify for the exposure cohorts will be identified annually and described with respect to baseline characteristics such as length of health plan enrollment, use of relevant medications, and comorbidities. Counts of outcomes, and the subset of outcomes eligible for medical record review, will be included in annual reports. Accrued pregnancies will also be assessed on an annual basis to determine whether there will be sufficient statistical power to detect a difference in risk across the study cohorts with respect to the outcomes of interest.

At the end of the study follow-up period, propensity scores that discriminate between use and non-use of PAXLOVID (separately for each comparator cohort and relevant exposure window) will be created from a wide variety of demographic, baseline comorbidity, disease severity, and co-medication indicators, as well as risk factors for the study outcomes. The propensity scores will be used to adjust for confounding via IPTW. Pending sufficient sample size, the prevalence of the pregnancy and infant outcomes among pregnant women who were exposed to PAXLOVID only will be contrasted with the 2 comparator cohorts.

Pregnancy and infant outcomes will be assessed using claims-based algorithms from the literature with adequate positive predictive values (PPVs) when available, otherwise confirmed via medical records. Given that most pregnancies result in a livebirth, a sample of livebirths will be selected for medical record confirmation of livebirth.

9.2. Setting

The base population for this study will include pregnancies that began (based on ECD) between 01 March 2021 and 01 December 2025, among women treated for COVID-19 or with a COVID-19 diagnosis.

9.2.1. Inclusion criteria

Pregnancies will be eligible for inclusion if they have complete medical coverage and pharmacy benefits and continuous enrollment for at least 6 months prior to ECD. Longer baseline periods (eg, 12 months) will allow for more complete capture of underlying conditions (eg, pregnancy outcome risk factors), at the potential cost of smaller sample sizes. Such factors will be considered and explored before finalization of the baseline period duration in the SAP, which will be dated, filed, and maintained by Pfizer. Pregnancies will be classified into the exposed and comparator pregnancy cohorts according to COVID-19 treatments received during pregnancy.

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

1. Age 12 to 49 years at ECD
2. ECD between 01 March 2021 and 01 December 2025
3. Continuous medical and pharmacy coverage for a minimum of 6 months prior to and including the ECD

Pregnancies meeting all of the inclusion criteria will be included in the base population, with the cohort entry date set to the ECD. Additional criteria for inclusion in the study cohorts are described in Section 9.2.6.

9.2.2. Exclusion criteria

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

1. Exposed to any known teratogens from 3 months prior to ECD through the end of the relevant exposure window.

The exclusion period of 3 months is a conservative approach given the relatively short half-life of many teratogens. Exposure to teratogens will be assessed via the presence of NDCs or medical procedure codes (Healthcare Common Procedure Coding System [HCPCS]). The list of known teratogenic drugs used for exclusion and accompanying half-lives is provided in ANNEX 2. ADDITIONAL INFORMATION.

9.2.3. Identification of pregnancy and estimation of LMP and ECD

Pregnancies will be identified using the Optum Dynamic Assessment of Pregnancies and Infants (DAPI) (Section 9.4.2). This process applies a set of algorithms comprised of International Classification of Diseases, 10th revision (ICD-10) diagnosis and procedure codes, Current Procedural Terminology[1] (CPT) codes, and HCPCS codes to the claims data to identify pregnancies, LMP date, pregnancy end date, and pregnancy outcome (Bertoia et al. 2022).

DAPI uses ICD-10 Z3A codes denoting weeks of gestation to estimate the LMP (Chomistek et al. 2021, Chomistek et al. 2022). The LMP date is the first day of the last menstrual period before pregnancy. Validation of Z3A-based LMP estimation has indicated good performance, with a median difference in days between LMP date based on Z3A codes and adjudicated (via medical record review) LMP date of 4.0 days (interquartile range: 2.0 – 10.0 days). Gestational age is anchored by the LMP date, where 12 weeks gestation is 12 completed weeks after LMP, 30 weeks gestation is 30 completed weeks after LMP, etc. Conception typically occurs about 2 weeks after the LMP date, around ovulation which is midway through the menstrual cycle. ECD will be calculated based on the estimated LMP (LMP + 14 days).

There is a small fraction of pregnancies that do not have Z3A codes; in these cases, DAPI assigns an average length of gestation for different pregnancy outcomes and uses that average length to estimate the accompanying ECD (eg, 39 weeks for full-term births and 10 weeks for all abortions), as described by Hornbrook et al. (Hornbrook et al. 2007). DAPI may be refined over the course of the project based on clinical input and review of published literature.

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9.2.4. Identification of COVID-19 episodes

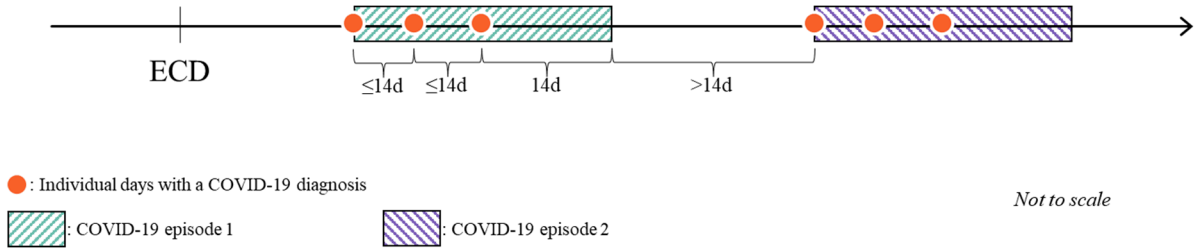
COVID-19 episodes will be identified through presence of the ICD-10 diagnosis code:

- U07.1 (COVID-19, virus identified [lab confirmed])

A recent paper found adequate validity when using ICD-10 diagnosis code U07.1 to identify hospitalized COVID-19 patients in 2020, with PPVs ranging from 70% to 93% in nationally insured patients (Kluberg et al. 2022).

Episodes of COVID-19 will be defined by clustering all COVID-19 diagnoses occurring within 14 days of one another, reflecting the upper range of the incubation period (WHO 2023). Because the duration of symptomatic COVID-19 is variable, a grace period of 14 days following the final COVID-19 diagnosis within a cluster will be added to conservatively capture the symptomatic duration of a single COVID-19 episode (Sudre et al. 2021) (Figure 3).

Figure 3. Example Pregnancy with Two Episodes of COVID-19



The frequency, duration and timing of COVID-19 episodes will be described. Eligibility for the overall study population will not be restricted based on the presence of COVID-19 during pregnancy or in proximity to COVID-19 treatments; rather, the frequency and characteristics of COVID-19 episodes will be summarized and described and may be used for subgroup analysis. COVID-19 episodes will be defined independently of any treatment(s) received for COVID-19; however, treatments received during COVID-19 episodes will be characterized with regard to the COVID-19 episode during which they occur (eg, time from COVID-19 diagnosis to treatment initiation, inpatient status at time of COVID-19 diagnosis, etc.; Section 9.3.3).

9.2.5. Exposure windows

From the base population, qualifying pregnancies will be classified according to the COVID-19 treatment received during the following relevant exposure windows:

- First trimester exposure window
  - Start date: ECD – therapy-specific window
  - End date: End of the first trimester

- Pregnancy exposure window
  - Start date: ECD – therapy-specific window
  - End date: End of the pregnancy

As different COVID-19 therapies will have varying rates of elimination, the length of each relevant exposure window will be extended (prior to the ECD) by a corresponding therapy-specific window, based on the indicated treatment duration (plus a grace period for self-administered drugs) and the time to non-detectable concentration in the body (defined as 5x the clearance half-life). This ensures the capture of exposure to COVID-19 therapies administered or dispensed prior to the ECD but which remain in the body at ECD. Sections 9.2.6.1 and 9.2.6.2 describe the therapy-specific windows for each of the study therapies.

9.2.6. Study cohorts

Three mutually exclusive study exposure cohorts will be created based on received COVID-19 treatment during each exposure window (first trimester, pregnancy) for a total of 6 study cohorts:

- Cohort 1 (PAXLOVID cohorts): at least 1 dispensing of PAXLOVID within the relevant exposure window, and no evidence of comparator medications within the relevant exposure window
- Cohort 2 (Treated Comparator Only cohorts): no evidence in the study database of a dispensing of PAXLOVID, and dispensing or administration of the following treatments indicated for the treatment of mild-to-moderate COVID-19 within the relevant exposure window
  - Remdesivir
  - Bebtelovimab
- Cohort 3 (Untreated Comparator cohorts): evidence of a COVID-19 diagnosis, and no evidence in the study database of a dispensing or administration of any COVID-19 treatments within the relevant exposure window

9.2.6.1. Cohort 1: PAXLOVID cohorts

Pregnancies will be included in the PAXLOVID cohorts (Cohort 1) if they meet the following criteria:

1. Dispensing of outpatient PAXLOVID between 7 days prior to ECD and the end of the exposure window.

AND

2. None of the following:
    a. Administration of remdesivir between 9 days prior to ECD and the end of the exposure window.

    OR

    b. Administration of bebtelovimab between 60 days prior to ECD and the end of the exposure window.

The 7-day pre-ECD window for PAXLOVID was chosen because of the 5-day recommended treatment course, plus 2 days to achieve 5x the clearance half-life. See Section 9.2.6.2 for justification for other pre-ECD windows.

Because the precise indication for PAXLOVID ("mild-to-moderate COVID-19") cannot be directly captured in claims data, and to improve comparability with comparator pregnancies, only PAXLOVID dispensings occurring in an outpatient setting will be eligible for inclusion.

9.2.6.2. Cohort 2: Treated comparator only cohorts

Pregnancies will be included in the Treated Comparator Only cohorts (Cohort 2) if they meet the following criteria:

1. Any of the following:
    a. Administration of remdesivir in an outpatient setting between 9 days prior to ECD and the end of the exposure window.

    OR

    b. Administration of bebtelovimab in an outpatient setting between 60 days prior to ECD and the end of the exposure window.

AND

2. No dispensing of PAXLOVID (any setting) between 12 days prior to first eligible comparator drug dispensing and the end of the exposure window.

The 9-day pre-ECD window for remdesivir was chosen because of the 3-day recommended treatment course and 6 days to achieve 5x the clearance half-life (FDA 2022b). The 60-day pre-ECD window for bebtelovimab was chosen because of the 60-day requirement to achieve 5x the clearance half-life (FDA 2022c).

Pregnancies with exposure to more than 1 Cohort 2 medication (eg, a pregnancy exposed to both remdesivir and bebtelovimab, or other future approved or authorized COVID-19 therapies included in Cohort 2) will be eligible for inclusion.

Lists of approved or authorized COVID-19 therapies for the definition of the treated comparator will be periodically reviewed and updated in the SAP as necessary.

