Mitigating Exposures to Teratogenic Medications Science & Practice

Chairperson: Sonja A. Rasmussen, Johns Hopkins School of Medicine

2:30 PM–2:50 PM FDA and REMS Programs to Mitigate Teratogenic Risk
Judy C Maro, Harvard Medical School

2:50 PM–3:10 PM Frequencies and Determinants of Prenatal Exposures to Teratogenic Medications
Yanning Wang, University of Florida

3:10 PM–3:20 PM Break

3:20 PM–3:40 PM Effectiveness of REMS Programs in Mitigating Prenatal Exposure to Teratogens
Nicole E Smolinski, University of Florida

3:40 PM–4:00 PM Teratogenic Risk Impact Mitigation (TRIM): How to Prioritize Medications for REMS
Almut G Winterstein, University of Florida

4:00 PM–4:15 PM Discussion

FDA and REMS Programs to Mitigate Teratogenic Risk

37th Annual OTIS Education Meeting
June 30th, 2025

Judith C. Maro, PhD
Associate Professor
Department of Population Medicine at Harvard Pilgrim Health Care Institute and Harvard Medical School

Guidelines for Pharmacovigilance and Risk Management

US Framework:

- Risk Evaluation and Mitigation Strategies (REMS) created in 2007 FDA Amendments Act, updating RiskMAPs.
- Goal: To use additional tools **to supplement the label** as a way to manage safe use of the medication and maintain a favorable benefit-risk profile.
- Primarily issued upon new approvals (with the exception of grandfathered programs) and reassessed periodically, however can be issued in response to a new safety concern.

European Framework:

- Risk Management Plan (RMP): a) Safety Profile of Product, b) the Pharmacovigilance Plan, c) the Risk Minimization Plan as described in Guidelines on Good Pharmacovigilance Practices

https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

Managing Teratogenicity: Is the Label Enough?

Label Warnings	
Generic Name	**Drug Approval Year**
Methotrexate	1953
Warfarin	1954
Valproic acid	1978
Lisinopril	1987
Simvastatin	1991
Paroxetine	1992
Topiramate	1996
Ribavirin	1998
Vismodegib	2012

REMS	
Generic Name	**Drug Approval Year**
Isotretinoin*	1982
Mycophenolate	1995
Thalidomide*	1998
Bosentan*	2001
Lenalidomide*	2005
Ambrisentan*	2007 (*REMS released 2025*)
Telavancin	2009 (*REMS released 2017)*
Fingolimod	2010 (*REMS released 2016)*
Phentermine/Topiramate	2012
Pomalidomide	2013
Riociguat	2013
Macitentan	2013 (*REMS released 2025*)

*These agents had RiskMAP programs before REMS scheme was enacted in 2007

When deemed necessary, a REMS is a required risk management plan that can include ≥1 elements to ensure that the benefits of a drug outweigh its risks.

Medication Guide* (may or may not be part of label or REMS)

Communication Plan

Elements to Assure Safe Use (ETASU)

A	Healthcare providers who prescribe the drug have certain training or certification
B	Pharmacies, practitioners or healthcare settings that dispense the drug are specially certified
C	The drug be dispensed to patients only in certain healthcare settings (e.g. hospitals)
D	The drug be dispensed to patients with evidence or documentation of safe-use conditions (e.g. laboratory test results)
E	Each patient using the drug be subject to certain monitoring
F	Each patient using the drug be enrolled in a registry

https://www.fda.gov/media/100307/download

REMS: FDA's Application of Statutory Factors in Determining when a REMS Is Necessary (2019 Final Guidance)

V. APPLICATION OF STATUTORY FACTORS IN REMS DECISION-MAKING

Section 505-1(a)(1) of the FD&C Act, as added by FDAAA, requires FDA to consider the following six factors[24] in making a decision about whether to require a REMS:

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- The expected benefit of the drug with respect to the disease or condition;
- The seriousness of the disease or condition that is to be treated with the drug;
- Whether the drug is a new molecular entity;
- The expected or actual duration of treatment with the drug; and
- The estimated size of the population likely to use the drug.

https://www.fda.gov/media/100307/download

There are currently 70* Active REMS a/o JUNE 2025, 64 of them have ETASU.

- There are technically 13 teratogenic REMS that belong to 9 products. There are some “parallel” system REMS and also some that are administered differently for the brand v. generic manufacturer(s).

The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

The table below provides links to currently approved individual and shared system REMS.

Information on historical and released REMS is available in downloadable: data files.

Filter by Keyword (e.g. REMS name, active ingredient, element)

Excel | CSV | Print

Name	REMS Approved	Last Updated	MedGuide (MG)*	Comm. Plan (CP)	ETASU	Imp. System (IS)
Abecma (*Idecabtagene vicleucel*), suspension, for intravenous infusion BLA #125736	03/26/2021	04/04/2024			ETASU	IS
Adasuve (*loxapine*), aerosol, powder NDA #022549	12/21/2012	01/27/2022			ETASU	IS
Alvimopan Shared System REMS Shared System REMS	12/19/2019	06/12/2023			ETASU	IS
Aveed (*testosterone undecanoate*), injection NDA #022219	03/05/2014	10/08/2024			ETASU	IS

https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

REMS focused on teratogenicity are mostly ETASU only. Qsymia also has a Medication Guide as part of the REMS.

Current (9ish)

- Bosentan
- Filspari
- Isotretinoin iPLEDGE
- Lenalidomide
- Mycophenolate, PS-Mycophenolate
- Pomalidomide, PS-Pomalidomide
- Qsymia, Phentermine and Topiramate Extended-Release Capsules
- Riociguat Shared System REMS
- Thalidomide, Thalomid

Retired (5)

- Ambrisentan (4/4/25)
- Macitentan (4/2/25)
- Aprocitentan (4/2/25)
- Telavancin (5/24/17)
- Fingolimod (11/29/16)

https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm,
PS = Parallel Systems – a specific REMS for a particular manufacturer

Managing Teratogenicity: Is the Label enough?

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*These agents had RiskMAP programs before REMS scheme was enacted in 2007

Consider Medication Guide within the Label for Topamax (topiramate), a non-REMS product. Birth Defects appear on Page 2.

MEDICATION GUIDE
TOPAMAX® (TOE-PA-MAX)
(topiramate)
TABLETS, for oral use
TOPAMAX® (TOE-PA-MAX)
(topiramate capsules)
SPRINKLE CAPSULES, for oral use

What is the most important information I should know about TOPAMAX?
TOPAMAX may cause eye problems. Serious eye problems include:

- any sudden decrease in vision with or without eye pain and redness.
- a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).
- These eye problems can lead to permanent loss of vision if not treated.
- You should call your healthcare provider right away if you have any new eye symptoms, including any new problems with your vision.

TOPAMAX may cause decreased sweating and increased body temperature (fever). People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition. If a high fever, a fever that does not go away, or decreased sweating develops, call your healthcare provider right away.
TOPAMAX can increase the level of acid in your blood (metabolic acidosis). If left untreated, metabolic acidosis can cause brittle or soft bones (osteoporosis, osteomalacia, osteopenia), kidney stones, can slow the rate of growth in children, and may possibly harm your baby if you are pregnant. Metabolic acidosis can happen with or without symptoms.
Sometimes people with metabolic acidosis will:

- feel tired
- not feel hungry (loss of appetite)
- feel changes in heartbeat
- have trouble thinking clearly

Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with TOPAMAX. If you are pregnant, you should talk to your healthcare provider about whether you have metabolic acidosis.

TOPAMAX can harm your unborn baby.

- If you take TOPAMAX during pregnancy, your baby has a higher risk for birth defects including cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.
- Birth defects may happen even in children born to women who are not taking any medicines and do not have other risk factors.
- There may be other medicines to treat your condition that have a lower chance of birth defects
- All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of TOPAMAX. If the decision is made to use TOPAMAX, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your doctor about the best kind of birth control to use while you are taking TOPAMAX.
- Tell your healthcare provider right away if you become pregnant while taking TOPAMAX. You and your healthcare provider should decide if you will continue to take TOPAMAX while you are pregnant.
- If you take TOPAMAX during pregnancy, your baby may be smaller than expected at birth. The long-term effects of this are not known. Talk to your healthcare provider if you have questions about this risk during pregnancy.
- Metabolic acidosis may have harmful effects on your baby. Talk to your healthcare provider if TOPAMAX has caused metabolic acidosis during your pregnancy.
- Pregnancy Registry: If you become pregnant while taking TOPAMAX, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of TOPAMAX and other antiepileptic drugs during pregnancy.

TOPAMAX may decrease the density of bones when used over a long period.
TOPAMAX may slow height increase and weight gain in children and adolescents when used over a long period.

REMS elements of Qsymia (which contains topiramate)

MEDICATION GUIDE

MEDICATION GUIDE
QSYMIA ®(Kyoo sim ee uh)
(phentermine and topiramate extended-release capsules)
for oral use, CIV

What is the most important information I should know about QSYMIA?
QSYMIA can cause serious side effects, including :

- **Birth defects.**If you take QSYMIA during pregnancy, your baby has a higher risk for birth defects including cleft lip and cleft palate. Your baby may also be smaller than expected at birth. The long-term effects of this are not known. These defects can begin early in pregnancy, even before you know you are pregnant.

Patients who are pregnant must not take QSYMIA.
Patients who can become pregnant should:

- Have a pregnancy test before taking QSYMIA and every month while taking QSYMIA.
- Use effective birth control (contraception) consistently while taking QSYMIA. Talk to your health care provider about how to prevent pregnancy.

