Study Information

Title	Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project
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Active substance	WHO ATC Code: L04AA29 Tofacitinb
Medicinal product	Xeljanz
Research question and objectives	What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes? <u>Objectives</u> 1. To monitor planned and unplanned pregnancies exposed to tofacitinib. 2. To evaluate the possible teratogenic effect of this medication on the primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, small for age for postnatal growth of live born children to one year of age. 3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up to one year of age. 4. To detect any increase in the

	prevalence or pattern of the above-mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program. 5. To describe pregnancy outcomes of all tofacitanib-exposed pregnancies enrolled in the exposure series (those not eligible for the cohort).
Author	Christina Chambers, PhD, MPH Professor of Pediatrics School of Medicine University of California San Diego 9500 Gilman Drive, MC 0828 La Jolla, CA 92093 Tel: +1 858-246-1704 Email: chchambers@ucsd.edu

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DMARD	Disease-modifying antirheumatic drug
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta congenital Defects Program
MRHD	Maximum Recommended Human Dose
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists
BPRER	Periodic Benefit-Risk Evaluation Report
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PsA	Psoriatic Arthitis
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
UC	Ulcerative Colitis
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Christina Chambers, PhD, MPH	Principal Investigator, OTIS Mother to Baby	University of California, San Diego	9500 Gilman Dr. #0828 La Jolla, CA, CA 92093-0828
Kenneth Lyons Jones, MD	Co-Investigator, OTIS Mother to Baby	University of California, San Diego	9500 Gilman Dr. #0828 La Jolla, CA, CA 92093
Ann Madsen, PhD, MPH	Epidemiologist	Pfizer, Inc.	235 East 42nd Street New York, NY 10017
Niki Palmetto, PhD, MPH	Epidemiologist	Pfizer, Inc.	235 East 42nd Street New York, NY 10017
Nana Koram, PhD, MPH	Epidemiologist	Pfizer. Inc.	235 East 42nd Street New York, NY 10017

4. ABSTRACT

Title: Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project, version 2.0, 24 June 2019.

Main author: Christina Chambers, University of California San Diego (UCSD) and the Organization of Teratology Information Specialists (OTIS)

Rationale and background: Many rheumatic diseases affect women of childbearing age. Although improvement of rheumatoid arthritis (RA) and psoriatric arthritis (PsA) disease activity spontaneously occurs in many women during pregnancy,[1,2] only a minority are reported to be in complete remission during pregnancy.[3,4] Therefore, many women still require maintenance disease-modifying drug (DMARD) therapy for their conditions, which may affect conception, pregnancy, and fetal development.[5]

Studies in women with ulcerative colitis (UC) have shown a higher risk of adverse birth outcomes compared with controls, including low birth weight, preterm delivery, and neonatal death.[6,7,8] In addition, UC active disease at the time of conception has been associated with a higher risk of disease relapse during pregnancy.[8,9]

Tofacitinib is an oral janus kinase (JAK) inhibitor and is currently approved in the US for adults with moderately to severely active RA and active PsA who have had an inadequate response to or intolerance to methotrexate or other DMARDs, and for the treatment of adults with moderate to severely active UC. Human pregnancy exposure data for tofacitinib is limited; however tofacitinib is likely to be utilized by pregnant women when they and their doctors believe that risk/benefit considerations favor its use. Also, given the frequency of unplanned pregnancies, information regarding the safety of tofacitinib in human pregnancy is essential from a public health perspective.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the Food and Drug Agency (FDA).

Research question and objectives: What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes? The objectives of the Tofacitinib Pregnancy Exposure Registry are to:

1. Monitor planned and unplanned pregnancies exposed to tofacitinib.

2. To evaluate the potential teratogenic effect of this medication relative to the primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age for postnatal growth of live born children to one year of age.

3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up to one year of age.

4. To detect any increase in the prevalence or pattern of the above mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program,[10] and

5. To describe pregnancy outcomes of all tofacitanib-exposed pregnancies enrolled in the exposure series (those not eligible for the tofacitinib-exposed cohort).

Study design: This is a prospective, observational, exposure cohort study of pregnancy and infant outcomes in women with a disease for which tofacitinib has an approved indication and enrolled in the registry prior to 20 weeks from the first day of the last menstrual period (LMP). The birth prevalence or incidence of outcomes in women exposed to tofacitinib within first 12 weeks post LMP and their infants will be compared to those observed in 2 unexposed comparator groups: a disease-matched comparison group of women who have not used tofacitinib during pregnancy (disease comparison group), and a comparison group of healthy women who do not have an autoimmune disease, have not had exposure to a known human teratogen, and have not taken tofacitinib in pregnancy (healthy comparison group).

Population: The study population includes pregnant women who reside in the U.S. or Canada, who do or do not have a disease for which tofacitinib has an approved indication, and have or have not used tofacitinib for any length of time in pregnancy.

Three groups of participants will be enrolled in the study cohort prior to 20 weeks gestation and followed for pregnancy and infant outcomes:

- Pregnant women with an approved indication exposed to tofacitinib within the first 12 weeks post-LMP;

- Pregnant women with an approved indication not exposed to tofacitinib during pregnancy;

- Pregnant women who do not have an autoimmune disease, have not had exposure to a known human teratogen, and have not taken tofacitinib during pregnancy.

Another group of participants who are tofacitinib-exposed but do not meet cohort study selection criteria will be enrolled in the exposure series.

Variables: Exposure will be defined as tofacitinib treatment by maternal report and verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. Outcome variables include major structural birth defects, spontaneous abortion, stillbirth, elective termination for any reason, preterm delivery, infant birth size, postnatal growth of live born children up to one year of age, and serious or opportunistic infections or malignancies in live born children up to one year of

age. These will be obtained by maternal report and verified by medical record review. Potential confounders or covariates to be collected include maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, prenatal tests, measures of disease severity, as well as indication.

Data sources: Data will be collected using maternal interviews, medical records (obstetric, delivery hospital, pediatric, rheumatologist, dermatologist, gastroenterologist, and/or other specialty provider), and pregnancy exposure diary. Maternal interview data will be recorded on hard copy forms, and medical record abstraction data will be recorded on electronic forms, which will be retained by OTIS. Maternal interview forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located at the OTIS Research Center and developed specifically for the OTIS studies.

Study size: The target sample size for the study is 300 pregnant women; 100 pregnant women in each of the three cohort groups: tofacitinib-exposed, disease-matched unexposed, and non-diseased unexposed.

Data analysis: Demographic and baseline characteristics will be compared between the cohorts. The primary analysis will be a comparison of the prevalence rate of major structural birth defects in live born infants between the tofacitinib-exposed cohort and the disease-matched unexposed cohort. Where numbers permit, multivariable analyses will be conducted to determine the relationship of tofacitinib with the primary outcome of major structural birth defects, and the secondary outcomes of small for gestational age, preterm delivery, spontaneous abortion, stillbirth, elective termination and small for age postnatal growth, as numbers permit.

Milestones: The study was originally planned for five years. In 2019, the protocol was amended to include any approved indication, and the data collection timeline was extended for an additional five years, with a final study report and analysis projected for March 2024. An interim report will be reviewed by the Scientific Advisory Board and Sponsor annually. The final report with statistical analysis according to the statistical analysis plan will be prepared at the end of the study.