9.2.6.3. Cohort 3: Untreated comparator cohorts

Pregnancies will be included in the Untreated Comparator cohorts (Cohort 3) if they meet the following criteria:

1. At least 1 COVID-19 diagnosis (ICD-10 U07.1) in an outpatient, inpatient, or emergency room setting between 7 days prior to ECD and the end of the exposure window.

AND

2. No exposure to any authorized COVID-19 therapies, regardless of setting (ie, outpatient/inpatient). Authorized therapies used to exclude pregnancies from the unexposed cohorts include:
    a. Study cohort drugs
    b. Other approved or authorized treatments (eg, molnupiravir, other monoclonal antibodies)
    c. Convalescent plasma (indicated for patients with immunosuppressive disease or receiving immunosuppressive treatment)

Lists of authorized COVID-19 therapies for the exclusion definition of the untreated comparator cohort will be periodically reviewed for completeness and updated in the SAP as necessary and will include all approved or authorized (EUA for the treatment of mild-to-moderate COVID-19) medications at any point during the study period. Medication-specific pre-ECD windows for exclusion for other monoclonal antibodies and convalescent plasma will be based on typical treatment durations and medication half-lives (as with other study cohort treatments) and defined in the SAP.

9.2.7. The index date for Cohort 3 will be the date of COVID-19 diagnosis plus the treatment interval (the median interval between COVID-19 diagnosis and treatment in Cohort 1; as defined in Section 4.3.3.1.1 in the SAP)Follow-up

For the assessment of pregnancy outcomes, follow-up for each pregnant woman will extend from the day following cohort entry (ECD) until the earliest of: disenrollment from the health plan, end of the pregnancy, or 01 September 2026.

For the assessment of infant outcomes, linked infants (the subset of pregnancies resulting in livebirths that are linked to the mother's data) will be followed from the date of delivery until the earliest of: disenrollment from the health plan or 1 year of age.

9.3. Variables

9.3.1. Outcomes

The primary outcome is MCM. The secondary outcomes are SA, induced termination, stillbirth, livebirth, SGA, preterm birth, postnatal growth deficiency and

infant developmental. The study outcomes will be identified by ICD-10 diagnosis and procedure codes, CPT®[2] procedure codes, and HCPCS procedure codes on claims. All outcomes will initially be identified via claims-based algorithms. Potential cases of MCM, induced termination, SGA, preterm birth, postnatal growth deficiency and infant developmental delay, and a sample of livebirths identified via claims-based algorithms will be adjudicated via medical records.

9.3.1.1. Pregnancy outcomes

The pregnancy outcomes to be assessed are:

- SA – defined as the loss of pregnancy before the 20th week of gestation
- Induced termination – defined as an intervention to end a pregnancy so that it does not result in a livebirth
- Stillbirth – defined as the loss of pregnancy at or after the 20th week of gestation
- Livebirth – a delivered fetus with any sign of life (eg, voluntary movement, heartbeat) regardless of gestational weeks

Lists of ICD-10 diagnostic codes are provided in ANNEX 2. ADDITIONAL INFORMATION.

9.3.1.2. Infant outcomes

The infant outcomes to be assessed are:

- MCM – defined as a structural abnormality with surgical, medical, or cosmetic importance and will exclude chromosomal abnormalities or physiological features due to complications of prematurity, such as cryptorchidism, inguinal hernia, or isolated patent ductus arteriosus in infants born less than 37 weeks of gestation. There are 3 main types of congenital malformations – deformation, disruption, and dysplasia. A deformation occurs when an intrinsically normal structure is prevented from normal intrauterine growth by an external constraint. In a disruption, a normally forming tissue or organ is destroyed by an abnormality of the intrauterine environment. Dysplasia is a morphologic anomaly arising either prenatally or postnatally from dynamic or ongoing alteration of cellular constitution, tissue organization or function within a specific organ or a specific tissue type (Hennekam et al. 2013). Classifications will be based on guidelines from the New York State Department of Health Congenital Malformations Registry and the European Surveillance of Congenital Malformations (EUROCAT 2020). All identified MCMs will be counted, overall, and classified by body system. If numbers allow, patterns of specific congenital malformations will be described.

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- SGA – defined as birthweight below the 10th percentile for gestational age
- Preterm birth – defined as a live birth at or before the 37th week of gestation
- Postnatal growth deficiency
- Infant developmental delay

Lists of ICD-10 diagnostic codes are provided in ANNEX 2. ADDITIONAL INFORMATION.

9.3.1.3. Medical record confirmation of outcomes

Pregnancy and infant outcomes will be assessed using claims-based algorithms from the literature with adequate PPVs when available, otherwise confirmed via medical records. Andrade et al. observed a PPV of 83% for their ICD-10-based stillbirth algorithm, developed within an electronic health record database (Andrade et al. 2021). A recent Optum publication observed a PPV of 84.7% for the identification of SA (Chomistek et al. 2022). Optum proposes to use these published algorithms to identify SA and stillbirth.

Given that most pregnancies are expected to end in a livebirth, a random sample of 200 livebirths will be selected for medical record confirmation and validation of the livebirth identification algorithm, which relies on the presence of outcome-related ICD-10 codes. This conservative sample size is sufficient to exclude from the 95% confidence interval (CI) a PPV <80% if the true PPV is 85% (Schaeffer et al. 1990). Livebirths are identified via ICD-10 codes shown in ANNEX 2. ADDITIONAL INFORMATION.

Using medical records to confirm pregnancy and infant outcomes allows for a highly sensitive and specific outcome definition because medical records may be sought for all potential outcomes (high sensitivity) and each potential outcome is adjudicated (high specificity). The literature will be re-assessed following delivery of the final accrual report to identify alternative stillbirth and/or SA algorithms and algorithms for the remaining outcomes. If suitable algorithms are found, the proposed approach may be modified to use algorithms for additional outcomes (Tonelli et al. 2016).

For outcomes for which medical record confirmation is deemed necessary, a detailed review of the chronological listing of relevant claims (ie, claims profile) will be reviewed for each of the potential cases in order to:

- Determine if the claims listing for each potential case contains sufficient information to be included in the medical record procurement process; and
- Determine the medical site of treatment most likely to yield medical records with the necessary information to confirm case status.

Optum, with input from a clinician, will develop a medical record review form that will include clinical elements necessary to confirm the outcome diagnosis. Providers will be asked to send all available medical information occurring during the period of interest

(surrounding the service date of the relevant claim). This information will include, but is not limited to:

- Labor and delivery records
- Office visit notes
- History and physical exam reports
- Laboratory reports
- Diagnostic imaging reports
- Hospital discharge summaries
- Surgical reports
- Histology/pathology reports
- Consultation/specialist notes

For each potential case, medical records will be sought if the patient is eligible for medical record retrieval. Approximately 50% of patients in the ORD are eligible for medical record retrieval. Patients who are ineligible for medial record retrieval include those from health plans that contract for administrative services only; access to medical records is not allowed for patients enrolled in these plans. For each eligible case, 1 medical record will be requested from 1 provider. Of those that are requested, approximately 70% to 85% of the medical records are expected to be successfully obtained (Johannes et al. 2007, Seeger et al. 2006). Therefore, the overall proportion of the ORD available for medical record validation is approximately 35 to 42.5%. Optum will seek up to 550 medical records.

Two clinical consultants with expertise in the field of teratology will be identified for the adjudication of MCMs, and 2 clinical consultants in the field of obstetrics will be identified for the adjudication of all other outcomes. Each pair of clinicians (blinded to study drug exposure) will review the clinical data for each potential case and adjudicate the outcomes. Each record will be adjudicated by 2 clinicians independent of one another, and consensus will be sought for discrepancies in adjudication results between the clinicians. Optum will work with the clinicians to arrive at consensus adjudications, and the Optum epidemiologist on the project will arbitrate the process. Optum will work with outside vendors as needed to procure the medical records and conduct the outcome adjudication.

9.3.2. Study drug exposures

9.3.2.1. Cohort 1: PAXLOVID exposure

Exposure to PAXLOVID will be identified through the presence of NDCs on pharmacy dispensing claims:

- 00069034506
- 00069034530

- 00069108506
- 00069108530
- 00069110104
- 00069110120

Codes will be periodically reviewed for completeness and updated as necessary.

9.3.2.2. Cohort 2: Treated comparator only exposures

Exposure to remdesivir and bebtelovimab will be identified through the presence of drug administration codes (HCPCS):

- J0248 Injection, remdesivir, 1 mg
- Q0222 Injection, bebtelovimab, 175 mg
- M0222 Intravenous injection, bebtelovimab, includes injection and post administration monitoring
- M0223 Intravenous injection, bebtelovimab, includes injection and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the COVID-19 public health emergency

Codes will be periodically reviewed for completeness and updated in the SAP as necessary.

9.3.2.3. Cohort 3: Untreated comparator exposures

Exposure to COVID-19 therapies used to identify pregnancies that are ineligible for the Untreated Comparator cohorts will be identified through the presence of NDCs and/or administration codes. Detailed code lists for this cohort will be included in the SAP.

Codes will be periodically reviewed for completeness and updated in the SAP as necessary.

9.3.3. Covariates

9.3.3.1. Time periods

The following dates and time periods will be used (Figure 4):

- Index date – the date of start of treatment (Cohorts 1 and 2) or COVID-19 diagnosis plus the treatment interval (Cohort 3)

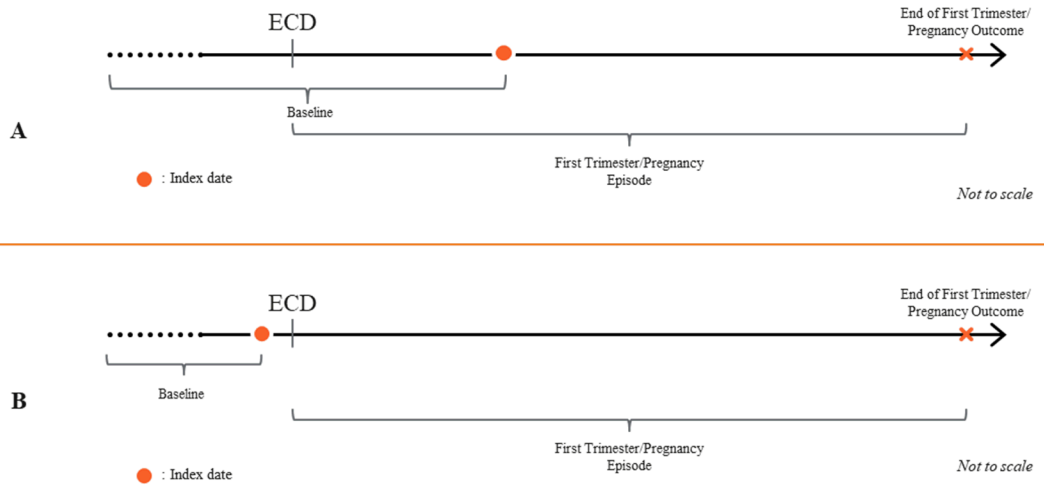
- Baseline – the 6 months prior to ECD through the index date, with potential variability in capture of time prior to EDC according to timing of treatment and COVID-19 diagnosis as described below. As an example, each patient with the same timing of an index exposure (eg, treatment/COVID-19 at Day 60 of pregnancy) will have the same amount of baseline, but by anchoring to treatment/COVID-19, there is

potential for variability in the baseline window length according to the timing of treatment or COVID-19 infection.