If you become pregnant while taking QSYMIA, stop taking QSYMIA immediately and tell your health care provider right away. Health care providers and patients who become pregnant should report all cases of pregnancy to:

- FDA MedWatch at 1-800-FDA-1088

Elements to assure Safe Use (ETASU)

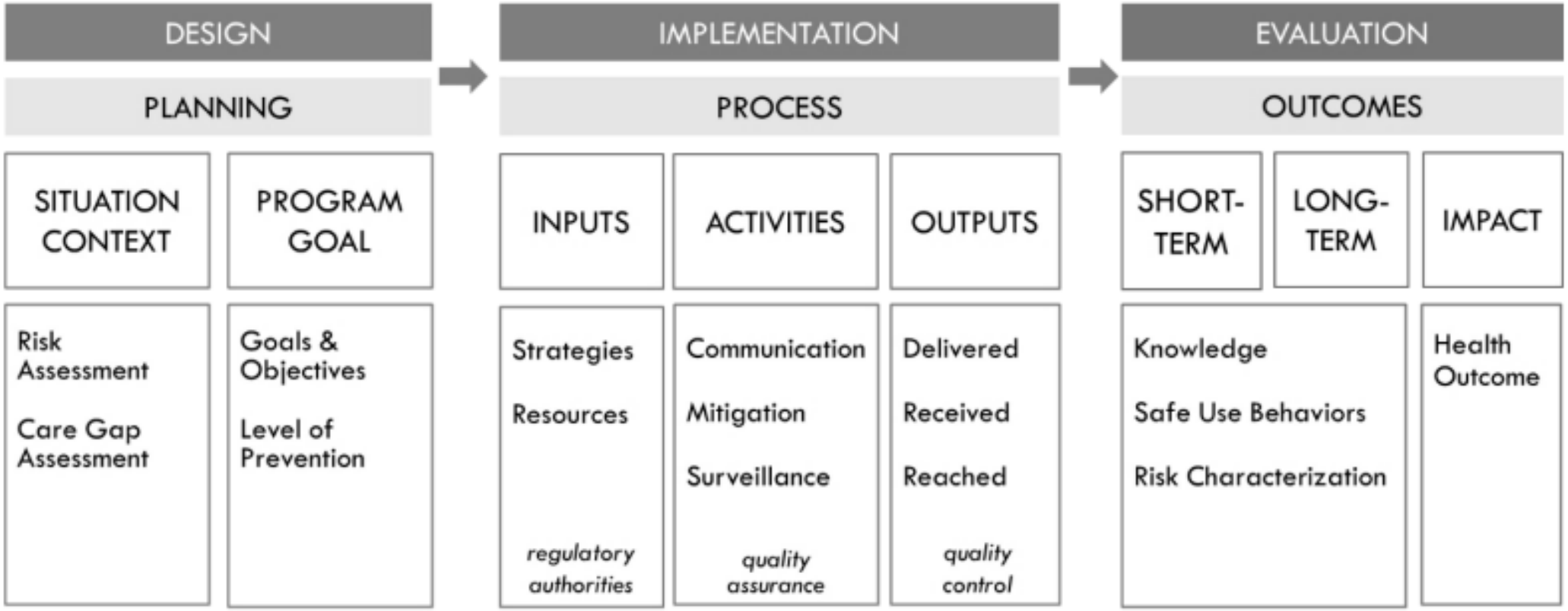
- Pharmacy Dispensing Certification and Procedure to Dispense the Medication Guide

REMS Elements in the Isotrentinoin REMS

- Prescriber Certification
- Prescriber assessment of pregnancy status (two methods, one CLIA-certified) and counseling of patient
- Prescriber limited to 30 days supply, no refills
- Pharmacy Dispensing Certification and Authorization from REMS program for each dispensing
- Patient Enrollment in Program, Routine Pregnancy Tests

REMS Logic Model: A Framework to Link Program Design with Assessment

Figure 1. REMS Logic Model



https://www.fda.gov/media/178291/download - 2024 Draft Guidance

Example Evaluation Metrics: Process Indicators v. Outcome Indicators

1. Program Outreach and Communication
   - Number of specific REMS materials distributed to target audience
2. Program Implementation and Operations
   - Number of prescribers, health care settings, and/or pharmacies that have certified or undergone training in the REMS program
3. Knowledge
   - Surveys to evaluate knowledge of REMS risks and safe use conditions
4. Safe Use Behaviors
   - Number of times a required laboratory test conducted before dispensing
5. Health Outcomes or Surrogates of Health Outcomes
   - Numbers and/or rates of a specific adverse event of interest such as severe neutropenia
   - Surrogate outcomes could include the number of inadvertent fetal exposures

https://www.fda.gov/media/178291/download - 2024 Draft Guidance

FDA Guidance on Aligning Strategies with REMS Goals

Table 2. Strategies and Substrategies Related to REMS*

Strategy	Substrategy
To affect **knowledge**	• Medication Guide • Communication plan • Training (e.g., prescriber, pharmacy, health care setting) • Certification (e.g., prescriber, pharmacy, health care setting, patient)
To affect **safe-use behaviors**	• Health care setting requirements necessary for dispensing (e.g., equipment, personnel) • Documentation of safe-use behaviors (e.g., verify completion of laboratory testing) • Monitoring the patient (e.g., observation, assessing results of laboratory testing) • Packaging (e.g., unit dose, limited supply, package warnings) • Disposal systems (e.g., mail back envelopes)
To inform **risk characterization/mitigation**	• Patient Registry

* REMS = risk evaluation and mitigation strategy.

https://www.fda.gov/media/178291/download - 2024 Draft Guidance

On Managing Burden….

- The feasibility and practicality of implementing the proposed strategies for each affected stakeholder and health care system. Applicants should evaluate if the REMS can be designed to be compatible with established clinical assessment, prescribing, dispensing, administering, and monitoring as well as the procurement and distribution processes. Applicants should also evaluate the potential ***burden*** of the proposed mitigation strategies on the health care delivery system and the intended patient population. For example, strategies that directly affect safe-use behavior (e.g., monitoring requirements) may be more effective but may also be more burdensome than knowledge-based strategies.

https://www.fda.gov/media/178291/download - 2024 Draft Guidance

Takeaways: Is the Current State Successfully Addressing the Ultimate Goal – To Prevent Teratogen-Exposed Pregnancies?

- All current teratogenic drugs do not all have a REMS designed to prevent teratogen-exposed pregnancies
- Of the teratogenic REMS, they may include a variety of elements (especially ETASU elements) that are designed to prevent teratogen-exposed pregnancies

Mitigating Exposures to Teratogenic Medications: Science & Practice

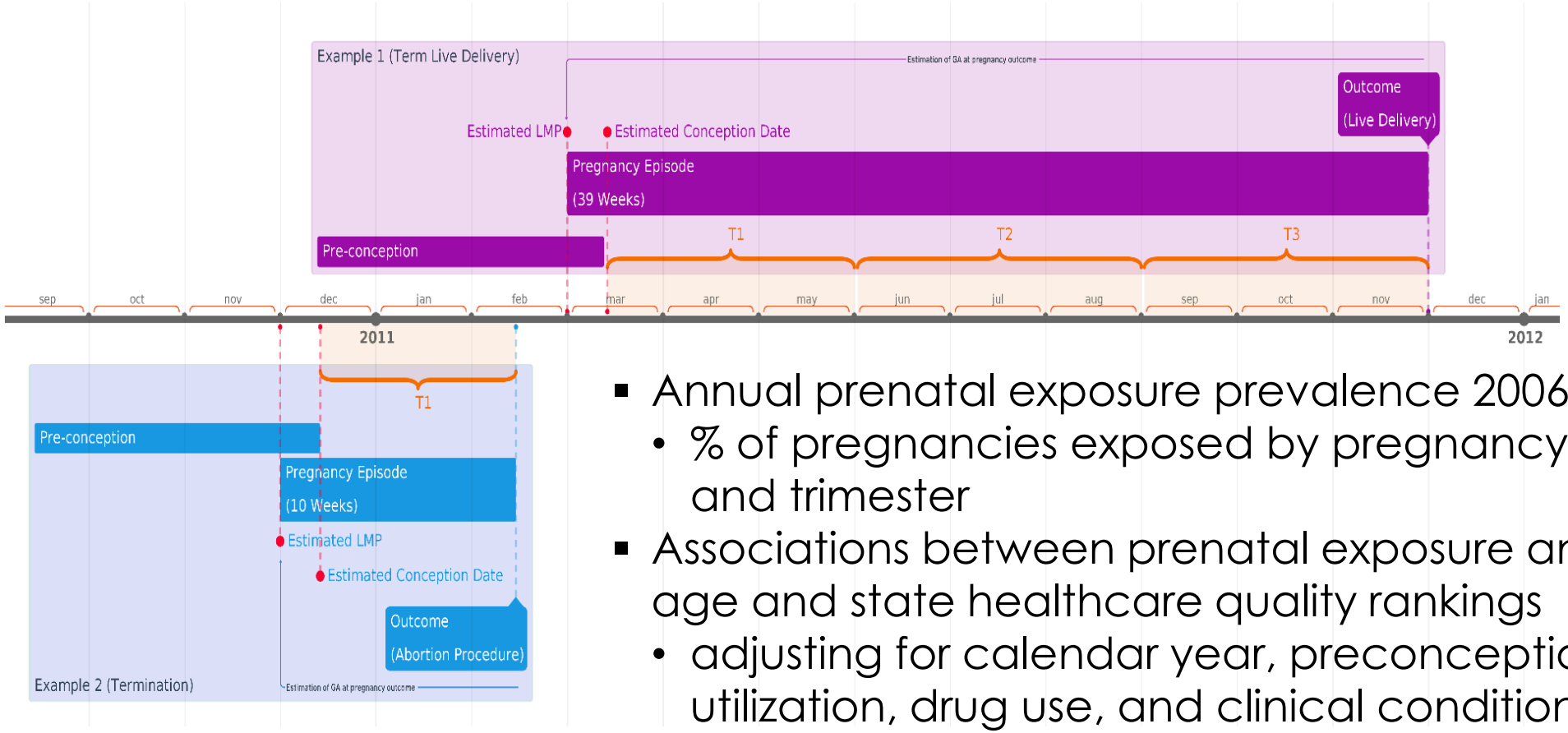
Prevalence and Determinants of Prenatal Exposures to Teratogenic Medications

Yanning Wang, MS
Department of Pharmaceutical Outcomes & Policy
Center for Drug Evaluation and Safety (CoDES)
University of Florida, USA

How often does prenatal exposure to teratogenic medications occur?

need for risk mitigation

Methods population-based study



- Annual prenatal exposure prevalence 2006-2017
  - % of pregnancies exposed by pregnancy outcome and trimester
- Associations between prenatal exposure and women's age and state healthcare quality rankings
  - adjusting for calendar year, preconception healthcare utilization, drug use, and clinical conditions

Sarayani A, Albogami Y, Thai TN, et al. Prenatal exposure to teratogenic medications in the era of Risk Evaluation and Mitigation Strategies. *Am J Obstet Gynecol*. 2022;227(2):263.e1-263.e38. doi:10.1016/j.ajog.2022.01.004

Methods medication exposure

- Selection of Medications
  - TERIS© Teratogen Information System
  - Clinical Pharmacology® monographs
  - medications with current and released risk mitigation strategies (e.g., REMS)
- Exclusion
  - sex hormones, hormone analogs, opioids, anti-obesity medications, medications for abortion, post-partum hemorrhage
- Medication Exposure
  - 141 medications
  - e.g., ACE-I/ARBs (excluding first-trimester exposure), select anticonvulsants, systemic antimycotics, antineoplastics, warfarin

