Use of Registries to collect pregnancy data

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- I am employed by Novartis
- This might not be a comprehensive overview and represents my personal assessment and views if not cited otherwise.

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Reproductive toxicity: the role of pregnancy registries

Definition

- FDA[1]: A pregnancy exposure registry is a **prospective** observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes.

[1] Guidance for industry – Establishing pregnancy exposure registries – FDA 2002
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdfFDA

Reproductive toxicity: the role of pregnancy registries

Potential objectives of pregnancy registries

- To describe the overall frequency of major and / or minor congenital malformations in the presence of exposure to a drug during pregnancy
- To describe the frequency of specific types of major and minor congenital malformations in the presence of exposure to a drug during pregnancy if sample size permits
- To characterize the nature of pregnancy and other fetal outcomes in the presence of exposure to a drug during pregnancy such as spontaneous abortions, stillbirths and elective terminations
- To describe the occurrence of physical developmental delays in infants in the presence of exposure to a drug during pregnancy
- To evaluate the effects of dose and gestational timing of exposure, as well as effect modification by maternal characteristics

Reproductive toxicity: the role of pregnancy registries

Potential outputs for objective 1 (real example of «drug X»)

Table x-x: Prevalence of Major Congenital Malformation in Prospective Cases

	No. pregnancy outcomes	*No. major malfomation*	*Prevalence (%)*	*95% CI*
Prevalence of major malformation without chromosomal anomalies/genetic disorders in all LB[1]	*xx*	*xx*	*xx.x*	*xx.x, xx.x*
Prevalence of major malformation with chromosomal anomalies/genetic disorders in all LB[2]	*xx*	*xx*	*xx.x*	*xx.x, xx.x*
Prevalence of major malformation without chromosomal anomalies/genetic disorders in all LB + FD + TOPFA[3]	*xx*	*xx*	*xx.x*	*xx.x, xx.x*
Prevalence of major malformation with chromosomal anomalies/genetic disorders in all LB + FD + TOPFA[4]	*xx*	*xx*	*xx.x*	*xx.x, xx.x*

Note: CI = Confidence Interval; LB = Liveborn; FD = Fetal deaths; TOPFA = Termination of Pregnancy due to Fetal Anomaly

1. Number of cases without major congenital malformations among all LB / number of all LB
2. Number of cases with major congenital malformations or chromosomal anomalies/genetic disorders among all LB / number of all LB
3. Number of cases without major congenital malformations among all LB + FD + TOPFA / number of all LB + FD + TOPFA
4. Number of cases with major congenital malformations or chromosomal anomalies/genetic disorders among all LB + FD + TOPFA / number of all LB + FD + TOPFA

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Potential outputs for objective 3 (real example of «drug X»)

Table x-x: Pregnancy Outcome

	Prospective Cases (N=xx)[1]	*Retrospective Cases (N=xx)*[1]	All Enrolled *(N=xx)*[1]
Number of pregnancies with known pregnancy outcome	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Overall pregnancy outcome[2]			
Ectopic pregnancy	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Spontaneous abortion	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Elective termination (fetal defects)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Elective termination (no fetal defects or unknown)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Stillbirth with fetal defects	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Stillbirth without reported fetal defects	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Neonatal death with fetal defects	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Neonatal death without reported fetal defects	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Term Live birth with congenital anomaly	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Term Live birth without reported congenital anomaly	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Pre-term live birth with congenital anomaly	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Pre-term live birth without reported congenital anomaly	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

1. Number of cases enrolled
2. All pregnancy outcome categories are presented. These include categories with 0 counts.

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Study characteristics causing statistical challenges I

- Selection bias
  - Women agreeing to participate in a pregnancy registry might differ with respect to risk factors related to pregnancy outcomes compared to those not participating[1]
    - » Real example of «drug X»: In order to assess the overall generalizability and representativeness of the data included in this registry demographics of the registry population and the population of all pregnancy cases reported to pharmacovigilance will be summarized.
  - Censoring of person-time «at risk»:[2]
    - Start of follow up (left censoring): Timing of enrollment matters -> gestational age at enrollment should be similar between exposed subjects and the comparator(s).
      - When an event may influence enrollment decisions (eg. prenatal screening), primary analysis must include only subjects who enrolled before this event
        - » Real example of «drug X»: Conclusion will be based on prospective cases only
    - End of follow up (right censoring):
      - Intrauterine survival and elective teriminations (problematic if teratogenic effect of a drug causes early pregnancy loss)
        - » Real example of «drug X»: Prevalence of major malformations will be calculated for in live births as well as in live births, still births and elective terminations of pregnancy due to fetal anomaly