- For individuals with index dates during pregnancy, the baseline period includes the ECD (Figure 4A)
- For individuals index dates prior to ECD (eg, PAXLOVID initiation 2 days prior to ECD), the baseline period ends prior to ECD (Figure 4B)
  - For these pregnancies, select characteristics at ECD will still be captured (ie, maternal age at ECD, calendar year of ECD)

- All available pre-pregnancy data – all available data from 01 January 2016 onward
- First trimester/pregnancy – the time between ECD and end of first trimester/end of pregnancy

Figure 4. Time Periods for the Assessment of Covariates.



The baseline window will be defined using the first eligible treatment or COVID-19 diagnosis during an exposure window. Descriptive characteristics that capture the total number of COVID-19 therapies (eg, multiple courses of PAXLOVID) will be described during the first trimester/pregnancy window.

9.3.3.2. Covariates

All members of the study cohorts will be classified according to covariates identified in the claims data. Note that only baseline (ie, pre-treatment) covariates will be considered for inclusion in the propensity score models. Covariates assessed during pregnancy, which may occur after treatment initiation or infection, will be described and/or used for subgroup analysis. Recognizing that a narrower (for time-varying covariates, etc.) or broader (for chronic conditions, etc.) window of assessment may better capture select patient attributes of

interest, specific covariates may be assessed using alternate time period(s), which are noted below.

In addition to the covariates listed below, Optum will identify baseline predictors on an empiric basis by examining the most frequently occurring diagnoses, drugs dispensed, and procedures performed among pregnancies with and without PAXLOVID exposure. These empiric covariates will be considered for inclusion in the propensity score models used for IPTW.

Detailed definitions and code lists for covariates will be included in the SAP.

9.3.3.2.1. Baseline covariates

- Demographics including age, geographic area, and month and year of ECD (at the time of ECD)
- Healthcare utilization
  - Length of health plan enrollment
  - Number of physician visits, emergency room visits, and hospitalizations (prior to and during pregnancy, separately)
- Vaccinations received (eg, Tdap)
- Diagnoses related to alcohol, recreational drug, and tobacco use
- Diagnoses associated with increased risk for evolution to severe COVID-19, and the subset with evidence of treatment (for select comorbidities)
- Diagnoses associated with increased risk for thromboembolic events
- Diagnoses related to contraindications for study drugs, including renal and hepatic impairment
- Receipt of medications listed as contraindications for study drugs, including drugs highly dependent on CYP3A for clearance and drugs with established or potentially significant interactions with PAXLOVID
- Receipt of COVID-19 vaccines through drug or procedure codes (Wong et al. 2022) (using all available pre-pregnancy data)
  - Time since most recent COVID-19 vaccination
- Diagnoses associated with an increased incidence of the pregnancy outcomes such as prior history of pregnancy complications, obesity, hypertension, chronic kidney disease, diabetes, infection during pregnancy, and cardiovascular disease
- Prior COVID-19 (using all available pre-pregnancy data; prior to and during pregnancy, separately)

- Characteristics of COVID-19 episode (up to and including treatment initiation or COVID-19 diagnosis) associated with cohort medication exposure (if applicable), including:
  - Site of diagnosis (eg, inpatient/emergency room)
  - Gestational age at start of COVID-19 episode
  - Time to cohort-defining treatment initiation
  - Receipt of supplemental oxygen
  - Critical care indicators
- Calendar time (month and year) of index date (first COVID-19 treatment initiation or COVID-19 infection)
- Duration between index date and ECD (this value will be positive if the index event occurred after ECD, and negative if the index event occurred prior to ECD)

9.3.3.2.2. First trimester/Pregnancy covariates

- Prenatal care during pregnancy, including but not limited to:
  - Vaccines received
  - Number and timing of prenatal care visits
  - Ultrasound
- Receipt of COVID-19 vaccines through drug or procedure codes (Wong et al. 2022)
- COVID-19 diagnoses and episodes during pregnancy, including:
  - Number of COVID-19 diagnoses and episodes during pregnancy
  - Duration of COVID-19 episode(s)
  - Time between COVID-19 episodes
  - Use of specific therapies (Westhoff et al. 2022) during COVID-19 episode(s)
  - Hospitalization for COVID-19 episode(s)
- Total number of COVID-19 treatments received (eg, total days' supply, number of dispensings, etc.)
- Diagnoses and procedures related to COVID-19 sequelae such as acute respiratory distress syndrome
- Diagnoses associated with an increased incidence of adverse pregnancy outcomes such as infection during pregnancy and hospitalization during pregnancy (using all pre-pregnancy data)

- Other medication dispensings such as off-label COVID-19 therapies

9.4. Data sources

9.4.1. The Optum Research Database

The patients included in this study will be drawn from the ORD, a proprietary research database containing eligibility and pharmacy and medical claims data from a large US health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US. As early as 1993, medical and pharmacy claims data are available for 70 million individuals with both medical and pharmacy benefit coverage. For 2021, data are available for approximately 12.6 million individuals with medical and pharmacy coverage. Optum Epidemiology research activities utilize de-identified data from the research database. In limited instances, patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

The data include demographics, details from pharmacy claims (reflecting dispensings), all medical and facility claims, including information on the types of services or procedures, and their accompanying diagnoses. The coding of medical claims conforms to insurance industry standards, including:

- Use of designated claims forms (eg, physicians use the Centers for Medicare & Medicaid Services [CMS]-1500 format and hospitals use the universal billing [UB]-04 format)
- ICD-10 diagnosis codes and procedure codes
- CPT codes[3]
- CMS HCPCS codes

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. These data allow for longitudinal tracking of medication refill patterns and changes in medications and include:

- NDC
- Drug name
- Dosage form
- Drug strength
- Fill date
- Days' supply

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- Cost information
- De-identified patient and prescriber codes

The machine-readable dataset of the ORD can be augmented on an ad hoc basis by further inquiry, including medical record review. The data are only re-identified following approval by an Institutional Review Board (IRB), and all data access conforms to applicable Health Insurance Portability and Accountability Act policies.

9.4.2. The Optum Dynamic Assessment of Pregnancies and Infants

The cohorts for this study will employ DAPI, a proprietary process that includes a set of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mothers' and infants' data in an ongoing manner, within the ORD (Bertoia et al. 2022). The algorithms are based on a combination of validated algorithms as reported in the literature and clinical input. Mother and infant records will be linked through the presence of a common unique family insurance ID. This number is used by health plans to identify all members of a family who are covered by the same insurance plan for the purposes of defining coverage, payment, and reimbursement, providing assurance that mother-infant pairs identified in this manner are accurate. In addition, claim(s) relating to the delivery must be within 7 days of the infant's birthdate (or 32 days for multiples).

In comparison with the broader US population, the women of child-bearing age who are included in the ORD (and DAPI) tend to be healthier, reflecting the underlying population of the commercial insurance enrollees, and likely have an age distribution more skewed toward older age, reflecting the age distribution of women within the work force.

Historically, there are approximately 200,000 pregnancies identified each year within the database, of which 80% (with observed outcomes) result in livebirths, 85% of which can be linked to an infant within the database. These linkages enable proactive monitoring of pregnancy outcomes to ascertain a range of outcome-specific risks associated with drug exposure during pregnancy. This linkage has been used to address regulatory questions by pharmaceutical companies about the effects of drugs on pregnancy (Cole & Modell et al. 2007, Cole & Ephross et al. 2007, Carman et al. 2017, Wyszynski et al. 2016).

The fraction of identified deliveries that cannot be matched to an infant is likely due to the infant being covered under a different health insurance plan from the mother. This may occur if the infant were to be added to the other parent's plan (rather than the birth mother's), if the parents were to switch from individual plans to a family health plan, or if the mother were covered under her parent's policy (in which case a separate plan would need to be purchased for the infant). While the reasons for switching of the infants' health plans may be related to coverage for treatments relating to infant outcomes, reasons for switching are likely non-differential with respect to maternal exposure to COVID-19 treatments. Therefore, while estimates of risk or prevalence may be underestimated due to the switching of health plans, estimates of relative risk should be unbiased.

For a subset of women and infants, Optum can (with appropriate approvals) access medical records for mothers or infants in order to confirm outcomes.

9.4.3. Medical records

As noted in Section 9.3.1.3 (Medical Record Confirmation of Outcomes), medical records will be sought for the adjudication of select outcomes. The medical record adjudication results will be incorporated into the final report.

9.4.4. Multiple research partners

Optum has extensive experience as both a participating research partner and as the coordinating center for multi-partner studies, including pregnancy studies performed for regulatory purposes. The potential for small numbers of either PAXLOVID-exposed or comparator pregnancies may mean that multiple research partners are required to achieve adequate sample size to provide sufficient statistical power for analyses of the less common outcomes. Accrual of eligible pregnancies will be assessed following the third interim report, at which point the addition of research partners will be considered.

9.5. Study size

The planned sample size incorporates several assumptions derived from published literature, including the following approximate prevalence of pregnancy outcomes:

- Under 1% of pregnancies result in stillbirth (FDA 2002)
- 14% of pregnancies result in SA or miscarriage (FDA 2002)
- 18% of pregnancies have historically been expected to end in induced termination (Jones et al. 2017)
- 3% of live born infants have a major birth defect in the US each year (March of Dimes 2015)
- 10% of live born infants are born preterm or SGA (CDC 2008, Ferré et al. 2016)

Based on these reference percentages, the following assumptions were made for sample size calculation:

- α=0.05
- Power=0.8
- 1:2 matching
- Outcome prevalence as cited above

Table 1 and Table 2 show the minimum required number of PAXLOVID-exposed pregnancies required to proceed to the secondary objective of comparative analyses. Comparative analyses will be conducted if the sample size to detect a RR > 2.0 is achieved for each outcome; target sample size may be achieved for some outcomes but not others.

To detect a RR > 2.0 at 80% power a minimum of 127 PAXLOVID-exposed pregnancies are required for SA, 251 for SGA and preterm birth, and 2,212 for stillbirth, the rarest of the outcomes (Table 1). A minimum of 938 PAXLOVID-exposed pregnancies during the first trimester are required for the primary outcome of MCM (Table 2).