Results

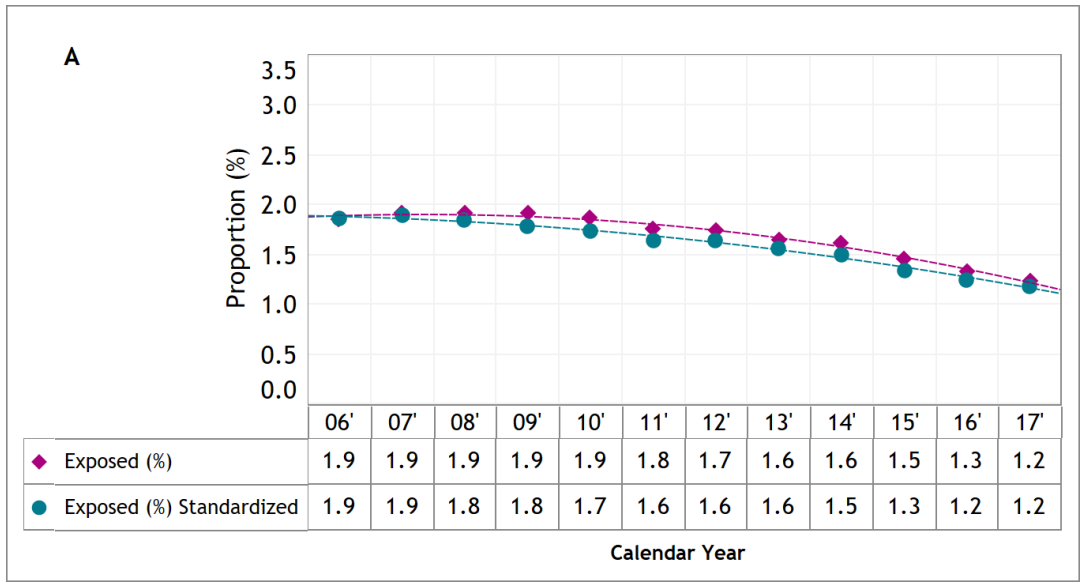
3,445,612 pregnancy episodes, 2,532,444 (73.5%) live births

Medication with known risk

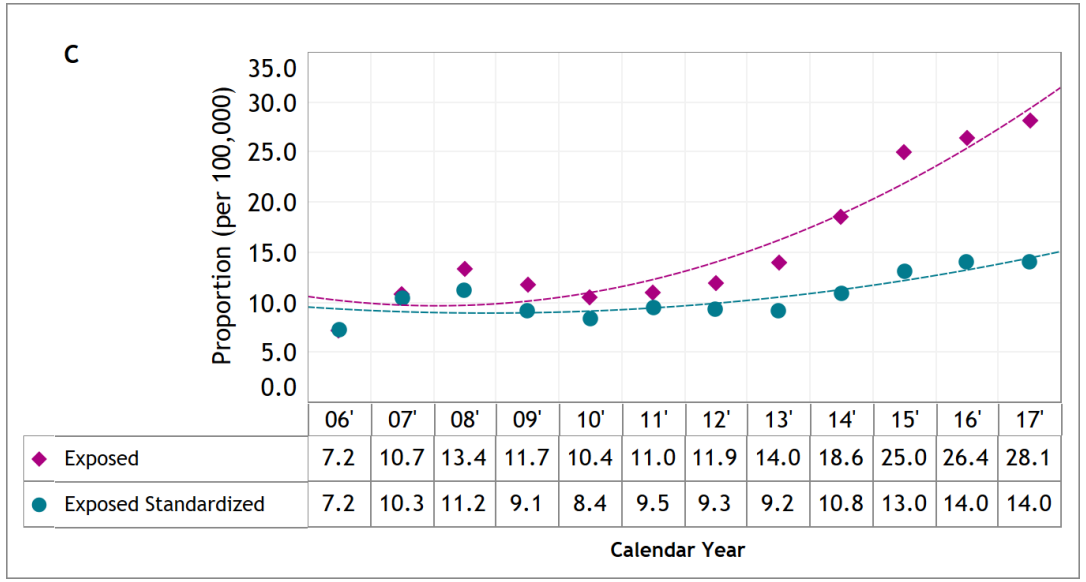
- Preconception: 2.35%
- During gestation: 1.71% (60% in T1)

Medications with REMS program

- Preconception: 0.03%
- During gestation: 0.02%



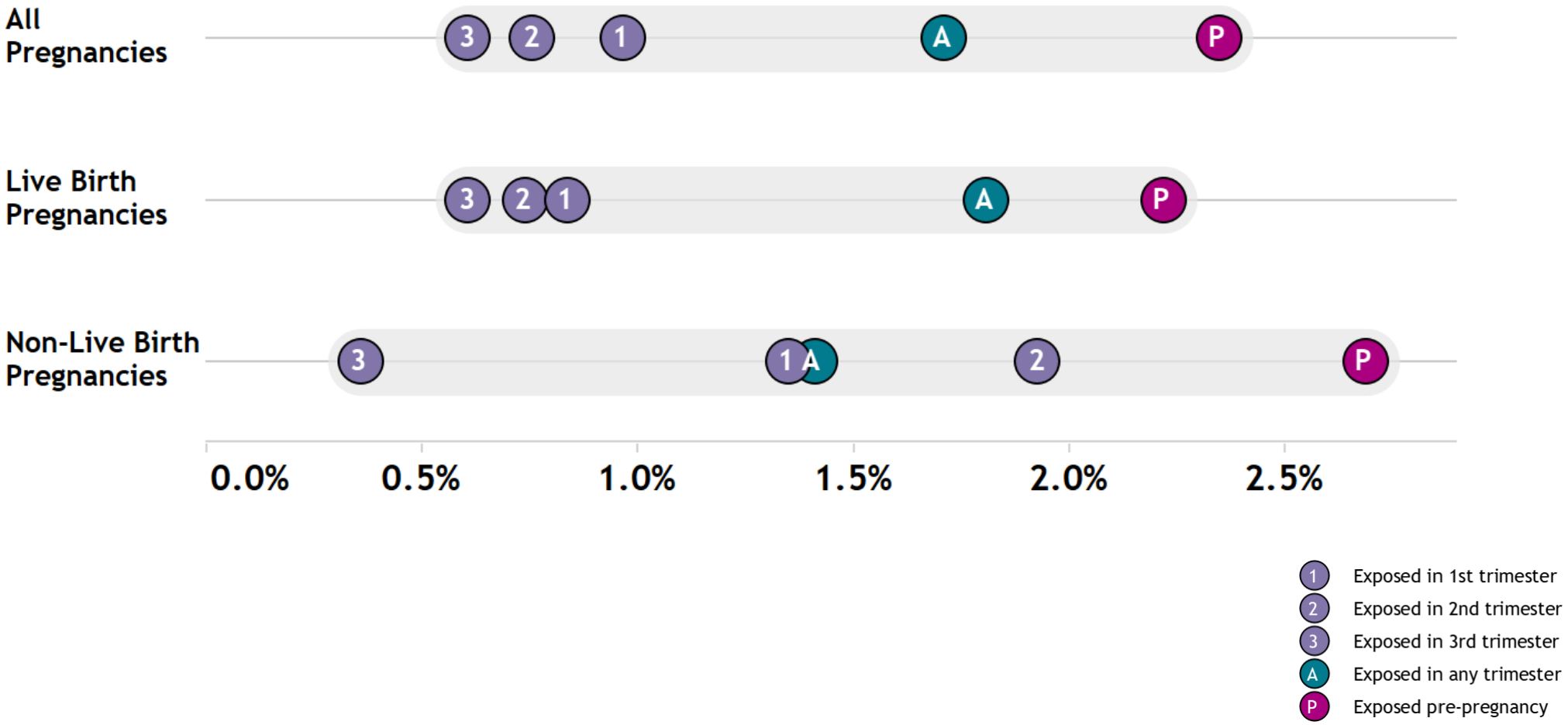
	06'	07'	08'	09'	10'	11'	12'	13'	14'	15'	16'	17'
Exposed (%)	1.9	1.9	1.9	1.9	1.9	1.8	1.7	1.6	1.6	1.5	1.3	1.2
Exposed (%) Standardized	1.9	1.9	1.8	1.8	1.7	1.6	1.6	1.6	1.5	1.3	1.2	1.2



	06'	07'	08'	09'	10'	11'	12'	13'	14'	15'	16'	17'
Exposed	7.2	10.7	13.4	11.7	10.4	11.0	11.9	14.0	18.6	25.0	26.4	28.1
Exposed Standardized	7.2	10.3	11.2	9.1	8.4	9.5	9.3	9.2	10.8	13.0	14.0	14.0

Results

Prenatal exposure to medications with known risk



Results

Determinants of prenatal exposure

Characteristics	% of unexposed (N= 3,386,802)	% of exposed (N= 58,810)	odds ratio*	95% CI
Healthcare Quality Ranking				
High-rank	16.8	12.7	REF	REF
Middle-rank	67.1	66.8	1.26	1.23, 1.30
Low-rank	16.1	20.6	**1.55**	1.51, 1.60
Age in years				
<20	4.3	7.6	**1.84**	1.77, 1.90
20-24	12.5	16.1	1.48	1.44, 1.52
25-29	27.1	24.6	1.12	1.10, 1.15
30-34	32.9	25.8	REF	REF
35-39	17.9	15.6	1.08	1.06, 1.11
40-44	4.7	5.7	1.44	1.39, 1.50
≥45	0.7	4.7	**6.83**	6.51, 7.17
Exposure during preconception	2.0	21.5	**8.69**	8.48, 8.90

*adjusted for calendar year, pre-conception healthcare utilization, and clinical conditions

Summary

- Slightly decreasing secular trend for prenatal exposure
- REMS drugs comprised a very small portion of overall prenatal exposure
- Prenatal exposure was higher in the first trimester
- Higher prenatal exposure for non-live pregnancy outcomes
- Patient characteristics (e.g., age) and settings (e.g., quality of healthcare system) seem to determine risk

When does prenatal exposure occur?