[1] Gliklich RE, Dreyer NA, Leavy MB, editors. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Registries for evaluating patient outcomes: a user's guide. 3rd edition

[2] Sonia Hernández-Díaz, Pregnancy registries: Methodological points and real examples, presentation

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Study characteristics causing statistical challenges II

- Information bias[1]
  - Recall bias (eg. exact timing of exposure)
    - Real example of «drug X»: exact timing of exposure to drug X might not always be available but questionnaire also allows for partial start and stop dates as well as trimester of exposure
  - Diagnostic bias and / or outcome misclassification (eg. those treated with the drug of interest might undergo more prenatal tests)
    - Real example of «drug X»: one of the comparators will be patients with the same disease exposed to other drugs for the targeted indication from external registries
  - Major malformations need to be adjudicated using the same guidelines as used for the comparator group
    - Real example from «drug X»: Both EUROCAT (European surveillance of Congenital Anomalies) and MACDP (Metropolitan Atlanta Congenital Defects Program) guidance are being used for adjudication

[1] Gliklich RE, Dreyer NA, Leavy MB, editors. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Registries for evaluating patient outcomes: a user's guide. 3rd edition

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Study characteristics causing statistical challenges III

- Confounding[1]
  - Potential confounders that might be related to, or impact, the exposure under study and are also risk factors for some pregnancy outcomes: Socioeconomic status, maternal age, tobacco and alcohol use, illegal drug use, maternal body mass index, vitamin use...
    - Real example of «drug X»: except for socioeconomic status information on all these risk factors are being collected. Depending on completeness and quantity of this data a logistic regression model will be used in the final analysis
  - Confounding by indication: difficult to separate the effect of the drug from the underlying disease
    - Real example of «drug X»: in addition to external comparators from the general population, patients with the same disease exposed as well as unexposed to other drugs for the targeted indication from external registries will be used.

[1] Gliklich RE, Dreyer NA, Leavy MB, editors. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Registries for evaluating patient outcomes: a user's guide. 3rd edition

Reproductive toxicity: the role of pregnancy registries

Sample size and power

- 18 (51%) out of 35 pregnancy registries assessed by the FDA pre-specified target enrollment[1]
  - Range: 150 – 500 exposed pregnancies (median 300)
- A sample size of 200 exposed live born infants, considering a background prevalence of major malformations in live births of 3%, would be sufficient to detect a 2.2-fold relative risk with a power of 80% at an alpha of 0.05[2]
- Same sample size of exposed live births would be sufficient to detect only a 10.4 or greater relative risk for cleft lip with or without cleft palate (prevalence approximately 0.1%)[2]

[1] Leyla Sahin, Melissa S Tassinari, Overcoming the challenges of conducting post-approval safety studies in pregnant women
[2] Covington D, Tilson H, Elder J, et al. Assessing teratogenicity of antiretroviral drugs: monitoring and analysis plan of the Antiretroviral Pregnancy Registry. Pharmacoepidemiol & Drug Safety. 2004;13:537–45.