Fewer PAXLOVID-exposed pregnancies are required to detect an RR of > 2.5 at 80% power: 63 for SA, 127 for SGA and preterm birth, and 1,142 for stillbirth. For MCM, the minimum number of pregnancies with PAXLOVID exposure during the first trimester is 482. These estimates are based on 1:2 matching; however, the analyses for this study will utilize IPTW for confounding adjustment. Sample size calculations are based on 1:2 matching as a conservative estimate due to the retention of all eligible pregnancies in IPTW. Power for the analysis of induced termination will be similar to that for SA. The majority of pregnancies end in livebirth; therefore, power is expected to be adequate for this outcome.

Table 1. Sample Size Required for 80% Power to Detect Relative Risks (As or More Extreme) for Pregnancy Outcomes, with 1:2 Matching

Outcome	Prevalence of Outcome	RR	PAXLOVID-Exposed Pregnancies with Observed Outcomes Needed*	PAXLOVID-Exposed Pregnancies Needed**
SA	14%	2	101	127
		2.5	50	63
Stillbirth	1%	2	1,769	2,212
		2.5	913	1,142

* Sample size calculated using PROC POWER function in SAS with a two-sided likelihood ratio chi-square test, and the specified relative risk and prevalence in the unexposed (SAS EG V8.2, SAS Institute Inc., Cary, NC).
** A divisor of 0.80, which is the proportion of ongoing pregnancies for which an outcome is eventually observed in DAPI, was used to calculate the number of exposed pregnancies needed.

Table 2. Sample Size Required for 80% Power to Detect Relative Risks (As or More Extreme) for Infant Outcomes, with 1:2 Matching

Outcome	Prevalence of Outcome	RR	PAXLOVID-Exposed Livebirths Needed*	PAXLOVID-Exposed Pregnancies Needed**
MCM	3%	2	572	938
		2.5	294	482
Preterm birth	10%	2	153	251
		2.5	77	127
SGA	10%	2	153	251
		2.5	77	127

Table 2. Sample Size Required for 80% Power to Detect Relative Risks (As or More Extreme) for Infant Outcomes, with 1:2 Matching

Outcome	Prevalence of Outcome	RR	PAXLOVID-Exposed Livebirths Needed*	PAXLOVID-Exposed Pregnancies Needed**

* Sample size calculated using PROC POWER function in SAS with a two-sided likelihood ratio chi-square test and the specified relative risk and prevalence in the unexposed (SAS EG V8.2, SAS Institute Inc., Cary, NC).
** A divisor of 0.61, which is the proportion of ongoing pregnancies for which an outcome is eventually observed and the outcome is a livebirth in DAPI, was used to calculate the number of total exposed pregnancies needed.
***Minimum sample size refers to the pregnancies with first trimester exposure

Following initial accrual results from the first interim report, it was observed that fewer Cohort 2 pregnancies were accrued than PAXLOVID-exposed pregnancies, at a ratio of approximately 5:1, suggesting that matching of 2 comparators to each PAXLOVID pregnancy is unlikely to be feasible. Assuming a final ratio of 5 PAXLOVID-exposed pregnancies to each Cohort 2 pregnancy, a minimum sample size of 3,352 PAXLOVID-exposed pregnancies (and 670 Cohort 2 pregnancies) will be required to be accrued during the first trimester exposure window to detect a RR ≥ 2.0 at 80% power for MCM. To detect a RR ≥ 2.5, 1,664 PAXLOVID-exposed pregnancies (and 333 Cohort 2 pregnancies) will be required.

Table 3 provides counts of total pregnancies, COVID-19 positive pregnancies, and pregnancies exposed to COVID-19 treatments within the ORD in 2020-2022. While 200,000 pregnancies are typically identified in any given calendar year within the ORD, this number has dropped slightly during the COVID-19 pandemic, as seen in Table 3 with roughly 180,000 pregnancies identified in 2020 and 2021. The counts include complete data through mid-2022; thus, some pregnancies in the latter half of 2022 may not be captured. Between 2020 and mid-2022, 35,303 of 460,062 pregnancies (7.7%) had a COVID-19 diagnosis code. Of the 35,303 COVID-19 positive pregnancies, 409 (1.2%) of pregnancies were exposed to bebtelovimab, while 382 (1.1%) were exposed to remdesivir. A total of 1,021 pregnancies were exposed to PAXLOVID, with roughly half of these also being diagnosed with COVID-19.

Annual interim reports will provide information on the uptake of PAXLOVID and the ability to reach adequate sample size for the study outcomes. If needed, a data partner may be added to increase statistical power (Section 9.4.4) to conduct the comparative analysis of MCM, per the secondary study objective. Even with multiple data partners, power may not be adequate for the assessment of stillbirth due to its rarity.

Table 3. Counts of Total and COVID-19 Positive Pregnancies in the Optum Research Database, 2020-2022

	2020	2021	2022 (partial)[a]	Total
All pregnancies	182,835	179,058	98,169	460,062

Table 3. Counts of Total and COVID-19 Positive Pregnancies in the Optum Research Database, 2020-2022

	2020	2021	2022 (partial)[a]	Total
Pregnancies with ≥1 PAXLOVID dispensing	--	295	726	1,021
Pregnancies with ≥1 COVID-19 diagnosis code	10,337	19,581	5,385	35,303
Subset of pregnancies with ≥1 COVID-19 diagnosis code and ≥1 PAXLOVID dispensing	--	185	379	564
Subset of pregnancies with ≥1 COVID-19 diagnosis code and ≥1 bebtelovimab administration	--	184	225	409
Subset of pregnancies with ≥1 COVID-19 diagnosis code and ≥1 remdesivir administration	165	206	11	382

a Data for 2022 is approximately complete through June 2022.

This count is for informational purposes only. Final sample size for the study could change depending upon criteria applied during the application of the protocol, incomplete infant linkage, incomplete medical record retrieval, and required approvals.

9.6. Data management

All analyses will be conducted using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina) and SAS Enterprise Guide 6.1 or later. The data will be extracted from the ORD once per report. The annual interim reports will include the structured ORD data only. The final report will additionally incorporate the adjudication results, as described in Section 9.3.1.3.

The following sections of the protocol (Sections 9.6.1 and 9.6.2) pertain to the data collected for the review of medical charts described in Section 9.3.1.3.

9.6.1. Data collection tools (DCTs)

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included patient for whom outcomes are being adjudicated via medical record review. The completed original DCTs are maintained by Optum and should not be made available in any form to third parties, except for appropriate regulatory authorities, without written permission from Pfizer. Optum shall ensure that the DCTs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Optum has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents)

and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs are completed and submitted by the clinician reviewer(s), with time, date, and name of the clinician reviewer(s) recorded, who by submitting the DCTs attest to their accuracy and completeness. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and all prior entries are maintained for documentation.

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

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Optum agrees to keep all study-related records, including sufficient information to link records, (eg, DCTs and hospital records), electronic copies of all DCTs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by Optum according to local regulations or as specified in the Optum contract, whichever is longer. Optum must ensure that the records continue to be stored securely for so long as they are retained.

If Optum becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified, and study records should be retained under an arrangement acceptable to Pfizer that protects the confidentiality of the records (eg, secure off-site storage). Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Optum and Pfizer have expressly agreed to a different period of retention via a separate written agreement.

If Pfizer would like the Study Records kept longer than the 15-year retention period, Pfizer will notify Optum prior to the end of the 15-year retention period.

9.7. Data analysis

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

9.7.1. Annual interim reports

For each annual interim report, Optum will identify the number of pregnancies that are accrued into each of the exposure cohorts by exposure window. Eligible pregnancies included in each of the study cohorts will be described with respect to demographic characteristics (age at the ECD, geographic region, etc.), year of cohort entry, select comorbidities, and COVID-19 characteristics during pregnancy (eg, number of COVID-19 episodes, hospitalization during COVID-19 episode, etc.). Interim reports 2-4 will include information on all pre-specified covariates. Flow charts describing attrition due to application

of inclusion and exclusion criteria, including exclusion due to receipt of cohort medications in an inpatient setting, will be included. Interim reports will also include a tabulation of claims-based outcomes, by cohort and exposure window. The number of claims-identified outcomes available for medical record request will also be indicated.

Outcome validation via medical record review will not be performed until the final analysis. By design, for study outcomes which will be validated via medical record review, the initial claims definitions will be highly sensitive to ensure that all potential events are captured and subsequently reviewed by clinicians. For this reason, it is expected that annual interim reports will overestimate the number of outcome events occurring in study cohorts. Interim reports 2-4 will therefore include an alternative definition of MCM (MCM2) using only ICD-10-CM codes associated with major malformations as defined by the New York State Department of Health (New York State Department of Health 2023). Pending results from interim reports, the claims algorithm used to identify potential MCMs for medical record confirmation may be modified prior to implementation of final analyses. In that case, the protocol and SAP will be amended prior to implementation of final analyses to specify the claims algorithm used for medical record confirmation.

Interim reports 2-4 will also include estimates of effective sample size using the estimated ATT weights described by Shook-Sa and Hudgens (Shook-Sa & Hudgens 2022).

The number of accrued pregnancies will be assessed following the third interim report to determine whether there will be sufficient statistical power to detect a difference in risk across the study cohorts with respect to the outcomes of interest. The study accrual period may be shortened if a sufficient number of pregnancies are accrued prior to the end of the proposed study accrual period. In the event that the accrual of PAXLOVID-exposed pregnancies is slower than expected, the extension of the accrual period and/or the addition of a data partner may be considered.

9.7.2. Final report

For the final report at the culmination of the study, the number of pregnancies with COVID-19 that are accrued into each of the exposure cohorts by exposure window will be reported. Eligible pregnancies included in each of the study cohorts will be described with respect to covariates (Section 9.3.3).

A flow chart depicting the number of pregnant women with COVID-19, pregnancies included in each study cohort, adverse pregnancy outcomes (as identified by claims), livebirths, linked infants, and infant outcomes (as identified by claims) will be provided in the final report. For each outcome confirmed by medical record review, the number of outcomes identified by claims will be reported as well as the subset eligible for medical record request, the subset with medical records retrieved, the subset with confirmed outcomes, and the PPV. Analyses describing the characteristics of medical-record eligible and ineligible pregnancy episodes and pregnancies resulting in a livebirth with linked and non-linked infants will be performed. Multi-gestation pregnancies will be described and sensitivity analyses may restrict to singleton pregnancies for specific outcomes.

The prevalence of pregnancy outcomes and infant outcomes will be described for each cohort separately. Pending sufficient sample size, comparative analyses will be undertaken for each of the pregnancy and infant outcomes comparing the PAXLOVID-exposed pregnancy cohorts (Cohort 1) to the comparator pregnancy cohorts separately (Cohorts 2 and 3), by exposure window.

9.7.2.1. Propensity score modeling

For the final analysis, each pregnancy will be assigned a propensity score, a measure of the probability of receiving PAXLOVID versus a comparator treatment (or no treatment), given the patient's baseline characteristics. This propensity score will be utilized to implement IPTW to adjust for confounding.