timing for risk mitigation

From Recognition to Action

opportunities for risk mitigation

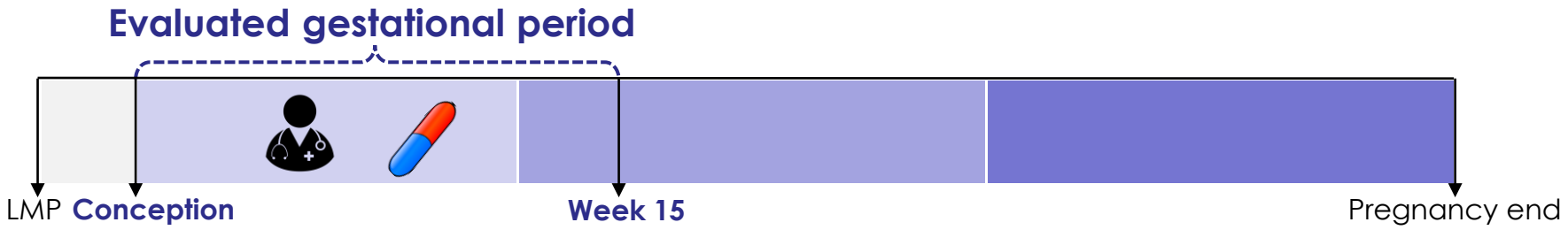
- Unintended pregnancies: 42% in 2019
- Time to pregnancy awareness is between 5 and 7 weeks' gestation
- Prenatal exposure to teratogenic medications is highest during the first trimester, suggesting some exposures are accidental and may precede prenatal care
- Delayed prenatal care initiation and teratogenic exposure mitigation

- Aim: understand the prevalence and timing of prenatal exposure to medications with known risk relative to the timing of prenatal care initiation

Winterstein AG, Wang Y, Smolinski NE, Thai TN, Ewig C, Rasmussen SA. Prenatal Care Initiation and Exposure to Teratogenic Medications. *JAMA Netw Open*. 2024;7(2):e2354298. Published 2024 Feb 5. doi:10.1001/jamanetworkopen.2023.54298

Methods study population

- Pregnancies ending in 2017-2019 from the Merative™ MarketScan® Commercial database
- Prevalence of first prenatal exposure to teratogenic medication and prenatal care initiation by gestational week
- For each gestational week, categorized pregnancies based on timing of exposure and prenatal care initiation as:
  - first prenatal care visit before teratogen exposure



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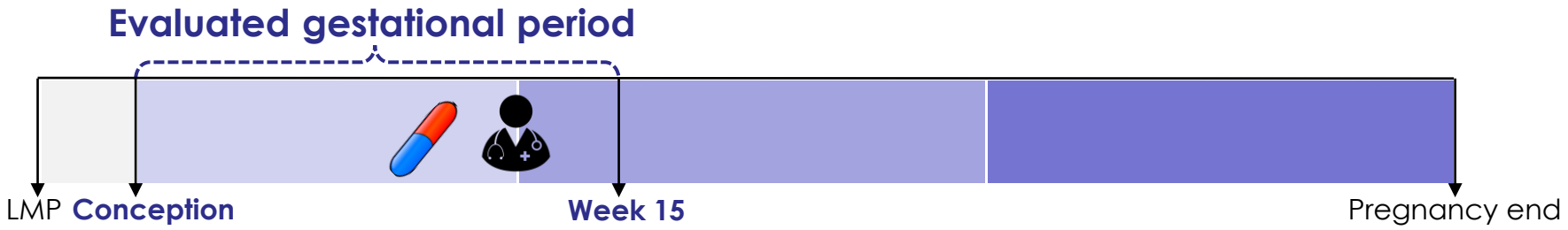
  - first prenatal care visit before teratogen exposure
  - first prenatal care visit after teratogen exposure but within the given gestational period



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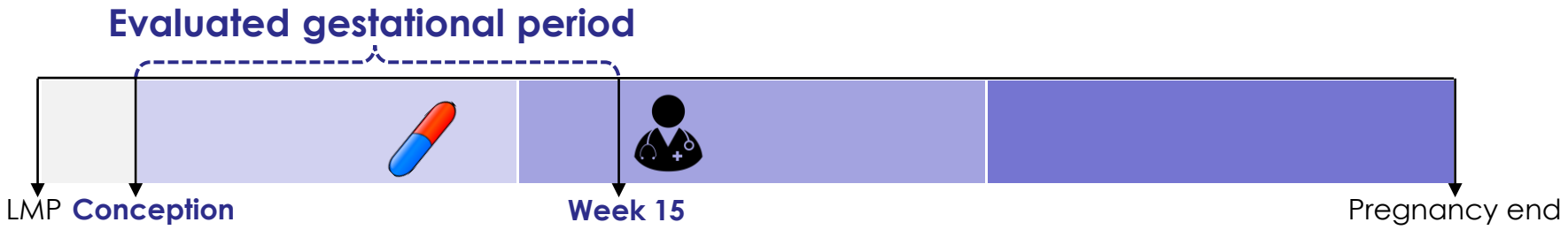
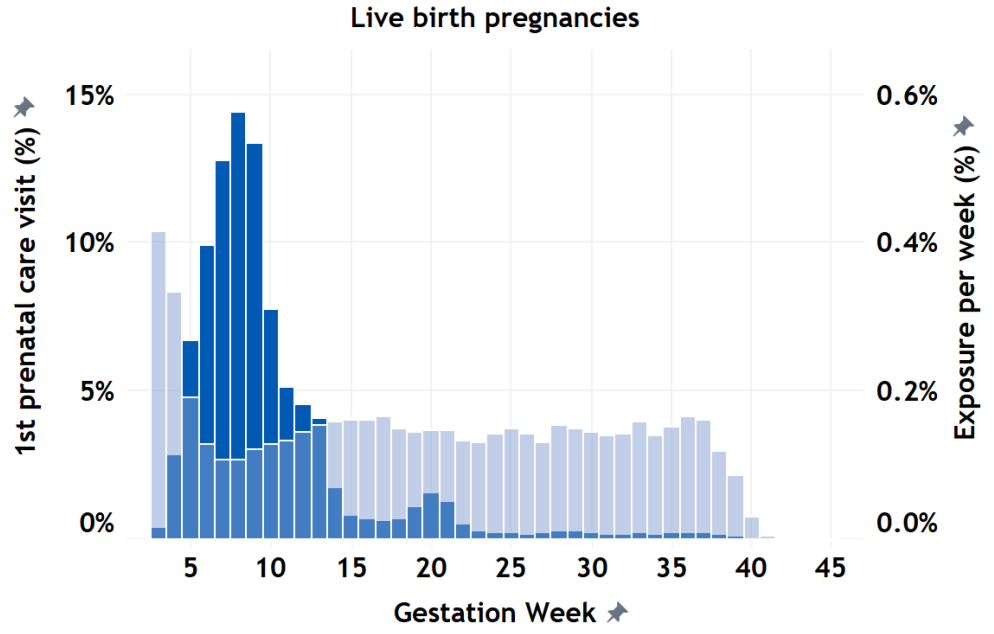


Results Timing of exposure & prenatal care initiation

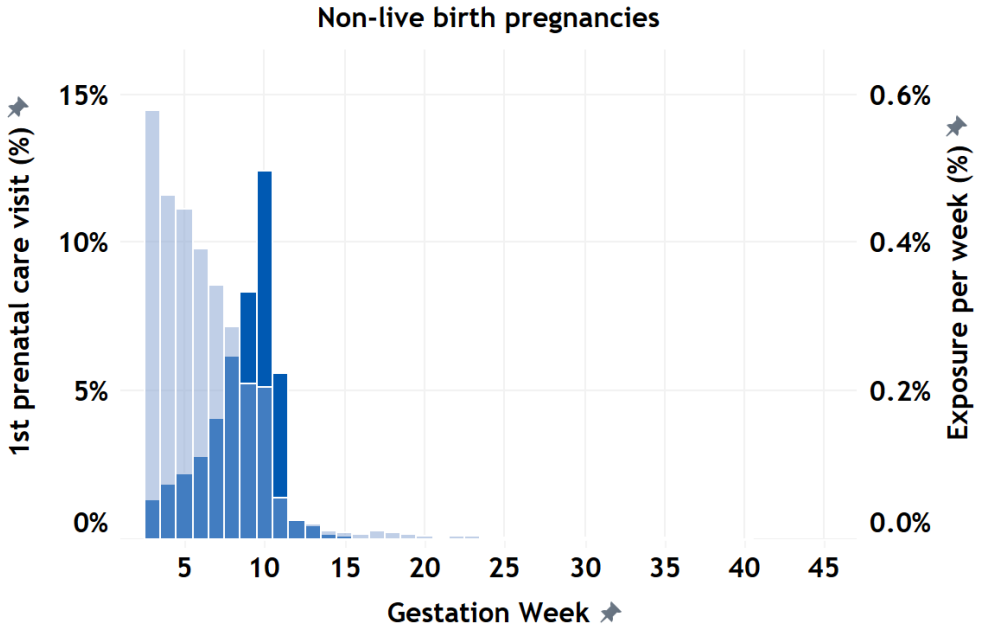
Live birth pregnancies (472,472)

- 5.8% exposed
- 78% with prenatal care in T1



Non-live birth pregnancies (167,522)