5. AMENDMENTS AND UPDATES

Amend-ment number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	24 Jun 2019	9.2.2	Inclusion of any approved tofacitinib indication in the exposed and disease comparison groups	Tofacitinib has recently received FDA approval for indications of psoriatic arthritis and ulcerative colitis. This is in addition to the previously approved rheumatoid arthritis indication. The protocol has been amended to include indications as they are approved.
1	24 Jun 2019	6	Amended final study report date from 31 Aug 2018 to 30 Mar 2024	Data collection and study report milestones extended to accommodate new indications, and continue data collection for RA indication, given low recruitment to date.
1	24 Jun 2019	Global	Edited protocol to adapt to new Pfizer protocol template	A new CT24 template had been approved since approval of initial protocol.

6. MILESTONES

Milestone[1]	Planned date
Original Contract Signed	31 July 2013
IRB Approval	31 August 2013
Start of data collection	01 November 2013[2]
End of data collection	30 September 2023
Registration in the EU PAS register	20 February 2014
Final study report	30 March 2024

[1] Annual study progress reports and mid-year recruitment and malformation table update reports will be included within the periodic benefit-risk evaluation report (PBRER) cycle for tofacitinib.
[2] This is the original start date of data collection for the rheumatoid arthritis indication. Planned start of data collection for PsA and UC indication is May 2019.

7. RATIONALE AND BACKGROUND

Many rheumatic diseases affect women of childbearing age potential and the medications used to treat these diseases may affect conception, pregnancy, and fetal development (Skomsvoll, 2001).[5] Although improvement of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) disease activity spontaneously occurs in a proportion of pregnancies many women still require maintenance disease-modifying drug (DMARD) therapy for their conditions. There is some suggestion that women with RA have decreased fecundity (probability of conception) and decreased fertility (ability to conceive) (Nelson, 1997).[1] However, there is no strong evidence that suggests an association between RA and adverse fetal outcome (Nelson, 1997).[1] Disease activity seems to improve in many women with RA during pregnancy, however only a minority are reported to be in complete remission during pregnancy (Barrett et al, 1999; de Man et al, 2008).[3,4] In 80% of women with psoriatic arthritis (PsA), the disease improved during pregnancy (Ostensen, 1992).[2] Children born to mothers with inflammatory arthritis have an increased incidence of preterm birth,small for gestational age, low birth weight, increased perinatal mortality and congenital malformations (Skomsvoll, 1999).[11] A 3.5% birth defect rate was reported in Norwegian women with specified and non-specified inflammatory arthritis including rheumatoid arthritis. However, the actual number of women with rheumatoid arthritis in this population may not be clear (Skomsvoll, 1999).[11] These adverse outcomes may be related to the underlying autoimmune disease or to concomitant rheumatic therapy. The safety of taking most anti-rheumatic drugs during pregnancy is not clear since experience in humans is usually anecdotal.

Studies in women with ulcerative colitis (UC) have shown a higher risk of adverse birth outcomes compared with controls, including low birth weight, preterm delivery, and neonatal death (Cornish, 2007, Stephansson, 2011, Mahadevan, 2018).[6,7,8] In addition, UC active disease at the time of conception has been associated with a higher risk of disease relapse during pregnancy (de Lima-Karagiannis, 2016, Mahadevan, 2018).[8,9]

Tofacitinib is an oral janus kinase (JAK) inhibitor and is currently approved in the US for adults with moderately to severely active RA and active PsA who have had an inadequate response to or intolerance to methotrexate or other DMARDs, and for the treatment for of adults with moderate to severely active UC. For RA, it may be used in combination with methotrexate or in monotherapy. Additionally, tofacitinib is approved for RA, PsA, and UC in Canada, the EU, and other global regions.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the U.S. Food and Drug Administration (FDA).

8. RESEARCH QUESTION AND OBJECTIVES

What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes?

8.1. Objectives

1. To monitor planned and unplanned pregnancies exposed to tofacitinib.

2. To evaluate the possible teratogenic effect of tofacitinib relative to primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, small for postnatal growth of live born children to one year of age.

3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up through one year of age.

4. To detect any increase in the prevalence or pattern of the above-mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program.[10]

5. To describe pregnancy outcomes of all tofacitinib-exposed pregnancies enrolled in the exposure series (see Section 9.2.4) (those not meeting inclusion/exclusion criteria (Section 9.2.2 and Section 9.2.3) for the tofacitinib-exposed cohort).

9. RESEARCH METHODS

9.1. Study Design

This is a prospective, observational cohort study of pregnancy outcomes in women with a disease for which tofacitinib has an approved indication who are exposed to tofacitinib during pregnancy compared to pregnancy outcomes in women with these same indicated diseases who have not been exposed to tofacitinib during pregnancy (disease-matched unexposed comparison group), and pregnancy outcomes in women without an autoimmune disease (non-diseased unexposed comparison group). Women with exposure to tofacitinib

during pregnancy who do not meet the eligibility criteria will be enrolled into the exposure-series (Section 9.2.3).

9.2. Setting

The cohort study will be conducted by the Organization of Teratology Information Specialists (OTIS) which is a network of university and health department based telephone information centers serving pregnant women and healthcare providers throughout North America.[12] These services receive spontaneous telephone inquiries from women and health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the U.S. and Canada will serve as a source of referrals not only for tofacitinib-exposed pregnancies but also for similarly-ascertained pregnant women with an approved indicated disease who have not used tofacitinib and similarly ascertained pregnant women without an autoimmune disease who have not used tofacitinib or any known human teratogen. As OTIS member services receive over 70,000 teratogen information telephone inquiries per year, OTIS members constitute a major source of identification and recruitment of exposed women and appropriate comparison women. Once women are in contact with the Registry Coordinating Center, enrollment in the Registry is voluntary and requires informed consent of the pregnant woman. The Registry will enroll pregnant women who are less than 20 weeks' gestation. This is accomplished by encouraging clinicians to refer patients, and following-up with women who are planning pregnancy who contact an OTIS service or who self-refer, and direct outreach efforts to target women who are less than 20 weeks' gestation. These efforts reduce possible bias based on prior knowledge of a normal ultrasound, and allow for better estimation of risk of spontaneous abortion.

The study population includes pregnant participants with a disease for which tofacitinib has an approved indication with exposure to tofacitinib during pregnancy, and two comparison groups without tofacitinib exposure during pregnancy (one disease-matched unexposed comparison group, and one non-diseased unexposed comparison group) who reside in the U.S. or Canada. With the addition of the approved indications, it is anticipated that approximately 20 pregnant women with exposure to the tofacitinib could be enrolled in the Registry each year of the additional five-year recruitment period.

9.2.1. Analysis Population ("cohort analysis")

Although the Registry will collect and follow up on reports of all types (ie, retrospective, paternal, off-label indication, etc.) involving pregnancy exposure to tofacitinib, regardless of inclusion/exclusion criteria ("exposure case series"), the core of the Registry will be a multicenter prospective cohort study ("cohort analysis") designed to ascertain and follow-up on cohort-eligible (meeting all inclusion and exclusion criteria) exposures to tofacitinib and to compare these to two internally-generated comparison groups and one external comparison group.

- Comparison Group I consisting of pregnant women who have a disease for which tofacitinib has an approved indication but did not take tofacitinib, including a subgroup of women who have taken an anti-TNF medication during pregnancy.

- Comparison Group II consisting of pregnant women who contact an OTIS member service and who do not have an autoimmune disease nor have exposure to any known teratogens. This will be a secondary comparison group.