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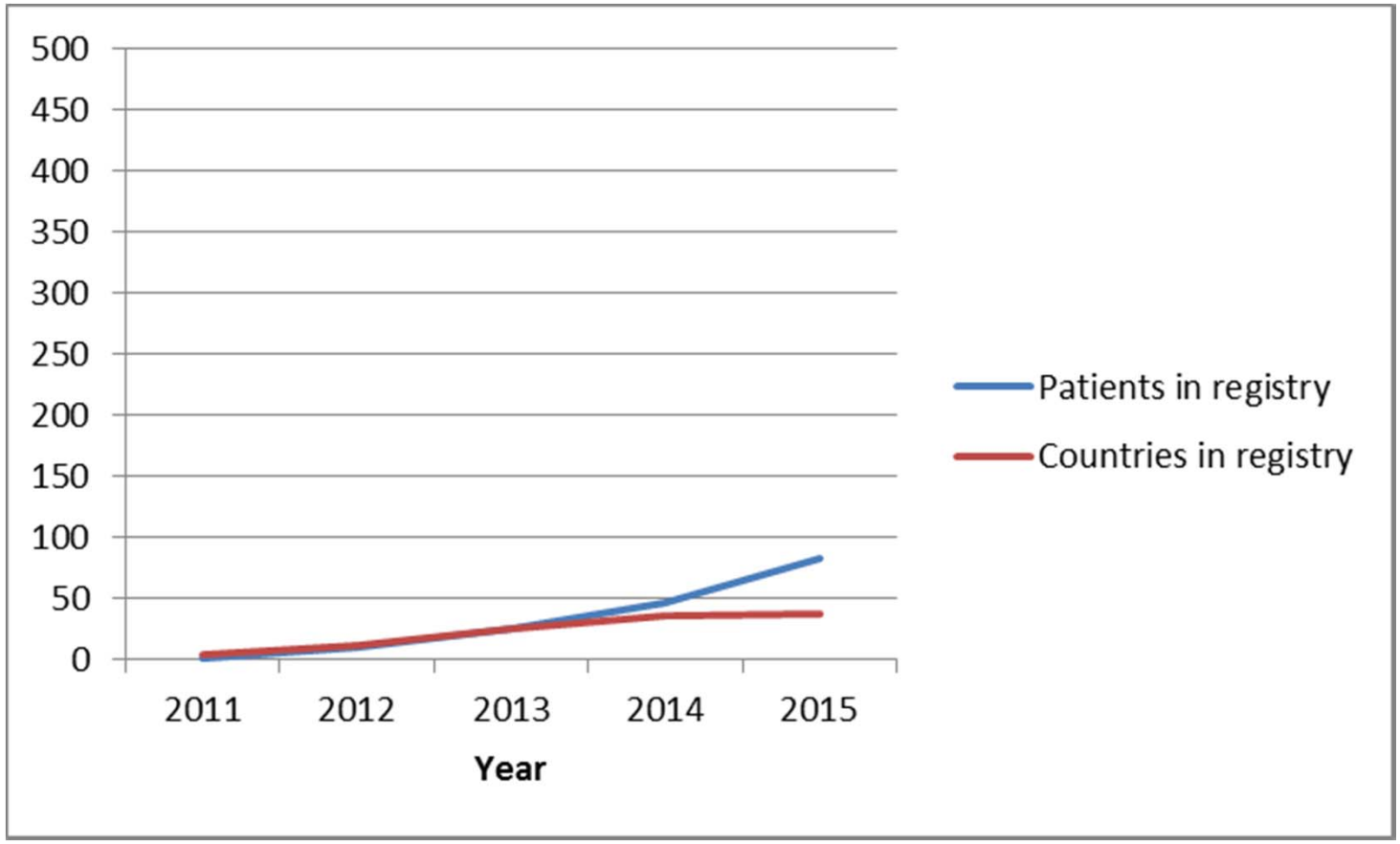
Sample size for registry of «drug X»



As per interim report 2015, 57 out of 83 (68.7%) enrolled patients reported the pregnancy outcome

Reproductive toxicity: the role of pregnancy registries

Comparator(s)

- Ideal comparator[1]:
  - Comparable outcome definition
  - Comparable assessment and timeframe for diagnosis
  - Comparable baseline risk for adverse pregnancy outcome
  - Comparable method for recruitment, enrollment and data collection
- External (Disease or general population)[2]:
  - Surveillance system
  - Background rates of grouped or individual outcomes
  - Other pregnancy registries
- Internal (Disease or general population)[2]:
  - Unexposed or exposed

[1]Sonia Hernández-Díaz, Pregnancy registries: Methodological points and real examples, presentation

[2] Guidance for industry – Establishing pregnancy exposure registries – FDA 2002 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdfFDA

Reproductive toxicity: the role of pregnancy registries

Advantages and limitations of pregnancy registries

- Advantages[1]:
  - Assess rare exposure: often the initial proactive step in assessing the safety of use during pregnancy of new drugs after they are first marketed
  - Estimation of absolute risk of pregnancy outcome due to longitudinal nature
- Limitations[1]:
  - Long time to enroll sufficient number of patients for the primary endpoint
  - Not enough power to evaluate rare outcomes
  - Often lack of comparable reference group
  - Limited generalizability to the broader population of all women who used the drug