- 3.1% exposed
- 46% with prenatal care in T1



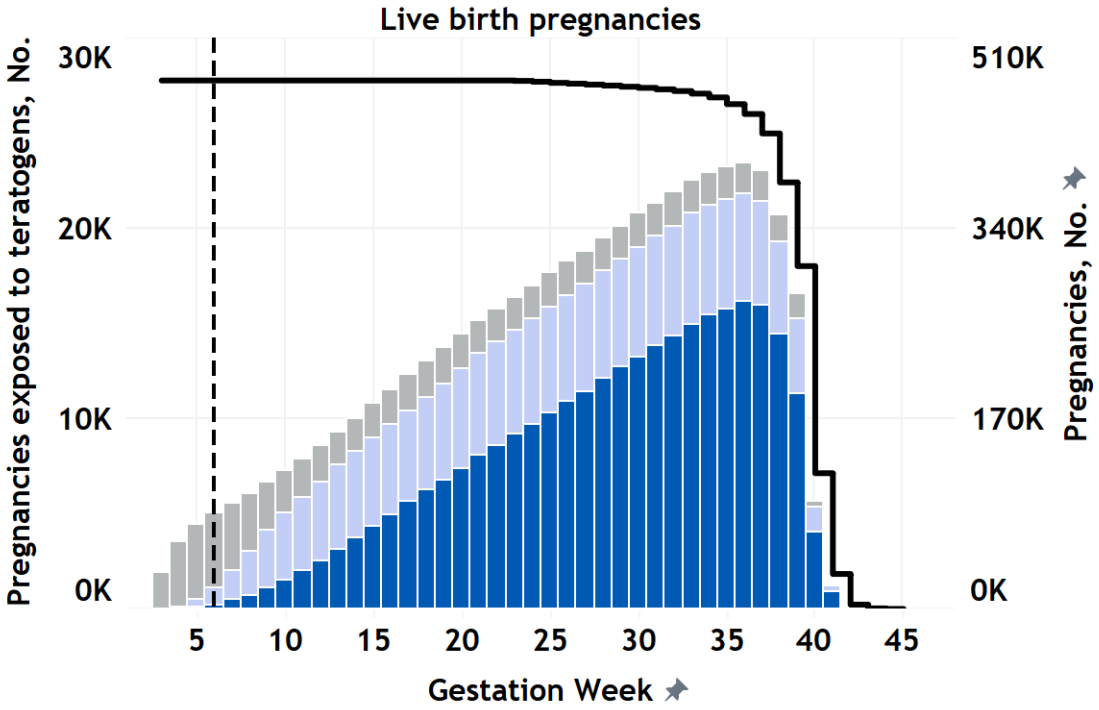
prenatal care teratogenic exposure

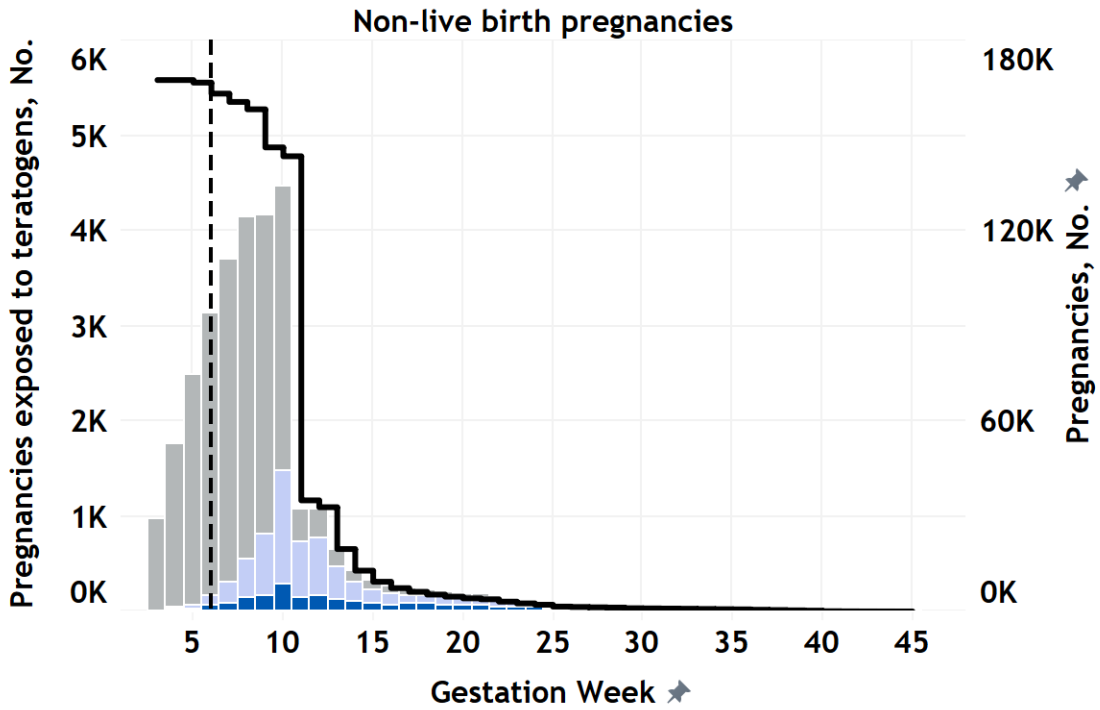
Results Timing of exposure & prenatal care initiation

By the end of **week 6**:

1.3% of all pregnancies exposed **(25.2%)**

- prenatal care before exposure: **3.8%**
- prenatal care after exposure but within week 6: **12.2%**
- prenatal care after week 6: **84.0%**



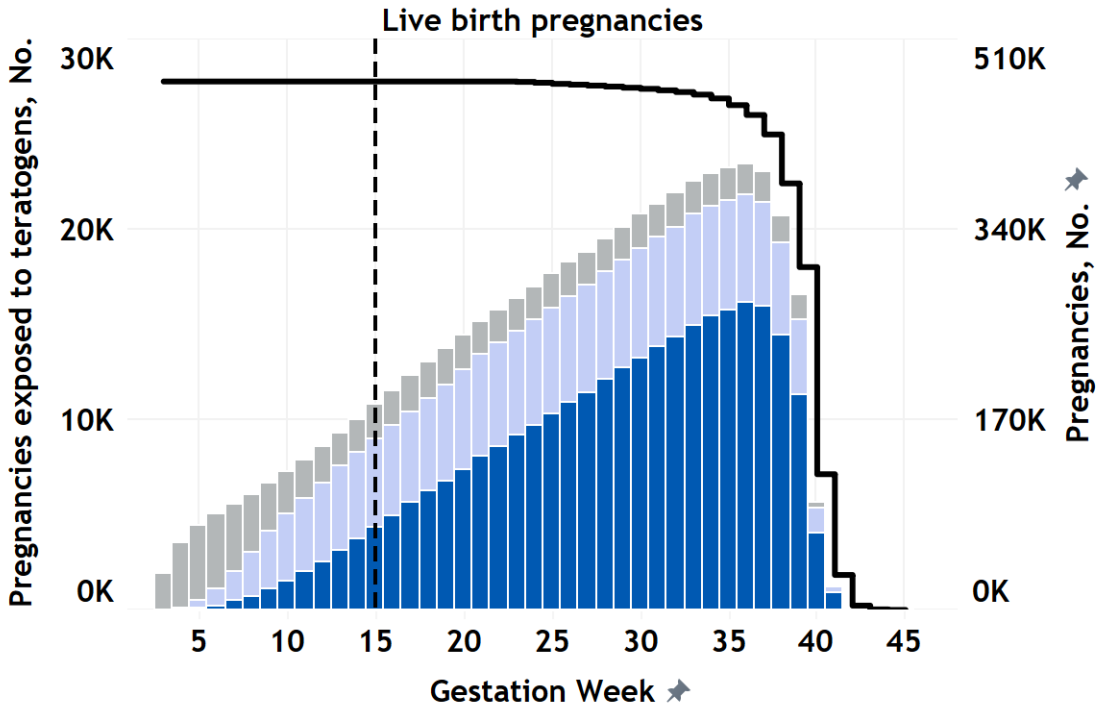


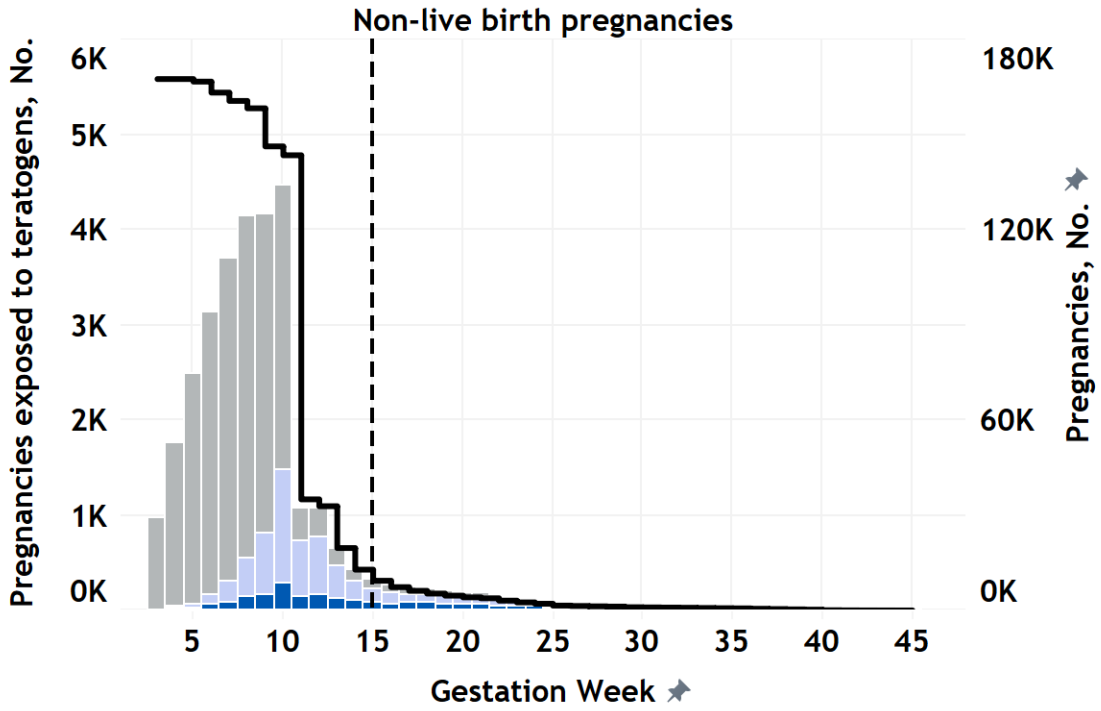
Results Timing of exposure & prenatal care initiation

By the end of **week 15**:

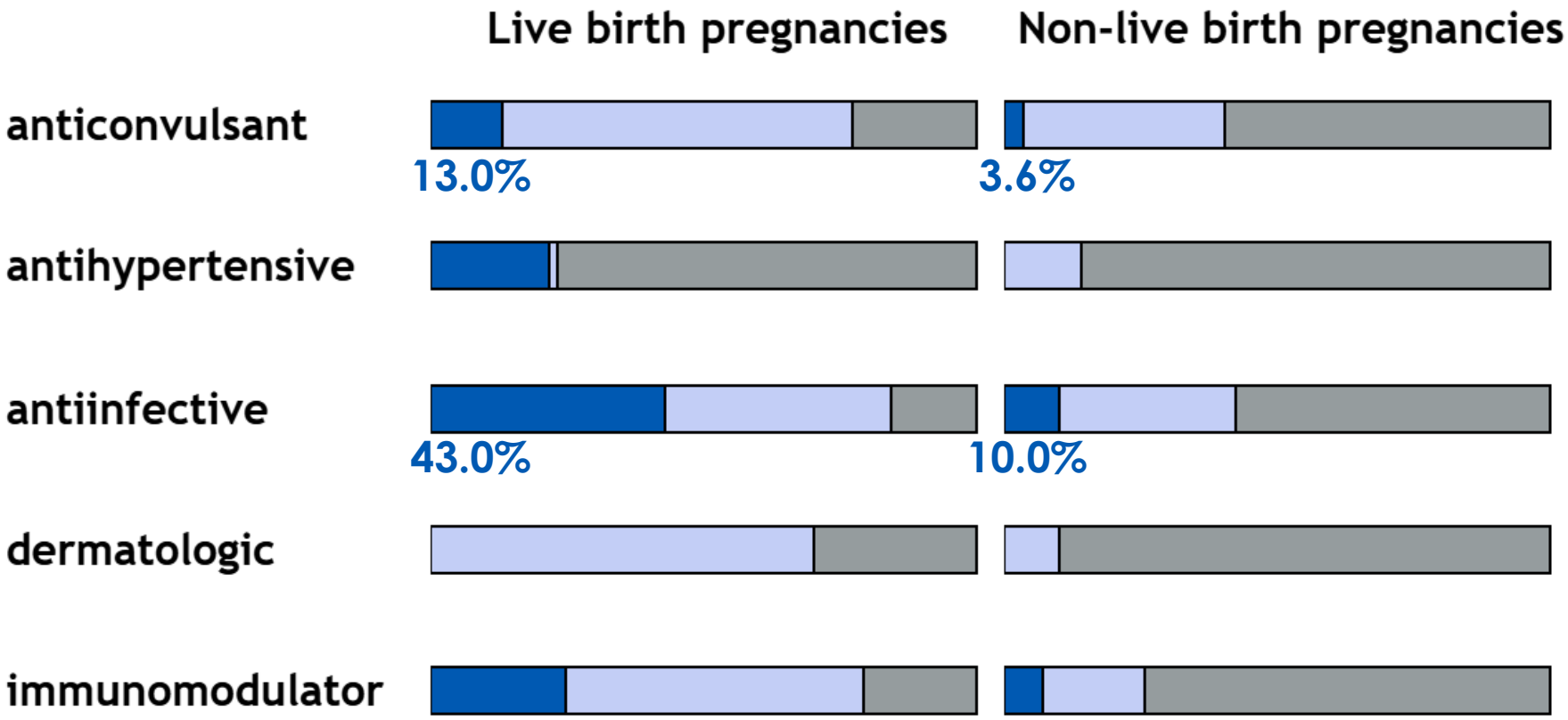
2.5% of all pregnancies exposed, **48.9%** of all exposed pregnancies

- prenatal care before exposure: **30.3%**
- prenatal care after exposure but within week 15: **39.6%**
- prenatal care after week 15: **30.1%**





Timing of Exposure & Prenatal Care Initiation
medication-specific differences



Summary

- Approximately 1 in 5 pregnancies did not receive prenatal care until after the first trimester (17% within the first 6 weeks of gestation)
- Large proportion of teratogenic exposures occurred during early gestation (about half within 15 weeks)—most of these exposures occurred before the first prenatal visit
- Prenatal care typically trailed behind teratogenic exposure and behind recently imposed earlier abortion cut-offs
- Limited opportunity for medication management decisions involving teratogenic risk during the etiologically relevant time window

How does prenatal exposure occur? Who is most at risk?

treatment-based risk measure

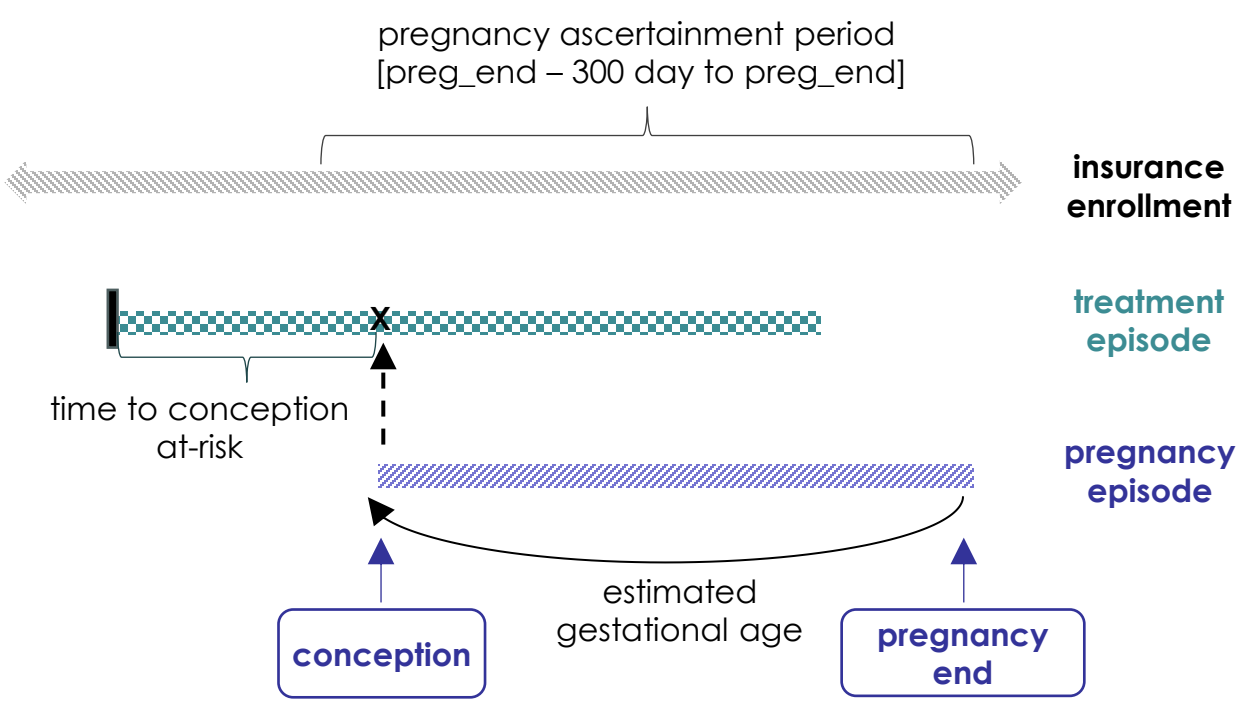
Background risk assessment

- Medication-specific exposure risk profiles support the design of effective REMS programs
- Existing studies focus on medication utilization during pregnancy, often limited to:
  - individual drugs or therapeutic classes
  - pregnancy-based measures (proportion of pregnancies with medication exposure) do not account for background use
- Risk of exposure
  - Treatment-based risk measure normalizes the risk by medication use duration
  - Net effect from multiple factors: compliance with safe-use behaviors, chronic medication use, drug-drug interactions, etc.