Regarding the risk of major structural defects (primary outcome) among tofacitinib users, an external comparison will also be made to the Metropolitan Atlanta Congenital Defects Program (MACDP), which is a population-based birth defects surveillance program in the U.S. with careful follow-up and classification of major structural defects identified up to six years of age. This particular program is considered appropriate for external comparison given the fact that it is population based and includes a relatively high level of validation of reported defects identified in children up to six years of age. The overall rate of major structural defects identified in the MACDP (approximately 3% in 2005) is comparable to the overall rates (2-3%) identified in larger samples of Teratogen Information Service cohort studies that involve a careful review of medical records and physician examinations.

9.2.2. Inclusion Criteria for "Cohort Analysis" Group

The study will enroll women in three cohorts:

1. **Tofacitinib-Exposed Group- Inclusion Criteria.**

    - Currently pregnant women who have had an exposure to tofacitinib, for the treatment of a disease for which tofacitinib has an approved indication, for any number of days, at any dose, and at anytime from the 1st day of the last menstrual period up to and including the 12th week after the first day of the last menstrual period (LMP). If the date of LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than one week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception, and

    - Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and

    - Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

2. **Comparison Group I: Disease-matched Unexposed (to tofacitinib) Cohort – Inclusion Criteria.**

   - Currently pregnant women with a diagnosis of a disease for which tofacitinib has an approved indication, by maternal report and validated by medical records, who have not taken tofacitinib any time since first day of last LMP to delivery in the current pregnancy but who may or may not have taken another medication for their disease including an anti-TNF or other biologic in the current pregnancy. To the extent that tofacitinib-exposed women enrolled in the cohort study also have methotrexate exposure, women in the disease-matched unexposed comparison group I with methotrexate exposure will be recruited to frequency match the number with tofacitinib plus methotrexate, and

   - Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and

   - Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

3. **Comparison Group II: Non-diseased Unexposed (to tofacitinib) Cohort -Inclusion Criteria.**

   - Currently pregnant women who have not had exposure to a known human teratogen or biologic agent as confirmed by the OTIS Research Center, and

   - Currently pregnant women who do not have an autoimmune disease,

   - Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and

   - Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

9.2.3. Exclusion Criteria for "Cohort Analysis" Group

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

1. **Tofacitinib-Exposed Group- Exclusion Criteria.**

    - Currently pregnant women who have had an exposure to tofacitinib during pregnancy but have also had an exposure to one or more of the following (either known human teratogens or medications of unknown safety used for the same indication) during the index pregnancy will not be qualified as subjects for the tofacitinib-exposure group in the cohort study:

        - Chlorambucil;
        - Cyclophosphamide;
        - Mycophenylate mofetil;
        - Adalimumab;
        - Abatacept;
        - Certolizumab pegol;
        - Etanercept;
        - Tocilizumab;
        - Infliximab;
        - Golimumab;
        - Vedolizumab;
        - Secukinumab;
        - Ustekinumab;
        - Ixekizumab;
        - Or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available;

    - Women who have first contact with the project after prenatal diagnosis of any major structural defect,

    - Women who have enrolled in the cohort study with a previous pregnancy,

- Women who have used tofacitinib for an indication other than an approved indicated disease,

- Note: Retrospective cases will be followed (see subsequent sections), but will not be included in the cohort study.

2. Comparison Group I – Exclusion Criteria

- Currently pregnant women who have had an exposure to the medications listed below that are known or suspected human teratogens:

  - Chlorambucil;

  - Cyclophosphamide;

  - mycophenylate mofetil;

  - or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available,

- Women who have first contact with the project after prenatal diagnosis of any major structural defect,

- Women who have enrolled in the cohort with a previous pregnancy.

3. Comparison Group II – Exclusion Criteria

- Currently pregnant women who incur an exposure to a known teratogen in the first trimester after the time of enrollment will be disqualified as subjects for purposes of the analysis,

- Women who have a diagnosis of an autoimmune disease,

- Women who have first contact with the project after prenatal diagnosis of any major structural defect,

- Women who have enrolled in the cohort study with a previous pregnancy.

9.2.4. Tofacitinib-exposed Pregnancies not Eligible for the Cohort Study ("exposure series")

By study design, pregnancies that do not meet the exposed cohort criteria for reasons described in Section 9.2.2. and 9.2.3 will be excluded from the cohort analysis, however, information on their birth outcomes can be useful for hypothesis generating when reviewing the cohort data. For this reason, women who do not meet the exposed cohort criteria will be invited to enroll in a separate "exposure series".

With informed consent, data will be collected from maternal questionnaires, medical records review and the physical examination using the same protocol as the cohort study to the extent possible.

9.2.5. Modalities of Recruitment

All exposed subjects and comparison subjects will be recruited through spontaneous callers to participating OTIS member services in locations throughout North America and through active recruitment strategies, eg, direct mailings to specialist, obstetric health care providers, pharmacists, web site, and professional meetings. Each OTIS service will provide exposure counseling in the routine manner for all exposed and unexposed women who initially make contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service will explain the study protocol to potentially eligible participants, and then will request permission to refer to the Research Center at the University of California, San Diego. Potential subjects who agree to be referred will contact the Research Center or be contacted if they prefer. OTIS member services will also refer callers to the Research Center whose exposure to tofacitinib does not appear to qualify for the cohort study (eg, post first trimester exposure,retrospective reports), as these will be handled as Exposure Case Series (See Section 9.2.3). Health care providers can also contact the Registry and refer patients; however, in all cases the mother is the individual who provides informed consent for participation and completes the interview-based data collection.

9.3. Variables

This study uses secondary data that is routinely collected as part of the OTIS Pregnancy Registy. Table 1 provides a description of variables to be included in this study.

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Exposure to tofacitinib	Exposure	Maternal report Medical record	Maternal report of exposure to tofacitinib of at least one dose any time from first day of last menstrual period (LMP) to end of pregnancy. Confirmation of exposure with medical records.
Dose of tofacitinib	Exposure	Maternal report Medical record	Dose of tofacitinib in mg per day (maternal report and confirmation with medical records).
Duration of tofacitinib use	Exposure	Maternal report Medical record	Weeks of tofacitinib use in pregnancy (maternal report and confirmation with medical records).

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Indication	Exposure	Maternal report Medical record	Indication for use of tofacitinib (maternal report and confirmation with medical records).
Major structural birth defect	Outcome - primary	Maternal report Medical record OTIS investigator review Dysmorphological Evaluation	The Registry adopts the term "major structural defect" (ie,birth defect) for an abnormality usually referred to as a "congenital abnormality" and defines major structural defect as follows: • Any major structural or chromosomal defect defined and classified, using the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects (CDC 2017). The CDC guidelines disqualify as major structural defects: • Those findings that are present in infants with outcomes at <36 weeks gestational age or if gestational age is unavailable, weighing <2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias. • Infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without major structural defects unless there is a possibility that the condition reflects an

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
			unrecognized major structural defect.
Minor structural defect	Outcome - secondary	Maternal report Dysmorphology Evaluation	A defect which occurs infrequently in the population but which has neither cosmetic nor functional significance to the child and is identified using a study-related checklist incorporated into the study dysmorphology examination of live born infants.
Spontaneous abortion	Outcome - secondary	Maternal report Medical record	Non-deliberate embryonic or fetal death that occurs prior to 20.0 weeks' gestation.
Stillbirth	Outcome - secondary	Maternal report Medical record	A non-deliberate fetal death that occurs at or after 20.0 weeks' gestation but prior to delivery.
Premature delivery	Outcome - secondary	Maternal report Medical record	A spontaneous or induced delivery at <37 gestational weeks (as counted from LMP), reported by the mother and validated through the medical record.
Small for gestational age	Outcome - secondary	Maternal report Medical record	Birth size (weight, length or head circumference) $\leq 10^{th}$ percentile for sex and gestational age using National Center for Health Statistics (NCHS) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants will be used for premature infants (Olsen 2010).[16]