[1] Gliklich RE, Dreyer NA, Leavy MB, editors. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Registries for evaluating patient outcomes: a user's guide. 3rd edition

Reproductive toxicity: the role of pregnancy registries

Ideas to improve enrollment

- Have a CRO being the principal investigator (US, Canada):
  - Multicenter central IRB approval with Quorum IRB
  - Can consent patients remotely
  - Data entry services for completed paper CRF and via phone (including information provided by patient)
- Direct data collection from patient by reporting physician
- Awareness campaign
- Streamline pharmacovigilance and registry data flows to reduce burden on physician
- Attempt to enroll pregnancy cases reported in the safety database (not enrolled so far in the registry) in the countries the registry is launched

Reproductive toxicity: the role of pregnancy registries

Other sources to address the risk of reproductive toxicity I

- Pharmacovigilance: the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. Most commonly associated with it is adverse event reporting.

Usual		**Enhanced / Targeted**	
Pros	Cons	Pros	Cons
Established system of pharma companies	Often limited to spontaneous reports of adverse outcomes	No operaterational hurdles like informed consent*	A lot of «drop outs» where not even pregnancy outcome is known*
Occurrence of several reports of a distinct congenital abnormality in the presence of exposure may constitute a signal*	Rarely permits determination of a causal link between a single product and an outcome -> Signal generating only	Collects also information on pregnancies with normal outcomes	A lot of missing data including key risk factors for adverse pregnancy outcomes*
			No clincial database which makes analysis difficult*

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Other sources to address the risk of reproductive toxicity II

- Databases:
  - Automated claims databases (eg. MarketScan)
  - Computerized medical records (eg. CPRD)
  - Registers (eg. Nordic countries)
- Different databases have different advantages and disadvantages with regards to the possibility of linking mother and baby cases, information on co-medications, timing of exposure to medication of interest, alcohol use etc.
  - Overall pro: - no recall bias
  - Overall con: - may take a couple of years until enough pregnancy cases exposed to the medication of interest are available

    - Original purpose of database is not to assess the risk of reproductive toxicity.

Reproductive toxicity: the role of pregnancy registries

Conclusion of use of data sources[1]

- To identify drugs with dramatic fetal risks, pregnancy registries have appropriate efficiency and power.
- To identify drugs with intermediate fetal risks, databases have appropriate efficiency and power if use is relative common.
- To identify drugs with moderate fetal risks, case-control surveillance has appropriate efficiency and power if use is relative common.
- If outcome is rare, relative risk is modest, and prevalence of use is low… no currently known approach would have the power.

[1]Sonia Hernández-Díaz, Pregnancy registries: Methodological points and real examples, presentation