IPTW produces groups (after weighting) that have similar patterns of the presence or absence of a large number of factors. The key to propensity score estimation is to perform a rich statistical analysis of the predictors of PAXLOVID exposure. The propensity score logistic regression model can incorporate demographic, comorbidity, treatment history, predictors of treatment choice, and co-medication indicators, as well as other potential confounders and risk factors.

In this study, all of the propensity score model variables will be determined from claims data and will be determined without respect to outcome status. For a given covariate pattern, the propensity score is the fitted value of the probability of being a member of the PAXLOVID group, given membership in the study population and the covariate pattern. To the extent that the decision to be dispensed PAXLOVID depends on the health characteristics of the patient at the time of the decision, the propensity score models the clinical decision-making process.

Four sets of propensity scores will be created: 1 for each of the comparator cohorts (Cohorts 2 and 3) versus Cohort 1, and 1 for each of the exposure windows (first trimester, full pregnancy). The decision to include variables in the model will be based on *a priori* knowledge (eg, expected confounder or known risk factor of adverse pregnancy/infant outcomes).

The covariates listed in Section 9.3.3.2.1 will be considered for inclusion in the model as independent (predictor) variables. The propensity score model will only include covariate information during the baseline period (prior to and including the index date). Hence, the propensity scores will incorporate characteristics at the start of the pregnancy. In addition to the pre-specified variables in Section 9.3.3.2.1, the most common diagnoses, procedures, and medications observed prior to estimated date of conception will be evaluated to ensure no important confounders are missed.

If there are too many variables given the number of pregnancies exposed to PAXLOVID (eg, < 10 exposed pregnancies for every variable in the propensity score model), the number of variables may be reduced using a LASSO model. Variables with an estimate of 0 in the LASSO model will be dropped from the propensity score variable list and a logistic regression model will be run using the remaining variables. For variable pairs that are highly correlated (eg, correlation coefficient > 0.9), 1 may be eliminated.

As patterns of prescribing tend to change over time, particularly for newly available products, with early adopters of the formulation (both physician and patient) tending to differ from late adopters, prediction equations need to account for these secular changes. As such, the propensity score models will incorporate calendar time to take into account the changing nature of the patient pool and COVID treatment guidelines over time. Incorporating calendar time may also account for changes in COVID-19 variants and severity over time (eg, Delta versus Omicron).

9.7.2.1.1. Inverse probability of treatment weighting

Propensity scores will be used to calculate IPTW weights and to weight each pregnancy in the exposure cohorts. For the IPTW analysis, a sample of comparators may be selected if a large number of pregnancies is accrued into the comparator cohorts (particularly the Untreated Comparator cohorts). This would be done to improve study efficiency through reducing the number of potential medical records to be sought among the comparator cohorts. If implemented for the final analysis, up to 5 comparators per PAXLOVID-exposed pregnancy will be sampled. Sampling of comparators will be performed via random sampling, without replacement, within strata of maternal age and calendar time based on the distributions within the PAXLOVID cohort. Sampling in this manner ensures that comparator pregnancies are approximately matched, at ECD, on the important covariates of maternal age and calendar time.

The IPTW weights will be defined such that the causal estimate is the average treatment effect among the treated (ATT) (Austin & Stuart 2015). Briefly, to estimate the ATT, the weights (w_{ATT}) are defined such that every PAXLOVID-exposed pregnancy receives a weight of 1, while the comparator pregnancies receive weights that are a function of the propensity score:

$$w_{ATT} = Z + \frac{e(1-Z)}{1-e},$$

where Z is the indicator for PAXLOVID exposure, e is the propensity score, and $\boldsymbol{X}$ is the covariate pattern used to predict PAXLOVID exposure (Section 9.7.2.1):

$$e = \Pr(Z = 1|\boldsymbol{X}).$$

Balance of covariates among the weighted cohorts will be assessed using the weighted standardized difference ($SD_{weighted}$) comparing the weighted study cohorts. Any variables with an absolute $SD_{weighted} > 0.1$ may be considered imbalanced. If specific variables remain imbalanced after IPTW, they may be included as independent predictors in outcome models. Trimming of extreme weights will be considered (Stürmer et al. 2014).

9.7.2.2. Descriptive analyses

For the descriptive analyses, the number of observations, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables, and the number and percentage of patients in each category will be presented for categorical variables. In addition to all characteristics reported in the interim reports, the study cohorts will be described according to the covariates listed in Section 9.3.3. Characteristics will be reported separately

for those with and without COVID-19 diagnoses prior to cohort medication exposure, as well as by hospitalization status at the time of the start of the COVID-19 episode associated with treatment (if applicable).

Crude prevalence estimates and corresponding 95% CIs for pregnancy outcomes, and separately for infant outcomes, will be calculated using robust Poisson regression models, with the denominator for the pregnancy outcomes being the number of pregnancies from which the cases arose, the denominator for the infant outcomes being the number of linked livebirths, and the numerator being the number of cases, as described in Table 4. Log-binomial regression models will be included as sensitivity analyses.

Table 4. Statistical Analyses of Study Outcomes

Outcome	Measure of Frequency	Measure of Association (Regression Model)	Timing of Outcome Ascertainment	Unit of Analysis
SA	Prevalence	Prevalence ratio (Poisson)	Before Week 20 of pregnancy	Pregnancy
Induced termination	Prevalence	Prevalence ratio (Poisson)	Before Week 20 of pregnancy	Pregnancy
Stillbirth	Prevalence	Prevalence ratio (Poisson)	At or after Week 20 of pregnancy	Pregnancy
Livebirth	Prevalence	Prevalence ratio (Poisson)	At end of pregnancy	Pregnancy
MCM	Prevalence	Prevalence ratio (Poisson)	At birth or during infant follow-up	Linked livebirths
SGA	Prevalence	Prevalence ratio (Poisson)	At birth or during infant follow-up	Linked livebirths
Preterm birth	Prevalence	Prevalence ratio (Poisson)	At birth or during infant follow-up	Linked livebirths
Postnatal growth deficiency	Prevalence	Prevalence ratio (Poisson)	At birth or during infant follow-up	Linked livebirths
Infant developmental delay	Prevalence	Prevalence ratio (Poisson)	At birth or during infant follow-up	Linked livebirths

9.7.2.3. Comparative safety analyses

The comparative analysis will estimate prevalence ratios and corresponding 95% CIs for each of the pregnancy or infant events comparing the PAXLOVID exposed pregnancy cohorts to the comparator pregnancy cohorts in the same exposure window (eg, Cohort 1 first trimester cohort versus Cohort 2 first trimester cohort; Cohort 1 first trimester cohort versus Cohort 3 first trimester cohort). Prevalence will be estimated for these outcomes because they develop during gestation but are only observable at birth; thus, only the prevalence at birth

can be calculated. Crude (unadjusted) and IPTW-adjusted prevalence ratios will be reported along with corresponding 95% CIs. The prevalence ratios will be estimated using robust Poisson regression models (Chen et al. 2018), with analysis of log-binomial models as sensitivity analysis.

Analyses based on claims-identified cases will be presented. However, the primary comparative analyses in the final report will only include outcomes that have been confirmed via medical record review or identified via published validated algorithms.

Planned analyses for each outcome are described in Table 4.

Comparative analyses will be performed overall and among subgroups according to presence of COVID-19 diagnoses occurring prior to exposure to cohort medications, as well as by hospitalization status at the time of COVID-19 diagnosis, sample size permitting.

Analyses will be conducted on MCMs collectively as a whole, with subgroup analyses by MCM subtype (for example, organ system affected) performed as sample size allows. The number of pregnancies with each outcome will serve to guide the analyses that are feasible.

Covariance between observations will be taken into account via robust standard errors if multiple pregnancies per woman are observed (Mansournia et al. 2021). Known confounders that are strongly associated with PAXLOVID use and the pregnancy or infant outcomes, or that remain imbalanced after weighting via IPTW, will also be included in the outcome regression models if standardized mean differences exceed >0.2 after IPTW (Austin 2009). Baseline covariates with an imbalance of 0.1-0.2 will be considered individually, taking into account their prevalence. Prior history of COVID-19 and the use of COVID-19 therapies during baseline and after cohort entry may be used for subgroup analysis. Other pregnancy characteristics (characteristics that are identified after baseline and that are therefore not incorporated into the propensity score models), such as COVID-19 severity, may also be considered for subgroups in secondary analysis.

9.7.3. Missing data

This study is based on an analysis of automated medical and prescription claims, supplemented by information abstracted from medical records. Using the standard approach in claims data analyses, the presence of a medication or disease claim will be assumed to indicate use of that medication or the presence of that disease and conversely, the absence of a medication or disease claim will indicate the absence of use of that medication or a diagnosis of that disease. Outcome data may be missing due to health plan disenrollment, or non-linked infants and missing or limited medical records. Sensitivity analyses are planned to assess the degree of bias potentially introduced by non-linkage of infants and missing or non-informative medical records. All retrieved medical records will be reviewed for mention of MCMs, as pregnancies that result in non-livebirths may not always capture MCMs in medical claims.

9.7.4. Additional analyses

9.7.4.1. Sensitivity analyses to account for exposure misclassification

As the association between maternal exposure and occurrence of pregnancy and infant outcomes may differ by timing of the exposure relative to fetal development, additional analyses will be conducted to assess the risk of MCMs by second and third trimester exposure (in addition to the primary analysis of first trimester and full pregnancy exposure windows). Additional alternative exposure windows (eg, a combined first and second trimester window of exposure, or weeks of gestation relating to organogenesis) may be considered, as sample size allows.

9.7.4.2. Quantitative bias analysis for unmeasured confounding

A quantitative bias analysis will be conducted to assess the potential magnitude of bias due to unmeasured confounding, including confounding by incompletely captured or missing covariates (eg, risk factors for progression to severe COVID-19 such as smoking or obesity). These analyses use informed estimates from the literature to identify the strength of unmeasured confounding that would be necessary to explain observed associations between the treatment (cohort membership) and outcomes (Schneeweiss 2006).

9.7.4.3. Quantitative bias analysis for unobserved outcomes

Because exposed pregnancies may be accrued (via observed Z3A codes) but which have no observed pregnancy outcome, and because completed pregnancies may not link to infants in the insurance databases, characteristics of pregnancies with and without observed outcomes, as well as livebirth pregnancies with and without linkage to infant(s) will be described according to baseline covariates. If substantial differences are observed, a sensitivity analysis will be performed in which comparative analyses are weighted to adjust for censoring due to missing pregnancy outcomes or non-linkage.

9.7.4.4. Comparator-specific analyses

Due to the differing mechanisms of action, routes of administration, and contraindications between comparator medications included in Cohort 2, an analysis will be performed in which, sample size permitting, each comparator drug is compared to PAXLOVID individually.