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Postnatal growth deficiency	Outcome - secondary	Medical record	Postnatal size (weight, length or head circumference) $\leq 10^{th}$ percentile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants.
Lost-to-follow-up	Outcome - secondary	Telephone attempts Mail/Email contact attempts Maternal report	An enrolled subject who withdraws or who fails to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within one year of the mother's estimated due date.
Serious or opportunistic infection	Outcome - secondary	Maternal report Medical record	Defined as those in appendices and infections requiring hospitalization, identified in newborn infants up to one year of age.
Malignancy	Outcome - secondary	Maternal report Medical record	Any malignancy reported in an infant up to one year of age.
Age	Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Race	Confounder	Maternal report	Maternal/Paternal race (Caucasian/White, Black, Asian/Pacific Islander, Native American, Other).
Ethnicity	Confounder	Maternal report	Maternal/Paternal ethnicity (Hispanic, Non-Hispanic).
Education	Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15).

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Socioeconomic Category	Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5).
Height	Confounder	Maternal report	Maternal height (cm).
Pre-pregnancy body weight	Confounder	Maternal report Medical record	Maternal pre-pregnancy body weight (kg) (confirm with medical record).
Pre-pregnancy BMI	Confounder	Maternal report	Maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, >=30).
Number of times pregnant	Confounder	Maternal report Medical record	Number of times ever pregnant (1, 2-3, 4-5, >=6) (confirm with medical record).
Previous live birth or stillbirth deliveries	Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5) (confirm with medical record).
Previous pregnancies ending in spontaneous abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, >=3) (confirm with medical record).
Previous pregnancies ending in elective termination	Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination (0, 1, 2, >=3) (confirm with medical record).
Gestational age	Confounder	Maternal report Medical record	Weeks of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, >=20): gestational age is calculated from the first date of LMP.
Referral source	Confounder	Maternal report	Source options: Sponsor, OTIS service, HCP, Internet, Other.

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Geographic area of residence	Confounder	Maternal report	Geographic area of residence (eg, US, Canada).
Disease Symptom/Severity measures	Confounder	Maternal report	Disease Symptom/Severity measures (exposed and disease-matched cohorts only).
Prenatal, Multivitamin, or Folic acid	Confounder	Maternal report	Prenatal, Multivitamin or Folic Acid supplement use by timing (began prior to conception, post-conception only, not taken at all).
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured.
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No.
Prenatal diagnostic tests prior to enrollment	Confounder	Maternal report Medical record	Tests performed prior to enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Prenatal diagnostic tests anytime during pregnancy	Confounder	Maternal report Medical record	Tests performed anytime in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Maternal pregnancy exposure to another known human teratogen	Confounder	Maternal report Medical record	Maternal pregnancy exposure to another known human teratogen (eg, methotrexate) (confirm with medical record).
Years since diagnosis of approved indicated disease	Confounder	Maternal report Medical record	Years since diagnosis of approved indicated disease.

Abbreviations: BMI = body mass index; CDC = Centers for Disease Control and Prevention; cm = centimeters; kg = kilograms; HCP = health care provider; LMP= last menstrual period; MACDP= Metropolitan Atlanta Congenital Defects Program; NCHS = National Center for Health Statistics; OTIS = Organization of Teratology Information Specialists; US = United States.

The Statistical Analysis Plan (SAP) will provide greater detail on the definitions of, the identification of and the controlling for confounders and/or effect modifiers.

9.4. Data Sources

The OTIS Research Center is responsible for verifying the subject selection criteria, enrolling each subject and securing informed consent, oral and written (when available or applicable), providing all pregnancy (intake/enrollment and interim I and II) and post-partum follow-up interviews and medical record review, scheduling dysmorphological physical examinations, recording and storage of all data, and subsequent data analysis and interpretation.

9.4.1. Intake/Enrollment Interview

Following oral administration of informed consent, a structured maternal intake telephone interview will be conducted by a trained Research Associate at the OTIS Research Center. This interview will include questions on the following: pregnancy history; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category, current medication use, both prescriptive and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; names and addresses of health care providers; and history of onset and other characteristics of an approved indicated disease if applicable. Women with an approved indicated disease will be asked to respond to an appropriate severity assessment questionnaire/quality of life questionnaire which is a validated measure of disease severity or quality of life that has been used in the current OTIS Autoimmune Diseases in Pregnancy Project as a means of assessing the potential contribution of severity of disease as represented by maternal symptoms to pregnancy outcome. Once the intake interview is complete, an enrollment packet will be sent to the participant including a written consent for signature, the U.S. Health Insurance Portability and Accountability Act (HIPAA) Authorization Addendum (when applicable), an obstetric medical record release form, and a diary to record information about any exposures or prenatal testing during pregnancy.

9.4.2. Interim Interviews I and II (20 and 32 Weeks' Gestation)

Women who have enrolled in the study prior to 18 weeks post-LMP will be interviewed by telephone at 20-22 weeks post-LMP, 32-34 weeks post-LMP and within two to six weeks after the expected due date. Women who have enrolled between 19 and 20 weeks post-LMP will be interviewed at 32-34 weeks post-LMP (See Table 2 Timing of Cohort Enrollment, Interviews, Examinations, Medical Record Request and Review).

The purpose of these interviews will be to update records of pregnancy exposures and results of prenatal tests, administer the severity assessment (when applicable) to remind women to maintain the exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date.

9.4.3. Pregnancy Outcome Interview

At any of the interim interview points, if the pregnancy has ended, the outcome interview will be conducted at this time or at the earliest convenient time for the mother. For women who are still pregnant at the 32-34 week interview, the outcome interview will be conducted within 0 to six weeks after the expected due date.

The outcome interview for live born infants will be a structured telephone interview and information will be elicited on the following: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.

The outcome interview for spontaneous or elective abortions will also be structured and information will be elicited on the following: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview. The outcome interview for stillborn infants will include all of the above plus information on sex, birth size and autopsy results if available.

Adverse pregnancy outcomes related to study endpoints will be reported to Pfizer as part of the annual study report; major structural defects, spontaneous abortions, elective terminations, fetal or neonatal deaths occurring in the tofacitinib-exposed group will be reported to the Sponsor within 24 hours of the Research Center staff learning of the event. These reports will be made using the FDA's MedWatch form. Pfizer will be responsible for directly reporting to the FDA for events involving their product according to regulatory guidelines.

9.4.4. Medical Records and General Pediatric Evaluation

Upon completion of the outcome interview, each woman will be mailed a packet containing medical records release forms for the delivery hospital, obstetrician, pediatrician, and spcialist if applicable. For women whose pregnancies have ended in spontaneous or elective abortion or stillbirth, records release forms will be mailed for the specialist's evaluation, if applicable, and if prenatal diagnosis, pathology or autopsy reports are available. Each woman will be asked to sign the forms and to return them along with the pregnancy exposure diary form.

Upon receipt of the signed medical records release forms, a standard physical evaluation form will be mailed to each pediatrician or other physician responsible for the care of each live born infant. This form includes information on infant size at the time of the latest examination and an open-ended question about postnatal complications and congenital anomalies.

At one year of age, another medical records release form for the pediatrician, or health care provider caring for the child, is sent to the mother for signature. The signed form with a standard physical evaluation form is sent to the health care provider to request updated information on growth, major structural defects, any serious or opportunistic infections, hospitalization, and/or malignancies.