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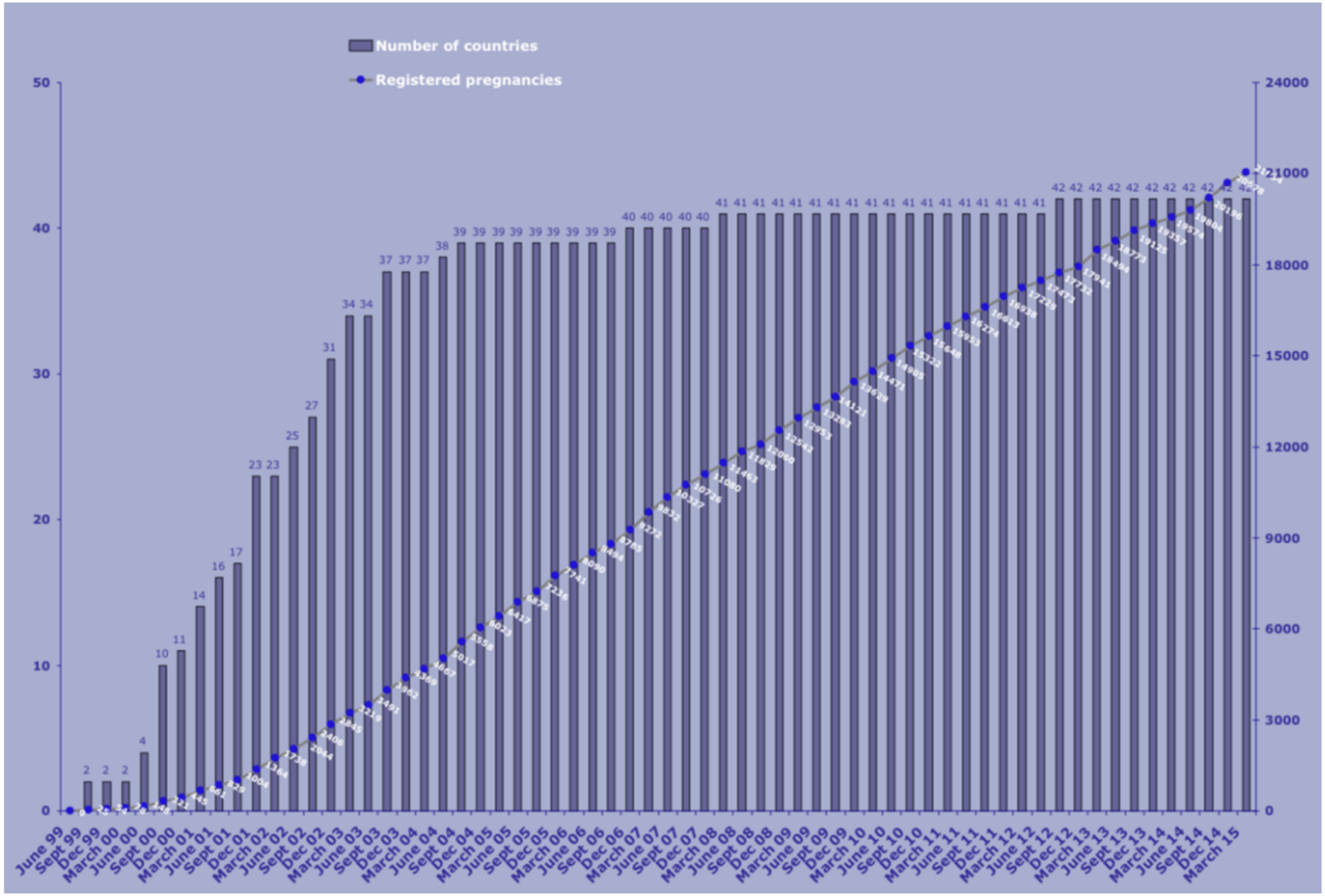
Disease Pregnancy Registries (relative to drug-specific pregnancy registries)

- Examples of disease pregnancy registries: NAAED, EURAP, Antiretroviral pregnancy registry
- Pros:
  - Usually more successful in enrolling patients
  - Comparators (exposed and unexposed) using the same data collection methods
  - More cost-effective
  - Raises awareness among healthcare providers and patients/streamline participation (centralized resource)
- Cons:
  - Less influence on study design, questionnaire, analyses and reporting as more parties are involved