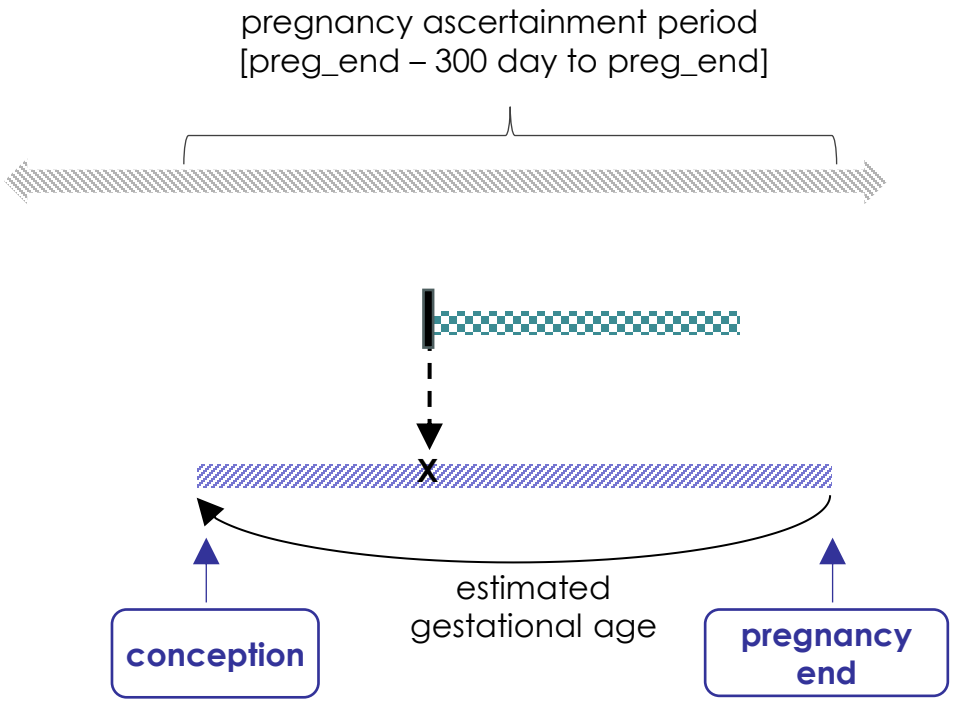
Methods

females aged 12-55 years

Exposure Scenario 1
Conception During Treatment



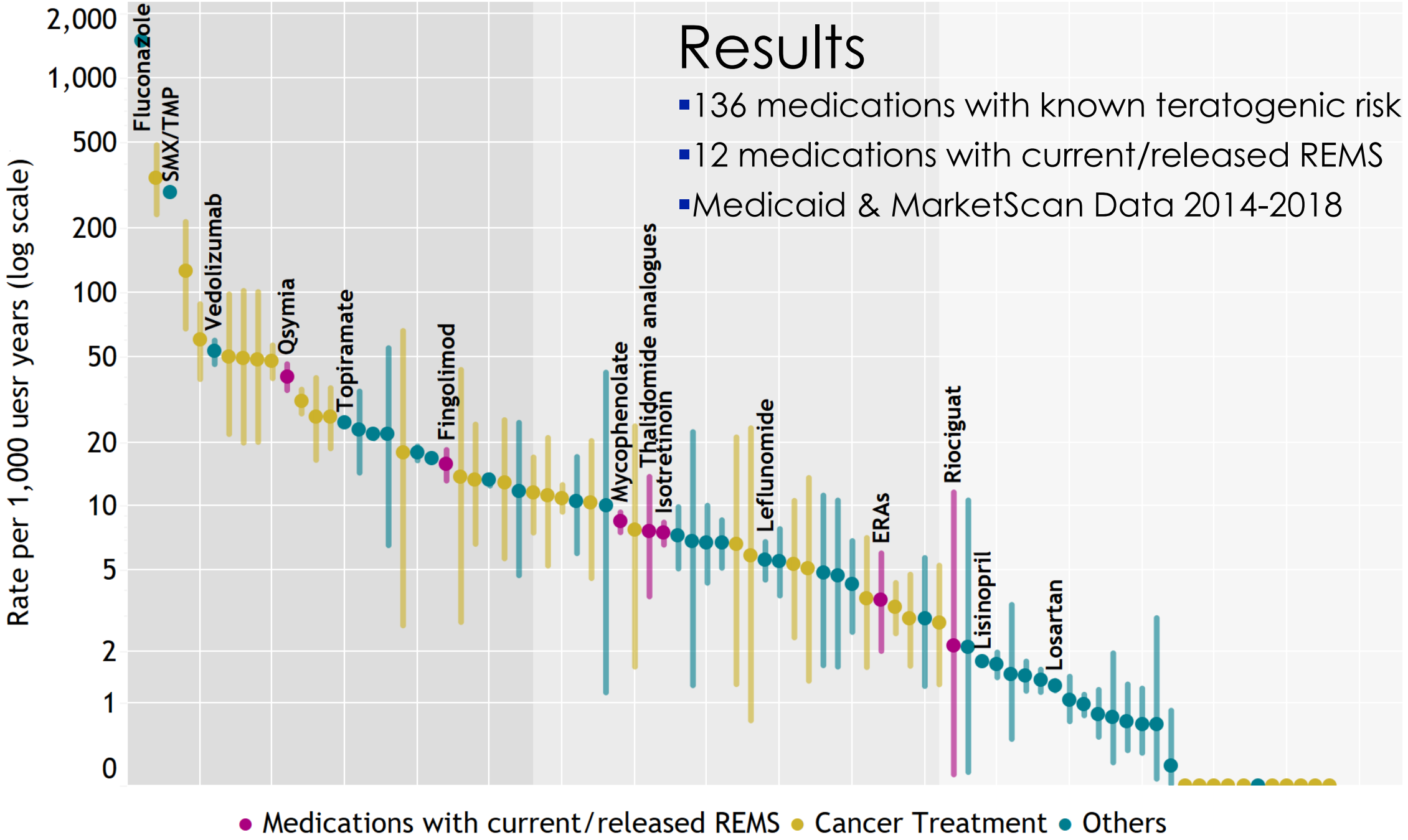
Exposure Scenario 2
Treatment Initiation During Pregnancy



Wang Y, Ewig CL, Smolinski NE, Toyserkani GA, LaCivita C, Zhou E, Thai T, Maro JC, Rasmussen SA, Winterstein A. Risk of Prenatal Exposure to Teratogenic Medications: Development of Evidence for the Teratogenic Risk Impact and Mitigation (TRIM) Tool. In Birth Defects Research 2024 May 1 (Vol. 116, pp. S66-S66).

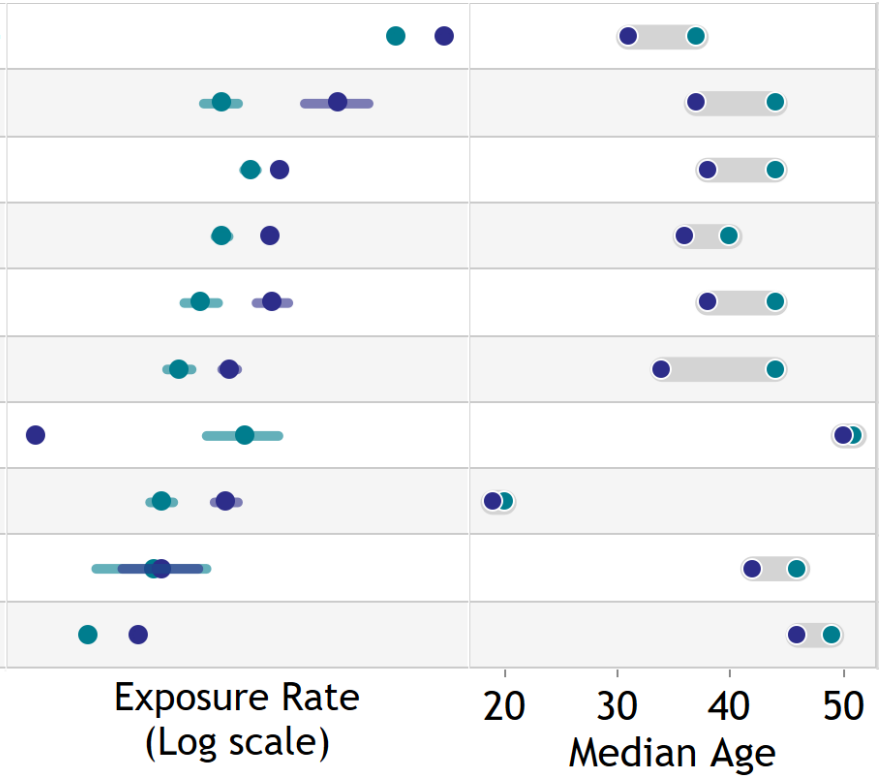
Results

- 136 medications with known teratogenic risk
- 12 medications with current/released REMS
- Medicaid & MarketScan Data 2014-2018



Results

		Rate per 1k user year (95% CI)	Scenario 2 Treatment Initiation During Pregnancy	% exposure occurring during pregnancy
	SMX/TMP	294.7 (292.0, 297.4)	87%	86%
●	Qsymia	40.7 (35.3, 46.7)	43%	21%
	Carbamazepine	22.0 (21.0, 23.0)	37%	33%
	Valproate	17.0 (16.4, 17.6)	34%	36%
●	Fingolimod	15.8 (13.3, 18.6)	36%	31%
●	Mycophenolate	8.5 (7.6, 9.5)	36%	36%
●	Thalidomide analogues	7.6 (3.8, 13.9)	NA	27%
●	Isotretinoin	7.5 (6.7, 8.5)	32%	31%
●	ERAs	3.6 (2.0, 6.1)	11%	0%
	Lisinopril	1.8 (1.7, 1.9)	28%	21%



■ Medications with active/released REMS
■ Medicaid ■ MarketScan

SMX/TMP: sulfamethoxazole and trimethoprim
ERAs: endothelin receptor antagonists (ERAs)—ambrisentan, macitentan, and bosentan

Summary

- Prenatal exposure through initiation of treatment during pregnancy occurred more frequently for teratogenic medications prescribed for acute conditions, while exposure for chronic medications occurred mostly because of conception during treatment
- Several medications with no active risk mitigation programs showed higher fetal exposure risk than those with active programs
- Publicly insured populations face a higher risk of teratogenic medication exposure compared to the privately insured populations

Takeaways

- 1 in 50 pregnancies are exposed to medications with known risks
- Prenatal care is often initiated after teratogenic exposure, limiting timely medication risk-benefit assessment and counseling
- Preconception care is critical, especially among women with chronic use of teratogenic medications
- Enhanced evidence on the benefits and burden of REMS is needed to guide optimal risk mitigation

Acknowledgments

- Dr. Almut Winterstein, Dr. Sonja Rasmussen, Dr. Judith Maro
- Dr. Celeste Ewig, Dr. Nicole Smolinski
- FDA collaborators

  HHS75F40121C00188 with the US Food and Drug Administration

  The views presented here are those of the authors and not necessarily those of the US Food and Drug Administration

- Awesome Research Team https://winterstein.pharmacy.ufl.edu/

Effectiveness of REMS Programs in Mitigating Prenatal Exposure to Teratogens

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Disclosures

- I own stock through inheritance in Baxter, Cardinal Health, CVS Health, Edwards Lifesciences, and Takeda.

Agenda

- Background
- Systematic review
- Isotretinoin case study
- Mycophenolate case study
- Qsymia case study

Background

- 57 non-cancer drugs and 83 cancer drugs are considered definite teratogens with known prenatal risk
- Currently there are only 9 drugs with an active Risk Evaluation and Mitigation Strategies (REMS) related to prenatal exposure
- Limited implementation of REMS is related to burden on patients and healthcare providers to follow restrictions
- To weigh burden against benefit, effectiveness studies are needed

Drug Name	Indication
Active REMS	
Bosentan	Pulmonary Hypertension
Thalidomide	Multiple Myeloma
Lenalidomide	Multiple Myeloma
Isotretinoin	Severe recalcitrant nodular acne
Phentermine/Topiramate	Chronic weight management
Mycophenolate	Prophylaxis of organ rejection
Pomalidomide	Multiple myeloma
Riociguat	Pulmonary Hypertension
Spartentan	Primary IgA Nephropathy
Retired REMS	
Fingolimod	Multiple Sclerosis
Televancin	Complicated SSTI
Aprocitentan	Hypertension
Ambrisentan	Pulmonary Hypertension
Macitentan	Pulmonary Hypertension

Study Design Considerations

- Outcomes to measure
  - Conception during treatment
  - Initiation during pregnancy
  - Use of contraception during treatment
- Comparator groups
  - Pre vs post intervention REMS period
  - Active comparator with no REMS because REMS are often implemented at drug approval
  - Male vs female users

Systematic review on the impact of risk minimization programs

Author (Year)	Drug	Comparison	Country	Finding
Sarayani (2019)	mycophenolate	Before/after REMS	USA	Decreased pregnancy risk at treatment initiation (RR 0.42 (0.24, 0.74)) No change in conception during treatment(RR 0.97 (0.63, 1.49))
Albogami (2021)	isotretinoin	Other acne meds	USA	Decreased pregnancy risk during treatment (RR 0.22 (0.18, 0.26))
Shin (2011)	isotretinoin	Before/after REMS	USA	No change in pregnancy risk (HR 0.74 (0.35-1.57))
Kerr (2016)	isotretinoin	Male users	USA	Male utilization dropped 23% post-REMS implementation compared to 46% drop in females
Pinheiro (2013)	isotretinoin	Before/after REMS	USA	Number of isotretinoin prescriptions decreased after REMS implementation
Sarayani (2023)	Qsymia	Topiramate and other anti-obesity meds	USA	Decreased pregnancy risk at treatment initiation (RR 0.40 (0.23, 0.70) No change in conception during treatment (RR = 0.62 (0.38, 1.02))
Abtahi (2023)	valproate	Before/after REMS	Italy	Decreased pregnancy prevalence during treatment: Pre (0.70/1000) vs Post (0.27/1000)
Abtahi (2023)	valproate	Before/after REMS	Spain	Decreased pregnancy prevalence during treatment : Pre (0.48/1000) vs Post (0.13/1000)
Abtahi (2023)	valproate	Before/after REMS	Netherlands	Decreased pregnancy prevalence during treatment: Pre (0.0.34/1000) vs Post (none observed)
Abtahi (2023)	valproate	Before/after REMS	United Kingdom	Increased pregnancy prevalence during treatment: Pre (1.13/1000) vs Post (5.07/1000)