9.4.5. Dysmorphological Evaluation

Live born infants will be examined by one of a team of study-dedicated dysmorphologists, led by Co-Investigator, Kenneth Lyons Jones, M.D., from the University of California, San Diego, all licensed pediatricians with subspecialty fellowship training in dysmorphology/genetics. This team of physicians has been functioning as the specialist examiners for the current OTIS Autoimmune Diseases in Pregnancy Project and have completed examinations for well over 1,500 infants throughout North America as part of this protocol using the same standard procedures as are incorporated in this Registry. The physical examinations evaluate infants for both major and minor structural defects which provide increased sensitivity for detecting a specific pattern of malformation should one exist (See Section 9.5 for sample size and power). All infants will be examined within the first year of life or as soon as the examination can be practically arranged, as is the protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project. The Research Center will group and schedule these follow-up examinations to meet the study criteria of infant age, to maximize physician blinding as to exposure status, and to minimize travel time and expense.

Infant examinations will be conducted using a standard checklist of approximately 130 minor malformations included in a standard physical evaluation form. In addition, in the tofacitinib-exposed group and in the disease-matched comparison group, digital photographs of the infant's minor malformations will be taken to aid in validating any findings across examiners.

Dysmorphologists will perform these examinations blinded to the exposure or comparison group status of the mothers. Because subjects with autoimmune diseases such as RA and PsA frequently have visible evidence of the disease, the use of a disease-matched comparison group allows for preservation of physician blinding.

Table 2. Timing of Cohort Enrollment, Interviews, Examinations, Medical Record Request and Review

	<20 weeks gestation	20-22 weeks gestation*	32-34 weeks Gestation	0-6 weeks after delivery	0-12 months after delivery	1 year after delivery
Referral	√					
Enrollment and Consent	√					
Intake Interview	√					
Interim Interview I		√				
Interim Interview II			√			
Outcome Interview				√		
Dysmorphological Examination					√	
Medical Record Request and Review				√	√	√
Pediatric Medical Record Review and Questionnaire at 1 Year						√

*If subject is enrolled and Intake Interview is conducted between 19 and 20 weeks' gestation, only one Interim Interview will be conducted during pregnancy at 32-34 weeks' gestation.

9.4.6. Outcome Classification for Structural Defects for Cohort Study

The method for classifying structural defects for purpose of analysis has been previously described by the study investigators and the OTIS Research Group[13,10] and has been used in previous studies conducted by this group, including all current OTIS Autoimmune Diseases in Pregnancy Project.

9.4.6.1. Criteria for Structural Defects – Counted/Included

- *Time period for identification:* major structural defects identified up to one year of age by the mother, the health care provider, or identified in the dysmorphological examination will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.

- *Confirmation of defects:* independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect that is ascertained by the examining dysmorphologist prior to one year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted in the dysmorphological examination will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies. In addition, minor structural defects that are reported only by the mother or medical record but not confirmed by the dysmorphological examination will not be included as valid defects.

- *Body measurements:* only those growth parameters for which actual measurements are available will be considered in the analysis. Measurements of head circumference, length, weight, palpebral fissure length, inner canthal distance, ear length, and philtrum length will be taken. These will be compared to mean values for infants of the same age and sex (where sex-specific normative data are available). Less than or greater than two standard deviations from the mean will be used to define such terms as microcephaly, hypertelorism, etc.

9.4.6.2. Criteria for Structural Defects – Not Counted/Excluded

- *Birthmarks:* isolated birthmarks will not be included as defined by the MACDP.[14]

- *Variations of normal:* features on the physical examination which occur in greater than 4 percent of the population and have no cosmetic or functional significance for the child, eg, 2,3 syndactyly of the toes less than one-third of the distance to the tip of the 3rd phalanx, will not be included.

- *Deformational defects:* Those deformational defects that do not require casting or surgery will not be included.

- *Time period for identification:* structural defects ascertained after 12 months of age will not be included in the analysis, but will be considered separately in the context of a possible pattern.

- *Defects identified in spontaneous abortions or elective terminations:* Defects identified by prenatal ultrasound or examination of the products of conception following elective or spontaneous abortion will be not be included in the primary analysis due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be considered in a separate analysis including all defects in the numerator over all pregnancies with known outcome in the denominator, and in the context of pattern.

9.4.7. Outcome Classification for Secondary Endpoints for Cohort Study

9.4.7.1. Definitions for Secondary Endpoints

- *Spontaneous abortion:* spontaneous abortion is defined as non-deliberate fetal death which occurs prior to 20.0 weeks post-LMP.

- *Elective abortion:* elective abortion is defined as deliberate termination of pregnancy at any time in gestation.

- *Stillbirth:* stillbirth is defined as non-deliberate fetal death anytime in gestation at or after 20.0 weeks post-LMP.

- *Premature delivery:* premature delivery is defined as live birth prior to 37.0 weeks gestation as counted from last menstrual period (or calculated from first-trimester ultrasound-derived due date if last menstrual period uncertain or more than one week discrepant). Elective caesarian deliveries or inductions prior to 37.0 weeks will be considered separately.

- *Small for gestational age:* small for gestational age is defined as birth size (weight, length or head circumference) less than or equal to the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants.[15,16,17]

- *Postnatal growth deficiency:* postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than one year of age.

- *Lost-to-follow-up:* Subjects will be considered lost-to-follow-up if they have completed the initial intake interview but subsequently fail to complete the outcome interview and medical records release despite repeated attempts after one year of the mother's estimated due date. Voluntary subject withdrawals will be considered separately.

- *Postnatal serious opportunistic infections, hospitalizations, or malignancies:* Through the one-year postnatal follow-up period, pediatric records will be requested with specific requests for documentation of serious opportunistic infections, hospitalizations or malignancies. Serious opportunistic infections are listed in Annex I.

9.4.8. Monitoring of Outcomes

9.4.8.1. Monitoring Methods

The intent of the Registry is to determine whether there is a signal that might indicate a potential risk of major structural defects in the offspring of pregnant women following an exposure to tofacitinib during pregnancy. The major strength of the Registry is that the cohort data is collected before known outcome of pregnancy with comparison to two appropriate comparison groups that are internally and contemporaneously generated. Furthermore, the prospective cohort study includes a level of outcome evaluation with a dysmorphological examination that exceeds that of any other method.

Reports outside of the cohort ("exposure case series"), can be used to illuminate knowledge gained from the cohort study. Therefore, it is necessary to determine in the evaluation of the cumulative data of all types, what the indicators of a signal or pattern are, and what course of action will be taken if a signal is noted. The cohort analysis may never have sufficient sample size to detect a teratogenic effect for a particular rare outcome following exposure to tofacitinib. However, the Registry Advisory Committee will develop a plan for determining

what constitutes a signal for a major structural defect, how it is reviewed, and what action might be taken should such a signal be seen. The Advisory Committee will review the data annually in the context of the annual interim report and will review the final report and analysis. The Advisory Committee is also available for ad hoc consultation, data review, and advice.

9.5. Study Size

Recruitment goals are set at 1-20 subjects per year in each of the three groups as shown below in Table 3 based on recruitment to date in each group (Year 1-5 actual, Year 6-10 projected). The sample size is based on estimates that may require revision as the study progresses. The sample size for the study is projected to be 300 participants for all indications and all cohort groups. However, if the sample size is met prior to the pre-determined recruitment end date, recruitment will continue during the allotted recruitment period to allow for 300 participants per indication and cohort group.