9.7.4.5. Any PAXLOVID exposure analysis

Because restricting the PAXLOVID cohort (Cohort 1) may select for patients with fewer risk factors for progression to severe COVID-19 by excluding patients requiring subsequent therapies after failure of PAXLOVID (ie, healthier patients), a sensitivity analysis will redefine the PAXLOVID cohort to include all pregnancies with any exposure to PAXLOVID during an exposure window, regardless of other therapies. This cohort will be compared, via IPTW, to the cohort of pregnancies exposed to other therapies but without exposure to PAXLOVID (Cohort 2).

9.7.4.6. Log-binomial analyses

Calculation of prevalence ratios will be conducted using log-binomial analyses instead of Poisson regression, following the approach described in section 9.7.2.

9.7.4.7. Subgroup analyses

Some women may be at a higher risk for certain pregnancy or infant outcomes. The balance of such high-risk attributes will be compared across cohorts, and an analysis will be performed that generates sub-group-specific estimates by the presence of these attributes. Additionally, descriptive and comparative analyses will be performed for different levels of the following baseline covariates: calendar time of first COVID-19 treatment initiation or infection, as well as by the duration between time of first COVID-19 treatment initiation or infection and ECD.

Additional sub-group analysis by risk factors for adverse pregnancy or infant outcomes observed during pregnancy (eg, infection during pregnancy, hospitalization during pregnancy) may be performed, with the acknowledgement that these may be post-treatment characteristics and thus susceptible to bias if they are affected by treatment. Sub-group specific estimates will be estimated from the Poisson regression model via inclusion of an indicator variable for the subgroup of interest, as well as an interaction term with the treatment indicator.

9.8. Quality control

The ORD contains data derived from claims submitted by providers and pharmacies to obtain payment for health care services rendered, data to track plan membership for premium billing, and provider data to track participating physicians who have contracts with health plans to provide services. The underlying administrative data are routinely captured, verified, automated, and de-identified. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. Although the health insurance claims data represent financial transactions and are not research records, the financial transactions related to the services provided create financial incentives to record them correctly and fully, so the billable medical services represented in the database are likely to be complete.

The conduct and reporting of this study follows Optum Epidemiology's Standard Operating Procedures (SOPs) that are consistent with the ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) (ISPE 2015) as well as the FDA's Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic) and FDA's Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance, September 2021 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory). For pregnancy safety studies such as this, the suggested study design and methodology are consistent with the FDA draft guidance document Postapproval Pregnancy Safety Studies Guidance for Industry

(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

The validation of analytic work typically involves a combination of a review of program logs and lists, independent coding, a review of program processes and documentation to ensure Optum SOPs are followed, and reconciliation of program code with the study protocol to ensure populations and results are consistent with what is needed for the study. Individual programs are documented and revised as needed until sign-off by a validation analyst using the validation/programming log.

9.9. Limitations of the research methods

This study is based on an analysis of automated and prospectively collected medical and prescription claims, supplemented by information abstracted from medical records. While claims data are extremely valuable for the efficient and effective examination of health-related outcomes and effects of different exposures to treatment on those outcomes, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment, not research. Presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Similarly, absence of a claim for a filled prescription does not preclude the possibility of exposure to a medication. Medications filled over-the-counter, provided as samples by the physician, or received during an inpatient hospital stay will often not be observed in the claims data. Presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Therefore, a medical record review will be conducted for select outcomes to confirm outcome events that are initially identified in medical claims.

COVID-19 infection will be assessed through the presence of a single diagnosis code, which was shown to have a high but decreasing PPV throughout calendar year 2020 (Kluberg et al. 2022), in a sample of hospitalized patients with known COVID-19 laboratory results covered by a national insurer. The literature regarding accuracy of ICD-10 COVID-19 diagnosis codes will be reassessed throughout the course of the study, and the algorithm for identification of COVID-19 may be modified if superior algorithms are published. If additional treatments with non-COVID-19 indications are included in study cohorts in the future, requiring a COVID-19 diagnosis prior to treatment may be considered for study eligibility.

Additionally, neither information on COVID-19 severity nor reasons for the test that determine the COVID-19 diagnosis are directly available in administrative claims data. Proxy measures for COVID-19 severity (eg, critical care services) have been added to the list of covariates (Section 9.3.3). Options for other proxies of severity and reason for diagnosis will continue to be explored; for example, co-occurrence of diagnoses on days with select other procedures (eg, diagnoses occurring on days with procedure codes for standard pre-natal visits) or site of diagnosis may serve as proxies for the reason of diagnosis.

Using ICD-10 Z3A codes to estimate the LMP date (and, subsequently, ECD) is expected to be accurate but, when Z3A codes are not present, using existing algorithms to estimate LMP (that are based on the presence of pregnancy outcomes) is expected to introduce a greater degree of measurement error for early pregnancy outcomes such as SA and induced termination. In addition, given the inexact estimation of LMP, classification of trimesters and the corresponding medication exposure could be inaccurate, with such non-differential misclassification of a binary exposure likely biasing study results toward the null.

In this study, the numbers of some pregnancy and infant outcomes are expected to be low. As the number of variables for inclusion in regression models is dependent on the number of study outcomes, the standard approach to controlling for confounding through regression modelling of the outcomes will yield estimates that are only adjusted for a small number of potential confounders. In contrast, propensity score modelling and IPTW allows for the inclusion of dozens of potential confounders and risk factors, resulting in greater validity of the estimates than what may be derived from regression modelling alone. While it is true that operationally, the IPTW analysis controls for variables that are included in the model and may not fully control for bias due to unknown confounders, it has been shown that, similar to randomization within clinical trials, propensity score modelling and adjustment often controls for confounding due to variables that are not explicitly included in the propensity score model through the inclusion of variables that are proxies for the non-included variables (Guertin et al. 2016).

Residual confounding is a concern due to the difficulty in defining appropriate comparator cohorts. While untreated (or inactive) comparator groups have known issues that limit exchangeability (eg, milder disease), the Untreated Comparator cohorts (Cohort 3) add value by providing an estimate of the background rate of the pregnancy and infant outcomes among diagnosed COVID-19 positive pregnant women. Moreover, though this study will account for a host of pre-pregnancy characteristics, the choice of PAXLOVID versus other COVID-19 therapies may be related to infection severity or other risk factors for progression to severe COVID-19, which could further be related to risk of pregnancy or infant outcomes. The potential magnitude of this bias will be assessed through a quantitative bias analysis which assesses the potential for unmeasured confounding to bias results, including by risk factors for COVID-19 severity.

As PAXLOVID may be the first-line therapy of choice for high-risk COVID-19 patients, restricting Cohort 1 to individuals not receiving other study cohort medications may select for patients with fewer risk factors for progression to severe COVID-19 (ie, healthier patients). This will be assessed by characterizing the number of different treatment types (eg, PAXLOVID followed by remdesivir) received both within and across COVID-19 episodes (if applicable) during a pregnancy, as well as in a sensitivity analysis in which pregnancies with any exposure to PAXLOVID, regardless of receipt of other treatments, are compared to Cohorts 2 and 3.

Identification of infant MCM within this study is limited to pregnancies that result in livebirths that are linked to the infants' data. Therefore, infant MCMs that result in SA,

induced termination, or stillbirth will not be included in the main analysis. Further, infant MCMs that may be noted in the mothers' claims at delivery (whose infants' data are not linked) may be missed. Finally, some infants will have less than a year of follow-up after birth (eg, due to disenrollment or deliveries at the end of the study period). As some MCMs can be diagnosed months after delivery this may result in the incomplete capture of some outcomes but is not expected to bias results (Wacholder et al. 1995). Sensitivity analyses will be conducted to quantify and to describe the potential infant MCMs among pregnancies that resulted in SA, induced termination, or stillbirth and those that may be missed due to non-linkage of the infant data or infant disenrollment from the health plan.

The study power will be limited until several years of cohort accrual have passed. Because accrual of PAXLOVID-exposed pregnancies depends on actual use within the insured population that is the source for the study, divergence in numbers of users from sample size projections might affect how rapidly the study power reaches an adequate level.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored by Optum in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Optum will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Optum shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws. There is no planned transfer of study data under this study protocol.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRBs. All correspondence with the IRB/independent ethics committee must be retained. Copies of IRB approvals must be forwarded to Pfizer.

Optum will prepare and submit the appropriate documents to a relevant IRB. Optum will communicate directly with the IRB to address any questions and/or provide any additional information in connection with the reviews. The IRB will monitor the study for the life of the project and may require formal re-review and approval on an annual basis. Changes to the project may also require re-review and approval by the IRB.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for GPP issued by the International Society for Pharmacoepidemiology (ISPE), and the European Medicines Agency, ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

The conduct and reporting of this study follow Optum Epidemiology's SOPs that are consistent with the ISPE's GPP (ISPE 2015).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve medical record review by the treating physician. External physician adjudicators will review medical records to confirm select outcomes among a subset of patients, as described in Section 9.3.1.3.

11.1. Structured data analysis

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

11.2. Human review of unstructured data

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

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

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool and reported, within 1 business day of awareness of the study team, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 1 business day of awareness, to Pfizer Safety using the NIS AEM Report Form.
- For exposure during pregnancy in studies of pregnant women, data on the exposure to PAXLOVID during pregnancy, are not reportable unless associated with serious or non-serious adverse events.
- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least 1 patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness,” “Study Drug,” and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members involved in the review of medical charts and completion of the NIS AEM Report Form must complete the following Pfizer training requirements:

- *“Your Reporting Responsibilities (YRR) Training for Vendors.”*

These trainings must be completed by research staff members prior to the start of unstructured data collection. All trainings include a “Confirmation of Training Certificate” (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current YRR training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will be posted on the HMA-EMA Catalogues of RWD Studies. Manuscripts based on specific outcomes of interest may be developed for publication purposes.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if Optum becomes aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Teratogenic drugs used for exclusion

Teratogenic Drugs	Half-life Range	Reference(s)
angiotensin-converting-enzyme (ACE) inhibitors	<1 to 17 hours	Sanders et al. 2011
angiotensin II receptor blocker*	2 to 24 hours	Burnier 2001
carbamazepine	18 to 65 hours	Bertilsson 1978
chemotherapeutic drugs for the treatment of cancer	Variable (maximum: 215 hours [mitoxantrone])	Ehninger et al. 1986
dolutegravir	14 hours	Mulligan et al. 2018
fluconazole	20 to 50 hours	Brammer et al. 1990
isotretinoin	Up to 29 hours	Brazzell et al. 1982
lithium	Up to 3 days following continuous therapy	Goodnick et al. 1981
methotrexate	Up to 69 hours	Shen et al. 1978
methylene blue	Up to 24 hours	Peter et al. 2000
misoprostol	<1 hour	Davies et al. 2001
mitoxantrone	215 hours	Ehninger et al. 1986
mycophenolate	Up to 17 hours	Fulton et al. 1996
penicillamine	Up to 6 days following treatment cessation	Munro et al. 1997
phenobarbital	Up to 132 hours	Nelson et al. 1982
phenytoin	Up to 42 hours	Ahn et al. 2008
teriflunomide	18 to 19 days	FDA 2012
thalidomide	<8 hours	Teo et al. 2004
topiramate	Up to 56 hours	FDA 1996
valproic acid	10 to 16 hours	Gugler et al. 1980
warfarin	Up to 40 hours	Walfisch et al. 2010

* Exposure in 2nd or 3rd trimester

Codes for the identification of pregnancy and infant outcomes

All codes are ICD-10 diagnosis codes unless otherwise specified.