Enrollment successful in EURAP registry, despite initial difficult start



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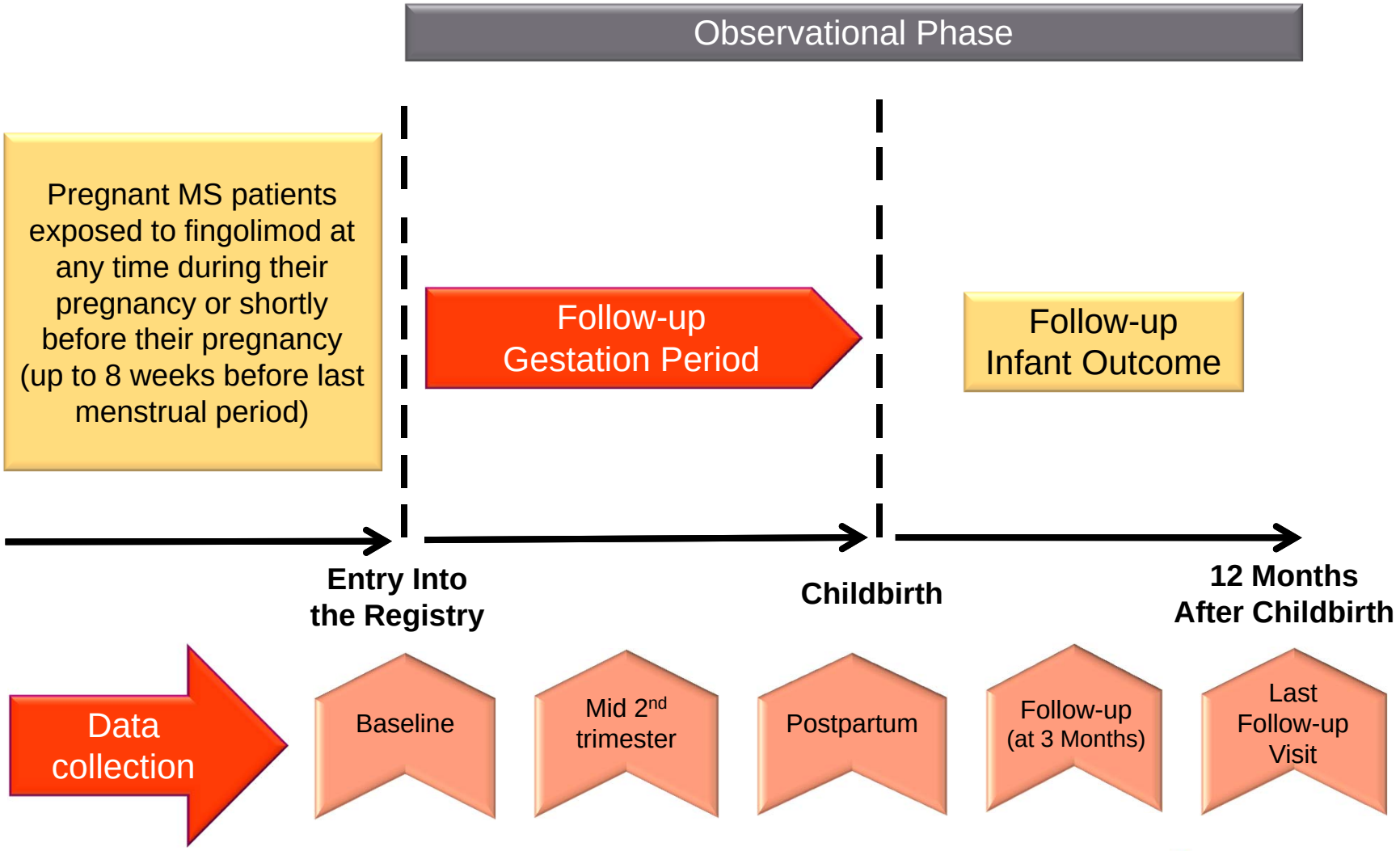
Drug-specific Pregnancy Registries

- Examples of drug-specific pregnancy registries from Novartis: Neoral, Tasigna / Glivec, Xolair and Gilenya Pregnancy Registry
- Pros:
  - Study design, questionnaire, analyses and reporting can be determined
- Cons:
  - Expensive (budget and internal resources)
  - Often no comparator
  - Difficulties enrolling patients

Gilenya Pregnancy Registry
Registry Design



http://clinicaltrials.gov/ct2/show/NCT01285479?term=fingolimod+pregnancy&rank=1. Accessed July 27, 2015.

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FDA perspective:what we know

- Pregnancy registries continue to have an important role in data collection and are considered to be the “gold standard” but improvements are needed in the methodology and conduct
- Multi-product or disease based approaches have generally been more successful for sustainability of the registry and collection of data
- A combination of approaches that include complementary study designs may help overcome the limitations of individual study designs

EMA perspective: what we know

- EMA accepted in some instance enhanced pharmacovigilance systems as an alternative
- Even though in favour EMA is not satisfied with the incompleteness of data eg. in the case of the European interferon beta pregnancy registry which is using spontaneous reports

Key messages / summary

- **Role of pregnancy registries**
  - Appropriate efficiency and power to identify drugs with dramatic fetal risks
- **Disease pregnancy registries work best**
  - Need to be either imposed by health authorities on pharma companies to collaborate
  - If established already by academic groups companies can contribute
  - Have internal comparators
- **Drug-specific registries are challenging but can be optimized** to a certain extent by adapting study design, awareness campaign and so on
- **Health authorities are currently evaluating the best way of assessing the risk of reproductive toxicity:**
  - FDA acknowledges challenges and need for complementary alternatives but still considers pregnancy registries to be the «gold standard»
  - For EMA enhanced pharmacovigilance systems are acceptable as an alternative