Table 3. Recruitment Timetable and Sample Size

Year/Cohort Group	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Exposed (Cohort I)	1	0	0	0	1	20	20	20	20	18
Disease Comparison (Cohort II)	25	0	0	0	1	16	15	15	14	14
Non-Disease Comparison (Cohort III)	14	13	4	2	11	12	12	11	11	10

9.5.1. Determination of Sample Size

Based on previous experience with the OTIS Autoimmune Diseases in Pregnancy Project, we estimate that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion and stillbirth rate is 10%, the estimated elective abortion rate is 10%, the estimated lost-to-follow-up rate is 5% (based on previous OTIS experience) resulting in approximately 75 live born infants in each group at the end of recruitment. Experience with the current OTIS Autoimmune Diseases in Pregnancy Project has demonstrated a yield of approximately 80% live born infants from the total proportion enrolled; therefore the estimated yield of 75% in this proposal is conservative. We estimate baseline rates of major

structural defects, spontaneous abortion, premature delivery, and small for gestational age (SGA) and the standard deviation for mean birth weight of full-term infants based on previous OTIS studies and on general population data. With this sample size, at 80% power, alpha of 0.05, two-tailed tests of significance (except as noted for pattern of minor anomalies), and each comparison group independently compared to the exposed group, the following minimum effect sizes will be detectable:

Table 4. Sample Size and Power for a Specified Effect Size

Endpoint	N in Each Group	Baseline Rate	RR Detectable	Power*
Major Structural Defects**	75	3%	5.5 (6.1)	80% (84%)
Specific Pattern of 3 or more minor structural defects	75	1%	10.0	71%***
Spontaneous Abortion	85	10%	2.7 (3.0)	80% (88%)
Premature Delivery	75	10% (6%)	2.8 (4.0)	80% (85%)
Small for Gestational Age	75	10% (7%)	2.8 (3.5)	80%

*based on Fishers Exact Test, 2 tailed, alpha 0.05, except for specific pattern of three or more minor anomalies as noted below; normal approximation using Open Epi software.
**primary endpoint.
***based on one-tailed Fishers Exact Test, alpha 0.05; power = 92% if two comparison groups are combined for n = 150.

The primary comparison group for all analyses will be the disease-matched tofacitinib- unexposed comparison group, consisting of two different populations: a) women with a disease for which tofacitinib has an approved indication, who have not taken tofacitinib, but who have been exposed to bDMARDS in pregnancy, including anti-TNF, (primary subgroup), AND b) women with a tofacitinib approved indicated disease who have not taken tofacitinib, and have also not been exposed to bDMARDs in pregnancy. Based on prior experience, it is expected that group "a" will almost exclusively comprise the sample, and that the power calculations shown in Table 4 are appropriate for comparison of tofacitinib exposed pregnancy outcomes to anti-TNF exposed comparison outcomes. To the extent that there are not differences between the disease-matched and healthy comparison groups, these can be combined; however, it is expected that there will be differences in selected endpoints such as preterm delivery and reduced birth size in the disease-matched group compared to healthy pregnancies.

The baseline prevalence of a specific pattern of three or more minor structural defects is estimated to be essentially zero as the occurrence of the same three low baseline frequency minor structural defects in any two children in a sample of 75 would be an extremely unlikely random event. However, for purposes of the power calculation, a hypothetical baseline prevalence estimate of 1% has been used. The relative risk detectable with this sample size (10.0) is based on approximately 71% power, and an alpha of 0.05 using a one-tailed Fishers Exact Test and 92% power to detect the same effect size if the two comparison groups demonstrate sufficiently similar baseline characteristics such that the groups can be combined. This represents a 10% birth prevalence of a specific pattern (ie, approximately seven children in the exposed sample), which is comparable to the birth prevalence of a specific pattern in other known human teratogens of moderate risk such as the anticonvulsant medications.

9.6. Data Management

Data will be collected using maternal interview, medical record, diary, and physical examination forms. Maternal interview data will be recorded on hard copies of forms, and these forms will be retained by OTIS. These forms are considered the primary data sources for the study. Medical records and medical record abstraction forms will be hard copies or electronic copies and will be retained on a secure server. Data from maternal interview and medical record abstraction forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS Autoimmune Diseases in Pregnancy Project.

The database itself has built in range limits for key variables that prevent certain data entry errors. In addition, all data entry forms will be reviewed for logical errors by the study data manager on a bi-monthly basis, and 100% of key variables are double-checked for data entry accuracy. The study statistician will also conduct reviews of the cumulative data from the study in the database for distributions and values that are illogical. The study manager will be responsible for working with the data manager and the supervisory staff to oversee the data validation procedures.

Access to the database will be controlled by password, with different access privileges assigned to the managers, interviewers and data entry staff, and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide (DMP), Data Entry Standard Operating Procedure (SOP), and supplements to these guides. An audit log is built into the database to archive all such entry edits. Hard copies of participant files and subject signed consent forms will be kept in a locked cabinets, in locked file rooms, under the supervision of the study investigators. Data collection and validation procedures will be detailed in appropriate operational documents.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

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

A DCT is required and should be completed for each included patient. The completed original DCTs are the sole property of the OTIS Research Center and should not be made available in any form to third parties, except for appropriate regulatory authorities, without written permission from the Principal Investigator. The OTIS Research Center shall ensure that the DCTs are securely stored at the the OTIS Research Center in paper form and will be secured in a locked room *t*o prevent access by unauthorized parties.

The OTIS Research Center has ultimate responsibility for the collection and reporting of data agreed to in the protocol, and 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* must be initialed by an authorized staff member to attest that the data contained on the *DCTs* are true. Any corrections to entries made in the *DCTs* or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Information in the medical records must match data collected on the DCTs (abstraction forms).

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities, the investigator agrees to keep all study-related records, including the identity of all participating patients, all original signed informed consent/assent documents, 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 the OTIS Research Center according to local regulations or as specified in the research agreement, whichever is longer. The OTIS Research Center must ensure that the records continue to be stored securely for so long as they are retained.

If The OTIS Research Center becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

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

The OTIS Research Center must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.3. Data Handling Conventions for the OTIS Pregnancy Registry

Initial identification of major structural defects is performed by the study Data Coordinator, and then verified and classified by the Study Manager using the CDC coding manual. Final validation of the classification of all major birth defects reported in the study will be conducted by the OTIS Co-Investigator with expertise in the diagnosis of birth defects. All

prenatal exposures to medications and vaccines are coded using the Slone Drug Dictionary (http://sites.bu.edu/slone-drug-dictionary/).

Twins or higher order multiples are handled as one pregnancy outcome. For example, if the pregnancy ends in at least one live born infant, the outcome is considered a live born outcome. If either or both twins have a major birth defect, the outcome is considered one major birth defect outcome. Twins are excluded from analyses of preterm delivery, small for gestational age infants, and postnatal growth.

Lost-to-follow-up status is designated if a participant withdraws from the study before the outcome of pregnancy is known or reported, or if study staff are unable to make contact with the study participant within 12 months of the estimated end of pregnancy in order to obtain outcome information. Before a subject is designated as lost to follow up, the subject or reporter receives at least 13 telephone attempted contacts by phone, email, written correspondence; and alternative contact information that is requested upon enrollment is utilized, as well. All follow-up attempts are documented. Participants who are lost-to-follow-up but who have at least one day of follow-up after enrollment are included in time-to-event outcomes such as spontaneous abortion if they are otherwise eligible for inclusion in that analysis. The current OTIS Autoimmune Diseases in Pregnancy Project has experienced extremely low losses to follow-up (<5% of enrolled subjects) by virtue of maintaining consistent contact with the pregnant woman. Losses to follow up are summarized in the Registry Interim and Final Reports.