Pregnancy Outcomes

The pregnancy outcomes to be assessed are:

- SA
  - O02.1 Missed abortion

- O03.0 Genital tract and pelvic infection following incomplete spontaneous abortion
- O03.1 Delayed or excessive hemorrhage following incomplete spontaneous abortion
- O03.2 Embolism following incomplete spontaneous abortion
- O03.30 Unspecified complication following incomplete spontaneous abortion
- O03.31 Shock following incomplete spontaneous abortion
- O03.32 Renal failure following incomplete spontaneous abortion
- O03.33 Metabolic disorder following incomplete spontaneous abortion
- O03.34 Damage to pelvic organs following incomplete spontaneous abortion
- O03.35 Other venous complications following incomplete spontaneous abortion
- O03.36 Cardiac arrest following incomplete spontaneous abortion
- O03.37 Sepsis following incomplete spontaneous abortion
- O03.38 Urinary tract infection following incomplete spontaneous abortion
- O03.39 Incomplete spontaneous abortion with other complications
- O03.4 Incomplete spontaneous abortion without complication
- O03.5 Genital tract and pelvic infection following complete or unspecified spontaneous abortion
- O03.6 Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion
- O03.7 Embolism following complete or unspecified spontaneous abortion
- O03.80 Unspecified complication following complete or unspecified spontaneous abortion
- O03.81 Shock following complete or unspecified spontaneous abortion
- O03.82 Renal failure following complete or unspecified spontaneous abortion
- O03.83 Metabolic disorder following complete or unspecified spontaneous abortion
- O03.84 Damage to pelvic organs following complete or unspecified spontaneous abortion
- O03.85 Other venous complications following complete or unspecified spontaneous abortion

- O03.86 Cardiac arrest following complete or unspecified spontaneous abortion
- O03.87 Sepsis following complete or unspecified spontaneous abortion
- O03.88 Urinary tract infection following complete or unspecified spontaneous abortion
- O03.89 Complete or unspecified spontaneous abortion with other complications
- O03.9 Complete or unspecified spontaneous abortion without complication
- O31.1--- Continuing pregnancy after spontaneous abortion of 1 fetus or more
- O31.2--- Continuing pregnancy after intrauterine death of 1 fetus or more
- O36.4--- Maternal care for intrauterine death
- CPT 59800[4] Treatment of spontaneous abortion, first trimester
- CPT 59801 Treatment of spontaneous abortion, first trimester
- CPT 59810 Treatment of spontaneous abortion, second trimester
- CPT 59811 Treatment of spontaneous abortion, second trimester
- CPT 59812 Treatment of incomplete abortion, any trimester, completed surgically
- CPT 59820 Treatment of missed abortion, completed surgically; first trimester
- CPT 59821 Treatment of missed abortion, completed surgically; second trimester

- Induced termination
  - O04.5 Genitl trct and pelvic infct fol (induced) term of pregnancy
  - O04.6 Delayed or excess hemor fol (induced) term of pregnancy
  - O04.7 Embolism following (induced) termination of pregnancy
  - O04.80 (Induced) termination of pregnancy with unsp complications
  - O04.81 Shock following (induced) termination of pregnancy
  - O04.82 Renal failure following (induced) termination of pregnancy

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- O04.83 Metabolic disorder following (induced) term of pregnancy
- O04.84 Damage to pelvic organs fol (induced) term of pregnancy
- O04.85 Oth venous comp following (induced) termination of pregnancy
- O04.86 Cardiac arrest following (induced) termination of pregnancy
- O04.87 Sepsis following (induced) termination of pregnancy
- O04.88 Urinary tract infection fol (induced) term of pregnancy
- O04.89 (Induced) termination of pregnancy with other complications
- O07.0 Genitl trct and pelvic infct fol failed attempt term of preg
- O07.1 Delayed or excess hemor fol failed attempt term of pregnancy
- O07.2 Embolism following failed attempted termination of pregnancy
- O07.30 Failed attempted termination of pregnancy w unsp comp
- O07.31 Shock following failed attempted termination of pregnancy
- O07.32 Renal failure following failed attempted term of pregnancy
- O07.33 Metabolic disorder fol failed attempt term of pregnancy
- O07.34 Damage to pelvic organs fol failed attempt term of pregnancy
- O07.35 Oth venous comp following failed attempted term of pregnancy
- O07.36 Cardiac arrest following failed attempted term of pregnancy
- O07.37 Sepsis following failed attempted termination of pregnancy
- O07.38 Urinary tract infection fol failed attempt term of pregnancy
- O07.39 Failed attempted termination of pregnancy w oth comp
- O07.4 Failed attempted termination of pregnancy w/o complication
- Z33.2 Encounter for elective termination of pregnancy
- ICD-10 Procedure 10A00ZZ Abortion of Products of Conception, Open Approach
- ICD-10 Procedure 10A03ZZ Abortion of Products of Conception, Percutaneous Approach
- ICD-10 Procedure 10A04ZZ Abortion of Products of Conception, Perc Endo Approach
- ICD-10 Procedure 10A07Z6 Abortion of Products of Conception, Vacuum, Via Opening
- ICD-10 Procedure 10A07ZW Abortion of Products of Conception, Laminaria, Via Opening

- ICD-10 Procedure 10A07ZX Abortion of POC, Abortifacient, Via Opening
- ICD-10 Procedure 10A07ZZ Abortion of Products of Conception, Via Opening
- ICD-10 Procedure 10A08ZZ Abortion of Products of Conception, Endo
- HCPCS S0190 Mifepristone ORAL 200 mg
- HCPCS S0191 Misoprostal oral 200 mcg
- HCPCS S0199 Medically induced abortion by oral ingestion of medication including all associated services and supplies
- HCPCS S2260 Induced abortion, 17-24 weeks
- HCPCS S2262 Abortion for maternal indication, 25 weeks or greater
- HCPCS S2265 Induced abortion, 25-28 weeks
- HCPCS S2266 Induced abortion, 29-31 weeks
- HCPCS S2267 Induced abortion, 32 weeks/greater
- CPT 01964[5] Anesthesia for abortion procedures
- CPT 01965 Anesthesia for incomplete or missed abortion procedures
- CPT 01966 Anesthesia for induced abortion procedures
- CPT 59840 Induced abortion, by dilation and curettage
- CPT 59841 Induced abortion, by dilation and evacuation
- CPT 59850 Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines;
- CPT 59851 Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
- CPT 59852 Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection)
- CPT 59855 Induced abortion, by 1 or more vaginal suppositories (eg, prostaglandin) with or without cervical dilation (eg, laminaria), including hospital admission and visits, delivery of fetus and secundines;
- CPT 59856[6] Induced abortion, by 1 or more vaginal suppositories (eg, prostaglandin) with or without cervical dilation (eg, laminaria), including

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hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation

- CPT 59857 Induced abortion, by 1 or more vaginal suppositories (eg, prostaglandin) with or without cervical dilation (eg, laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed medical evacuation)

- Stillbirth
  - O31.2--- Continuing pregnancy after intrauterine death of 1 fetus or more
  - O36.4--- Maternal care for intrauterine death
  - P95 Stillbirth
  - Z37.1 Single stillbirth
  - Z37.3 Twins, 1 liveborn and 1 stillborn
  - Z37.4 Twins, both stillborn
  - Z37.60 to Z37.64, Z37.69 Multiple births, some liveborn
  - Z37.7 Other multiple births, all stillborn
- Livebirth
  - Z37.0 Single livebirth
  - Z37.2 Twins, both liveborn
  - Z37.50 Multiple births, unspecified, all liveborn
  - Z37.51 Triplets, all liveborn
  - Z37.52 Quadruplets, all liveborn
  - Z37.53 Quintuplets, all liveborn
  - Z37.54 Sextuplets, all liveborn
  - Z37.59 Other multiple births, all liveborn
  - Z38.00 Single liveborn infant, delivered vaginally
  - Z38.01 Single liveborn infant, delivered by cesarean
  - Z38.1 Single liveborn infant, born outside hospital
  - Z38.2 Single liveborn infant, unspecified as to place of birth
  - Z38.30 Twin liveborn infant, delivered vaginally
  - Z38.31 Twin liveborn infant, delivered by cesarean
  - Z38.4 Twin liveborn infant, born outside hospital

- Z38.5 Twin liveborn infant, unspecified as to place of birth
- Z38.61 Triplet liveborn infant, delivered vaginally
- Z38.62 Triplet liveborn infant, delivered by cesarean
- Z38.63 Quadruplet liveborn infant, delivered vaginally
- Z38.64 Quadruplet liveborn infant, delivered by cesarean
- Z38.65 Quintuplet liveborn infant, delivered vaginally
- Z38.66 Quintuplet liveborn infant, delivered by cesarean
- Z38.68 Other multiple liveborn infant, delivered vaginally
- Z38.69 Other multiple liveborn infant, delivered by cesarean
- Z38.7 Other multiple liveborn infant, born outside hospital
- Z38.8 Other multiple liveborn infant, unsp as to place of birth

The following livebirth codes are used to identify livebirths in multiple gestation pregnancies with more than 1 outcome type:

- Z37.3 Twins, 1 liveborn and 1 stillborn
- Z37.60 Multiple births, unspecified, some liveborn
- Z37.61 Triplets, some liveborn
- Z37.62 Quadruplets, some liveborn
- Z37.63 Quintuplets, some liveborn
- Z37.64 Sextuplets, some liveborn
- Z37.69 Other multiple births, some liveborn

Infant Outcomes

The infant outcomes to be assessed are:

- Preterm birth
  - O60.1 Preterm labor with preterm delivery
  - P07.2 Extreme immaturity of newborn
  - P07.3 Preterm [premature] newborn [other]
  - P07.30 Preterm newborn, unspecified weeks of gestation
  - P07.31 Preterm newborn, gestational age 28 completed weeks
  - P07.32 Preterm newborn, gestational age 29 completed weeks
  - P07.33 Preterm newborn, gestational age 30 completed weeks
  - P07.34 Preterm newborn, gestational age 31 completed weeks

  - P07.35 Preterm newborn, gestational age 32 completed weeks
  - P07.36 Preterm newborn, gestational age 33 completed weeks
  - P07.37 Preterm newborn, gestational age 34 completed weeks
  - P07.38 Preterm newborn, gestational age 35 completed weeks
  - P07.39 Preterm newborn, gestational age 36 completed weeks
- SGA
  - P05.10 to P05.19 Newborn small for gestational age
- MCM

The following list of congenital malformation subcategories and codes is based on the EUROCAT Guide 1.4 dated 28 December 2018 (EUROCAT) and the New York State Department of Health Congenital Malformations Registry coding manual dated 22 October 2019 (NY State Department of Health), consistent with those tracked by the Metropolitan Atlanta Congenital Defects Program (MACDP; CDC 2021). Question marks indicate code subcategories where clinician input is desired.