Any study participant may withdraw from the study at any time for any reason; however, data that have been collected up to the time of withdrawal may be used. Women who withdraw from the study after the collection of birth outcome will not be considered lost-to-follow-up. Women who withdraw from the study prior to the collection of birth outcome will be considered lost-to-follow-up and the statistical analysis plan addresses the method whereby these data will be reported.

Duplicate reporting is possible. However, because participant identifiers are collected for this study, any duplicate report should be readily recognized. At times a report of a pregnancy exposure may come to the Registry from more than one source, eg, the Sponsor, a physician, as well as the pregnant woman. The identification of duplicate reports is conducted by routinely reviewing the database. Duplicate reports will be identified through participant identifiers and by comparing exposure, outcome, event dates and descriptions if the participant identifiers are not available from both sources. If a duplicate is identified through a systematic check for duplicates, the case reported earliest or the one with the most complete data is maintained as the valid case and updated with any data from the other report not already captured.

The primary source for information collected on demographics and exposures is by maternal interview, as the participant typically provides more accurate information than the medical records, especially in regards to non-prescription medications and any medications not taken as prescribed. Doses, dates, and timing of exposure are confirmed with medical records. If the medication is administered in the office, the medical record is the primary source; if the

medication is administered at home and there is a discrepancy between the record and maternal report, the participant is contacted and asked about the discrepancy.

The medical record is the primary source for type of prenatal test, date, and results of prenatal tests, disease diagnosis, and infant outcomes, including birth and postnatal growth, and major structural defects.

Data included in the interim annual reports is cumulative, therefore data may change when additional information is received either by maternal report or by medical records.

The method and duration of storage of data is addressed in the informed consent. Access to the database will be controlled by password. Hardcopies of participant files, original oral consent signed and dated by the interviewer, signed consent forms, and original signed medical record release forms will be kept in a locked file room, in locked cabinets, and scanned into an electronic file, under the supervision of the OTIS Research Center.

Missing values for the critical data for OTIS studies are typically very few and nearly always less than 10%. There is generally no need to include imputation strategies; however, depending on the prevalence of missingness, sensitivity analyses will be conducted. These will be specified in the SAP.

9.7. Data Analysis

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

The primary population for analysis will be those enrolled in the prospective cohort study (see Section 9.2.1). Statistical analyses of those enrolled outside the cohort study (see Section 9.2.4) will be descriptive only. These cases constitute an exposure case series, so tables of pregnancy characteristics, exposures and outcomes will be included in the interim and annual reports, and tabulations of the frequencies of events will be included by category of report: retrospective vs. prospective, reasons for exclusion, timing of exposure, and indication for use of the medication.

Demographic and baseline characteristics will be compared between groups. Discrete variables will be compared between groups using chi-square tests or Fishers Exact test as appropriate.

The primary analysis for the cohort study will be a comparison of the prevalence of major structural defects in live born infants between the tofacitinib-exposed group and the primary Comparison Group I (see Section 9.2.2 and 9.2.3). Comparison between each of the groups will be carried out using chi-squared or Fisher's exact tests. A point estimate of the crude (ie, unadjusted) risk ratio (RR) of the exposed group versus the comparison group, as well as its 95% confidence interval (CI) will be computed. When the expected frequency of any of

the cells of the contingency table is less than five, the CI will be obtained by an exact method using the software StatXact. Due to the observational nature of the study, the above crude estimate of RR will be further adjusted for confounders summarized in a propensity score (PS) to obtain the estimated causal risk ratio. The primary analysis of the primary endpoint will be conducted at the end of the study. It is unknown to what extent pregnancies with the combination of tofacitinib and methotrexate exposure will enroll in the cohort study; however, to the extent that this occurs, the disease-matched comparison group will incorporate a similar number of pregnant women with methotrexate exposure with or without concomitant exposure to any other systemic therapies.[18]

Table 5. Denominators by Outcome

Outcome	Denominator
Major Structural Birth Defects Among Live Births	Within each cohort the denominator is the number of cohort-eligible pregnancies ending in live birth. At least one malformed infant in an individual pregnancy is considered one malformed outcome in all cohorts.
Major Structural Birth Defects Among All Pregnancies	Within each cohort the denominator is cohort eligible pregnancies with any outcome excluding those lost-to-follow- up. At least one malformed fetus/infant in an individual pregnancy is considered one malformed outcome in all groups.
Spontaneous Abortion	Pregnancies enrolled in the study prior to 20.0 weeks' gestation with at least 1 follow-up data collection point after enrollment date. Exposure can occur any time in pregnancy prior to the event.
Preterm Delivery	Pregnancies enrolled prior to 37.0 weeks' gestation and ending in at least one live born infant. Excludes twins or higher order multiples due to inherent higher risk of preterm birth in multiples. Exposure can occur any time in pregnancy prior to the event.
Small for Gestational Age Infants	Pregnancies ending in at least one live born infant; excluding twins or higher order multiples due to the inherent higher risk of reduced birth size in multiples. Exposure can occur any time in pregnancy prior to the event.
Stillbirth	All pregnancies, excluding lost-to-follow-up. Exposure can occur any time in pregnancy prior to the event.
Elective Termination	All pregnancies, excluding lost-to-follow-up. Exposure can occur anytime in pregnancy prior to the event.

Outcome	Denominator
Postnatal Growth	Pregnancies ending in at least one live born infant with pediatric growth records available at approximately 1 year of age. Multiples are excluded. Exposure can occur anytime in pregnancy.

Indication-specific analyses will also be conducted pending sufficient sample size. The sample size for the study is projected to be 300 participants for all indications and all cohort groups. However, if the sample size is met prior to the recruitment end date in the contract, recruitment will continue during the allotted recruitment period to allow for 300 participants per indication and cohort group. Only descriptive analyses will be presented if achieved sample size does not allow for analytic comparisons. The study may be terminated at any time based on these findings. This decision will be considered by OTIS and the Sponsor, and a recommendation made upon review by the Advisory Committee.

- External comparisons:
  - The overall rate/proportion of major structural defects can be compared to the most recently available rate/proportion from the MACDP.
- The evaluation for a pattern of defects will be conducted using the following steps:
  - A review of major structural defects will be made by category (as outlined in Section 9.4.6). A review of specific malformations will be conducted taking into consideration timing, dose, and biological plausibility.
  - Structural defects identified in aborted fetuses will be reviewed separately from the primary analysis. Pregnancy outcome in subjects who did not meet the study qualifying criteria (ie, prior prenatal diagnosis of fetal abnormality, late gestational age, or retrospective cases) will also be reviewed separately.
  - A comparison among groups of the proportion of infants with any three or more minor structural defects will be made without regard to pattern.
- Among infants with three or more minor defects, the tofacitinib-exposed group will be examined for evidence of a specific pattern of three or more defects in any two or more children. If such a pattern is identified, Control Groups I and II will be evaluated for any evidence of the same pattern.
- Inter-rater reliability:
  - There may be variability in the assessment of minor structural defects among the study dysmorphologists. This possibility will be addressed in three ways:

The participating dysmorphologists have been working with this study protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project and have participated in group training and evaluation exercises. These reliability evaluations involve having examiners independently examine the same infant and comparisons of exam results and measurements are made. These evaluation exercises will continue periodically throughout the duration of this Registry.