EUROCAT subgroups	**ICD-10 code**
All anomalies	Q-chapter, D21.5, D82.1, P35.0, P35.1, P37.1
Nervous system	Q00*, Q01*, Q02, Q03, Q04*, Q05*, Q06*, Q07**
Neural tube defects	Q00*, Q01*, Q05*
Anencephaly and similar malformations	Q00*
Encephalocele	Q01*
Spina bifida	Q05*
Hydrocephalus	Q03
Microcephaly	Q02
Arhinencephaly/holoprosencephaly	Q04.1, Q04.2
Eye	Q10*, Q11*, Q12*, Q13**, Q14*, Q15*
Anophthalmos/microphthalmos	Q11.0, Q11.1, Q11.2
Anophthalmos	Q11.0, Q11.1
Congenital cataract	Q12.0
Congenital glaucoma	Q15.0
Ear, face, and neck	Q16*-Q18*
Anotia	Q16.0
Circulatory System	Q20*, Q21*, Q22*, Q23*, Q24*, Q25**, Q26*, Q27**, Q28*
Severe congenital heart defects	Q20.0, Q20.1, Q20.3, Q20.4, Q21.2, Q21.3, Q22.0, Q22.4, Q22.5, Q22.6, Q23.0, Q23.2, Q23.3, Q23.4, Q25.1, Q25.2*, Q26.2
Common arterial truncus	Q20.0
Double outlet right ventricle	Q20.1
Transposition of great vessels	Q20.3
Single ventricle	Q20.4
Ventricular septal defect (VSD)	Q21.0
Atrial septal defect (ASD)	Q21.1
Atrioventricular septal defect (AVSD)	Q21.2
Tetralogy of Fallot	Q21.3
Tricuspid atresia and stenosis	Q22.4

EUROCAT subgroups	**ICD-10 code**
Ebstein's anomaly	Q22.5
Pulmonary valve stenosis	Q22.1
Pulmonary valve atresia	Q22.0
Aortic valve atresia/stenosis	Q23.0
Mitral valve anomalies	Q23.2, Q23.3
Hypoplastic left heart	Q23.4
Hypoplastic right heart	Q22.6
Coarctation of aorta	Q25.1
Aortic atresia / interrupted aortic arch	Q25.2*
Total anomalous pulmonary venous return (TAPVR)	Q26.2
Patent ductus arteriosus (PDA) as only congenital heart disease (CHD) in term infants (gestational age +37 weeks)	Q25.0
Respiratory	Q30*-Q34*
Choanal atresia	Q30.0
Cystic adenomatoid malformation of lung	Q33.0
Oro-facial clefts	Q35*-Q37*
Cleft lip with or without cleft palate	Q36*, Q37*
Cleft palate	Q35*
Digestive system	Q38*-Q45*, Q79.0
Esophageal atresia with or without trachea-esophageal fistula	Q39.0, Q39.1
Duodenal atresia or stenosis	Q41.0
Atresia or stenosis of other parts of small intestine	Q41.1, Q41.2, Q41.8
Ano-rectal atresia and stenosis	Q42.0-Q42.3
Hirschsprung's disease	Q43.1
Atresia of bile ducts	Q44.2
Annular pancreas	Q45.1
Diaphragmatic hernia	Q79.0
Abdominal wall defects	Q79.2, Q79.3, Q79.5*
Gastroschisis	Q79.3
Omphalocele	Q79.2
Urinary	Q60*, Q61**, Q62**, Q63*, Q64**, Q79.4
Bilateral renal agenesis including Potter syndrome	Q60.1, Q60.6
Multicystic renal dysplasia	Q61.4
Congenital hydronephrosis	Q62.0
Bladder exstrophy and/or epispadias	Q64.0, Q64.1*
Posterior urethral valve and/or prune belly	Q64.2, Q79.4
Genital	Q50**, Q51***, Q52***, Q54*, Q55**, Q56*
Hypospadias	Q54*
Indeterminate sex	Q56*
Musculoskeletal	Q65**, Q66***, Q67*, Q68*, Q69*, Q70**, Q71***, Q72***, Q73*, Q74*, Q75*, Q76***, Q77*, Q78*, Q79**
Limb reduction defects	Q71***, Q72***, Q73*
Club foot – talipes equinovarus	Q66.0*
Hip dislocation and/or dysplasia	Q65.0*, Q65.1, Q65.2, Q65.80, Q65.81
Polydactyly	Q69*
Syndactyly	Q70**
Other anomalies/syndromes	
Skeletal dysplasias	Q74.0?, Q77*, Q78.0?, Q78.2-Q78.8

EUROCAT subgroups	ICD-10 code
Craniosynostosis	Q75.0
Congenital constriction bands/amniotic band	Q79.8?
Situs inversus	Q89.3
Conjoined twins	Q89.4
Congenital skin disorders	Q80*-Q82*
VATER/VACTERL	Q87.2?
Laterality anomalies	Q20.6, Q24.0, Q33.8?, Q89.0?, Q89.3
Teratogenic syndromes with malformations	Q86*, P35.0, P35.1, P37.1
Fetal alcohol syndrome	Q86.0
Valproate syndrome	Q86.8?
Maternal infections resulting in malformations	P35.0, P35.1, P37.1
Genetic syndromes and microdeletions	Q44.7?, Q61.9?, Q74.8?, Q75.1, Q75.4, Q75.8?, Q87**, Q93.51?, D82.1
Chromosomal	Q90*, Q91*, Q92**, Q93**, Q95*-Q99*
Down syndrome	Q90*
Patau syndrome/trisomy 13	Q91.4-Q91.7
Edwards syndrome/trisomy 18	Q91.0-Q91.3
Turner syndrome	Q96*
Klinefelter syndrome	Q98.0-Q98.4

* Indicates how many additional decimal places should be included in the wildcard, including the number listed. For instance, Q93
** should include the following: Q93 (non-billable), Q93.0, Q93.1, Q93.2, Q93.3, Q93.4, Q93.5 (non-billable), Q93.51, Q93.59, Q93.7, Q93.8 (non-billable), Q93.81, Q93.82, Q93.88, Q93.89, Q93.9.
? Inclusion to be considered with clinician consultation.

Codes that were included in the MACDP ICD-9 code list but are no longer classified as congenital malformations in the new ICD-10 categorization will be considered for inclusion, with clinician input if possible.

- E78.71 Barth syndrome
- E78.72 Smith-Lemli-Opitz syndrome
- M21.021 Valgus deformity, not elsewhere classified, right elbow
- M21.022 Valgus deformity, not elsewhere classified, left elbow
- M21.029 Valgus deformity, not elsewhere classified, unspecified elbow
- M21.121 Varus deformity, not elsewhere classified, right elbow
- M21.122 Varus deformity, not elsewhere classified, left elbow
- M21.129 Varus deformity, not elsewhere classified, unspecified elbow
- P02.8 Newborn affected by other abnormalities of membranes
- P29.3 Persistent fetal circulation (typically a birth complication and not a defect)

- **Postnatal growth deficiency**

- E34.30 Short stature due to endocrine disorder, unspecified

- E34.31 Constitutional short stature
- E34.32 Genetic causes of short stature
- E34.321 Primary insulin-like growth factor-1 (IGF-1) deficiency
- E34.322 Insulin-like growth factor-1 (IGF-1) resistance
- E34.328 Other genetic causes of short stature
- E34.329 Unspecified genetic causes of short stature
- E34.39 Other short stature due to endocrine disorder
- M89.20 Other disorders of bone development and growth, unspecified site
- M89.21* Other disorders of bone development and growth, shoulder
- M89.22* Other disorders of bone development and growth, humerus
- M89.23* Other disorders of bone development and growth, ulna and radius
- M89.24* Other disorders of bone development and growth, hand
- M89.25* Other disorders of bone development and growth, femur
- M89.26* Other disorders of bone development and growth, tibia and fibula
- M89.27* Other disorders of bone development and growth, ankle and foot
- P05.0* Newborn light for gestational age (newborn light-for-dates; weight below but length above 10th percentile for gestational age)
- P05.2 Newborn affected by fetal (intrauterine) malnutrition not light or small for gestational age
- P05.9 Newborn affected by slow intrauterine growth, unspecified
- P92.6 Failure to thrive in newborn
- R62.50 Unspecified lack of expected normal physiological development in childhood
- R62.51 Failure to thrive (child)
- R62.52 Short stature (child)
- R62.59 Other lack of expected normal physiological development in childhood
- Z00.71 Encounter for examination for period of delayed growth in childhood with abnormal findings

*indicates wildcard, to include all sub-codes

- **Infant developmental delay**
  - F80.0 Phonological disorder
  - F80.1 Expressive language disorder

- F80.2 Mixed receptive-expressive language disorder
- F80.4 Speech and language development delay due to hearing loss
- F80.81 Childhood onset fluency disorder
- F80.82 Social pragmatic communication disorder
- F80.89 Other developmental disorders of speech and language
- F80.9 Developmental disorder of speech and language, unspecified
- F70 Mild intellectual disabilities
- F71 Moderate intellectual disabilities
- F72 Severe intellectual disabilities
- F73 Profound intellectual disabilities
- F78.A1 SYNGAP1-related intellectual disability
- F78.A9 Other genetic related intellectual disability
- F79 Unspecified intellectual disabilities
- R41.83 Borderline intellectual functioning
- F82 Specific developmental disorder of motor function
- F84.0 Autistic disorder
- F84.2 Rett's syndrome
- F84.3 Other childhood disintegrative disorder
- F84.5 Asperger's syndrome
- F84.8 Other pervasive developmental disorders
- F84.9 Pervasive developmental disorder, unspecified
- F88 Other disorders of psychological development
- F89 Unspecified disorder of psychological development
- R41.842 Visuospatial deficit
- R41.843 Psychomotor deficit
- R62.0 Delayed milestone in childhood
- Z13.40 Encounter for screening for unspecified developmental delays
- Z13.41 Encounter for autism screening
- Z13.42 Encounter for screening for global developmental delays (milestones)
- Z13.49 Encounter for screening for other developmental delays

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