If a pattern of minor structural defects is identified in the interim or final analysis of the study data, photographs of the infants exhibiting this pattern will be independently evaluated by other examiners, and if deemed necessary, affected children can be re-examined by one of the other dysmorphologists to ensure agreement.

In previous studies involving the evaluation of minor structural defects, certain minor structural defects tended to be less reliably detected than others. This raises the possibility of missed identification of a pattern that includes one or more of those defects. If the interim or final analysis suggest that one or two minor defects occur substantially more frequently among exposed infants regardless of examiner, and among these children an additional defect or defects has been identified only by certain examiners, it may be necessary to have infants with those defects re-examined by a one of the other dysmorphologists.

9.8. Quality Control

Data used in this study are secondary use of data collected as part of the existing OTIS registry, which has established quality control practices. Interview, and examination data will be recorded on hard copies of forms, and medical records and medical record abstraction forms will be electronic or hard copies of forms. These records and forms will be retained at the Research Center. Data from these forms will be extracted and entered into a customized database located at the Research Center. The data will be extracted and entered by trained study personnel with extensive experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. The method and duration of storage of data is addressed in the informed consent, that each subject will agree to in order to receive medical record information. All records are maintained for a minimum of 10 years following study completion.

Access to the database will be controlled by password. Hard copies of participant files and subject signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

The data will be entered by trained study personnel with extensive experience with this type of information. Data will be collected and entered into the database according to the SOPs for data collection and data entry established for this study.

The data manager will calculate monthly error rates for each data entry staff person and for the study overall, and will recommend and initiate training/retraining where quality standards are not being met. The study manager will oversee this process and verify that training standards are achieved.

For the primary study endpoint of major structural defects, verification of the outcome identified and classification is performed on a monthly basis is provided by blinded review by co-investigator, Kenneth Lyons Jones, MD.

9.9. Limitations of the Research Methods

The primary limitation of a cohort study utilizing volunteer subjects is potential selection bias. The use of comparably selected controls in both groups will address this concern to some extent. However, women who agree to enroll in the cohort study may represent particularly high or low risk pregnancies.[19] The study results will therefore be strictly generalizable to women fitting the profile of the sample of women who enroll. Over 5 years of the original RA study, only two tofacitinib-exposed patients in the "cohort analysis" group were recruited. Due to this, several measures including expanded marketing and promotional materials and targets have been taken to help ensure eligible patients are referred to OTIS.

Another limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, ie, at 7-9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion will be limited to relative risk for late first-trimester and early second-trimester pregnancy loss.

Because early prenatal testing is so prevalent in the U.S. and Canada, it may be difficult to achieve adequate numbers of participants if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the Registry will include pregnancies enrolled prior to outcome but after a prenatal test has been performed as long as the test does not indicate the presence of a major structural defect. The FDA guidance document[20] acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall estimate of the prevalence of major structural defects.[21] The data analysis will address this by stratifying on use of prenatal testing and on gestational timing of enrollment.

The calculation of frequency of major structural defects excludes fetal losses (spontaneous abortions, induced abortions, or fetal deaths) for which no major structural defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or pregnancies with major structural defects. The Registry attempts to obtain information on major structural defects detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. For this reason, the primary comparison for the primary endpoint of the study will be conducted among pregnancies ending in live birth, and a secondary analysis of the primary endpoint will include all pregnancies with known outcome.

It is expected that many exposures to tofacitinib will occur in unintended pregnancies. Although more than half of all pregnancies in the U.S. are unintended,[22] the possibility of confounding by age, race, and other demographic variables will be considered. For example, the rate of unintended pregnancies is higher among low-income women/families than among the other socioeconomic groups. It is possible that demographic variables will be associated with treatment as well. As such, these factors will be taken into consideration in the recruitment of comparison groups and in the analysis.

Another factor to be considered in a study anticipated to encompass a five to ten-year recruitment period is the potential impact of changing trends in prescribing practices along with physician and maternal attitudes toward the use of tofacitinib in pregnancy. The sample size is based on estimates that may require revision as the study progresses. In addition, as more post-marketing experience with the medication is accumulated, the number and characteristics of exposed pregnancies, the proportion electively terminated, and the length of exposure may change. These trends will need to be addressed in the analysis.

The study design has strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on a variety of factors which may be related to exposure and to pregnancy outcome, and the use of a disease-matched comparison group can aid in addressing confounding by indication. Misclassification bias due to poor recall is thought to be reduced in prospective study designs such as this, as each subject is interviewed at several predetermined intervals during pregnancy. Misclassification bias in outcome is minimized in this study design through the use of a specialized physical examination and a standardized evaluation protocol. Another strength of the study design is the anticipated minimal lost-to-follow-up rate. Based on previous experience of the investigators in the OTIS Autoimmune Diseases in Pregnancy Project and other similar studies, and the frequent subject contact, lost-to-follow-up is expected to be <5%, and therefore not expected to pose a threat to the validity of study results.

Finally, despite the small sample size, one of the strengths of this study is the capacity to investigate the possibility of minor anomalies via physical examination by trained experts. Although clusters of such malformations are rare, evaluations of patterns have been used with success to detect moderate level teratogens (eg, anticonvulsants).

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 at the OTIS Research Center in paper form and will be secured in a locked room to ensure that only authorized study staff have access. Medical records will be stored electronically on secure servers that are password protected. The study site 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, the study site 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 selected 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 authorized parties will be identified by this single, patient-specific 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.

10.2. Patient Consent

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.

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 vendor contract and applicable privacy laws.

10.3. Patient Withdrawl

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral,or administrative reasons. In any circumstance, every effort should be made to documentsubject outcome, if possible. The investigator should inquire about the reason for withdrawaland follow-up with the subject regarding any unresolved adverse events. If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

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

This protocol and informed consent documents have been approved by the Institutional Review Board (IRB) at the University of California, San Diego. The chairman or the recording secretary of the IRB have signed a form indicating approval. Notification of the Board's approval of the study was provided to the Sponsors prior to initiation of the Registry.

10.5. 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 International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States , US FDA regulatory requirements, in accordance with the ethical principles of the Declaration of Helsinki (1995), and the HIPAA (Health Insurance Portability and Accountability Act).[23,24,25]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 adverse events (AE) 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 MedWatch Report Form are as follows:

- All serious and non-serious AEs with explicit attribution to **Pfizer drug** that appear in the reviewed information must be recorded on the Interview Form and reported, within 24 hours of awareness, to Pfizer Safety using the MedWatch Report Form.

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

For these AEs with an explicit attribution involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is summarized in the Event Narrative section of the report form. No follow-up on related AEs will be conducted.

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

- "YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)".

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

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study endpoints will be prepared by the OTIS Research Center and provided to the tofacitinib clinical program teams. The Sponsor will communicate the results to the FDA and the EMA, and as requested by other relevant regulatory authorities. Conference abstracts and manuscripts based on specific endpoints of interest may be developed for external publication purposes. A final report will be disclosed on the EU PAS register.

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 the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not Applicable.

ANNEX 1. LIST OF SERIOUS OPPORTUNISTIC INFECTIONS UP THROUGH ONE YEAR INFANT FOLLOW-UP

Tuberculosis
X-ray proven pneumonia (requiring antibiotic treatment and/or hospitalization)
Neonatal sepsis
Meningitis (asceptic or culture proven)
Bacteremia
Invasive fungal infection (biopsy proven)
Pneumocystis
Septic arthritis
Osteomyelitis
Abcess (deep tissue)

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not Applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not Applicable.

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