Case Study #1: Isotretinoin

Drug Safety (2021) 44:447–454
https://doi.org/10.1007/s40264-021-01053-3

ORIGINAL RESEARCH ARTICLE

Check for updates

Real-World Fetal Exposure to Acne Treatments in the United States: A Retrospective Analysis from 2006 to 2015

Yasser Albogami[1,2,3] · Amir Sarayani[1,3] · Juan M. Hincapie-Castillo[1,3] · Almut G. Winterstein[1,3]

Accepted: 3 February 2021 / Published online: 8 March 2021

Background

- Isotretinoin is a vitamin A retinoid initially approved in May 1982
- Indications include severe cystic acne
  - Off-label uses include neuroblastoma and rosacea
- Black box warning for life-threatening birth defects (e.g., central nervous system malformations, cleft palate, cardiac defects, and eye anomalies)
  - Relative risk of malformations: 25.6 (95% CI 11.4-57.5)[1]

1. Lammer EJ et al. Retinoic acid embryopathy. N Engl J Med. 1985 Oct 3;313(14):837-41.

Isotretinoin REMS (iPLEDGE)

- iPLEDGE approved in Mar 2006
  - Previously had an unnamed risk minimization program
- One of the most stringent REMS programs in the US
- Main components:
  - Patient: negative pregnancy test prior to each dispensing, at least 2 forms of contraception
  - Prescriber: prescriber training
  - Pharmacy: maximum 30-day supply, pharmacy certification
- Primary contraception examples include intrauterine devices, combined oral contraception, and injections

Study Design

- Database: MarketScan research databases (Mar 2006 - June 2015)
  - Administrative claims data for privately insured patients in the US
- Study Population: Female patients 15-44 years old with at least 1 outpatient diagnosis of acne
- Outcomes measured: percent of users with contraception use and conception rates during treatment
- Comparison groups: patients using 3 groups of acne medications:
  - Oral isotretinoin: REMS → iPLEDGE
  - Oral doxycycline/minocycline: potential teratogenic risk
  - Topical erythromycin/clindamycin: no teratogenic risk

Results: Contraception Differences

Contraceptive Use	iPLEDGE (isotretinoin), N = 84,204	Potential Risk (doxycycline/minocycline), N = 473,167	No Risk (erythromycin/clindamycin), N = 422,318
Overall Contraceptive Use	41,734 (49.5%)	118,695 (21.5%)	96,757 (22.9%)
Oral contraceptive	38,389 (91.9%)	105,728 (89.1)	86,480 (89.5%)
Proportion of users by age group, years			
15–19	45%	20%	17%
20–29	62%	38%	36%
30–39	41%	21%	21%
40–44	23%	13%	12%

Results: Comparing Risk of Pregnancy

- Pregnancy incidence rate per 1,000 person-years of treatment:
  - iPLEDGE: 5.0 (4.3-5.8) | Potential Risk: 25.2 (24.3-26.2) | No Risk: 57.6 (55.3-60.0)

Pregnancy Risk	iPLEDGE vs. Potential Risk	iPLEDGE vs. No Risk	Potential Risk vs. No Risk
Incidence rate difference per 1,000 person-years	-20.1 (-21.3 to -18.9)	-52.5 (-55.0 to -50.1)	-32.4 (-34.9 to -29.8)
Incidence rate ratio per 1,000 person-years	0.20 (0.17 to 0.23)	0.09 (0.07 to 0.10)	0.43 (0.41 to 0.46)
Age group adjusted rate differences			
15–19	-2.9 (-3.8 to -2.1)	-3.7 (-5.0 to -2.5)	-0.5 (-1.7 to 0.7)
20–29	-40.2 (-43.5 to -37.0)	-83.5(-89.6 to -77.5)	-41.3 (-47.6 to -35.0)
30–39	-45.9 (-50.2 to -41.6)	-130.0 (-139.0 to -121.0)	-78.1 (-87.1 to -69.1)
40–44	-4.5 (-8.2 to -0.8)	-11.0 (-16.5 to -5.5)	-6.2 (-11.2 to -1.2)

Conclusion

- Contraception rates were < 50% for isotretinoin with < 30% for other acne treatment options
- Fetal exposure to acne treatments varied across the treatment groups studied
  - Isotretinoin had the lowest
- Teenagers had lower pregnancy rates, but less differences across treatment groups in pregnancy rates

Case Study #2: Mycophenolate

ORIGINAL RESEARCH

Comparative effectiveness of risk mitigation strategies to prevent fetal exposure to mycophenolate

Amir Sarayani [1], Yasser Albogami [1,2], Mohannad Elkhider [1], Juan M Hincapie-Castillo [1], Babette A Brumback [3], Almut G Winterstein [1,4]

Background

- Mycophenolate is an antimetabolite immunosuppressant initially approved in May 1995
- Indications include prophylaxis of organ rejection for kidney, heart, and liver transplants
  - Off-label uses include lupus, myasthenia gravis, atopic dermatitis, gout
- Black box warning for increased pregnancy loss and congenital malformations (e.g., cleft palate, heart defects, microtia)
  - Rate of pregnancy loss: ~50%[1]
  - Rate of malformations: ~25%[2]

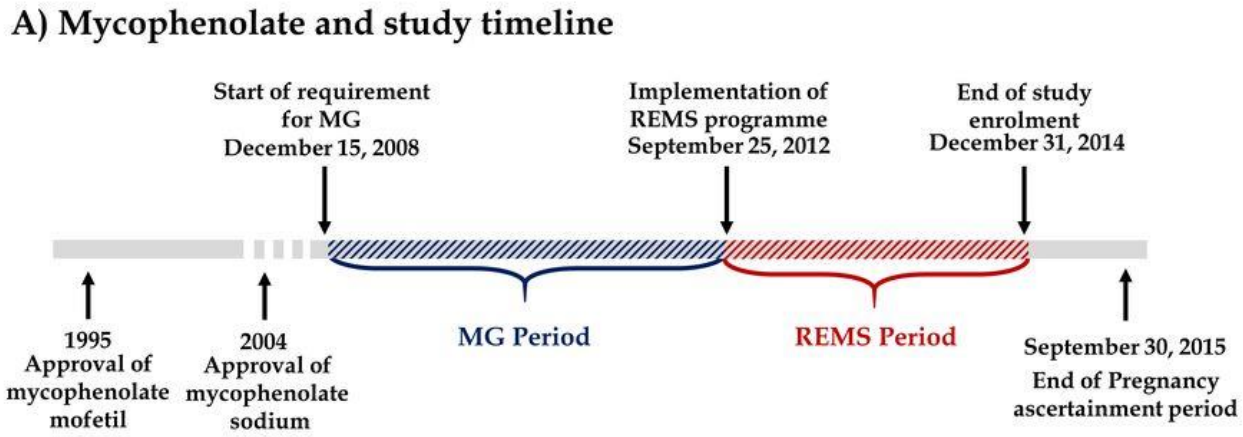
1. Thai TN et al. Risk of pregnancy loss in patients exposed to mycophenolate compared to azathioprine: A retrospective cohort study. Pharmacoepidemiol Drug Saf. 2020 Jun;29(6):716-724.
2. Le HL et al. Usage of Tacrolimus and Mycophenolic Acid During Conception, Pregnancy, and Lactation, and Its Implications for Therapeutic Drug Monitoring: A Systematic Critical Review. Ther Drug Monit. 2020 Aug;42(4):518-531.

Mycophenolate REMS

- Established in September 2012
- Initially included mandatory prescriber training and a patient + provider acknowledgement form
- Prior to the REMS, relied only on black box warning and medication guide
- The currently approved REMS has removed the requirement for prescriber training

Study Design

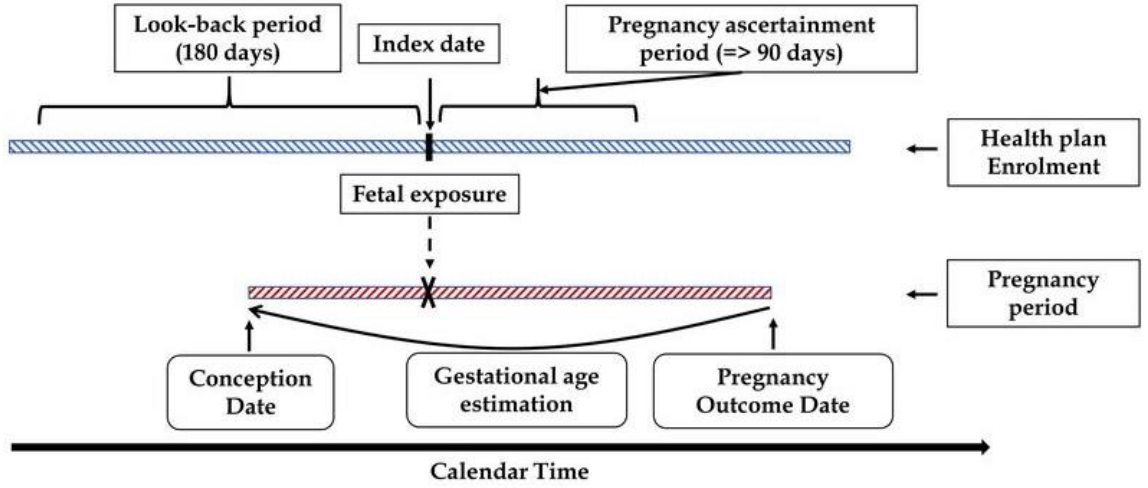
- Data Source: MarketScan research databases (2008-2015)
- Population: Female patients 15-44 years old with at least 1 prescription fill of mycophenolate
- Outcomes measured: pregnancy at initiation and conception during treatment
- Comparison: pre-REMS Medication Guide only period versus post-REMS period



Results: Pregnancy at Initiation

Study Period	Prevalence per 1,000 treatment episodes	Prevalence Difference per 1,000 treatment episodes	Prevalence Ratio
REMS Period	1.7 (1.0 to 2.9)	-2.4 (-3.8 to -1.0)	0.42 (0.24 to 0.74)
Medication Guide Period	4.1 (3.2 to 5.4)	Reference	

B) Study Design for Analysis 1 (Mycophenolate initiation during pregnancy)

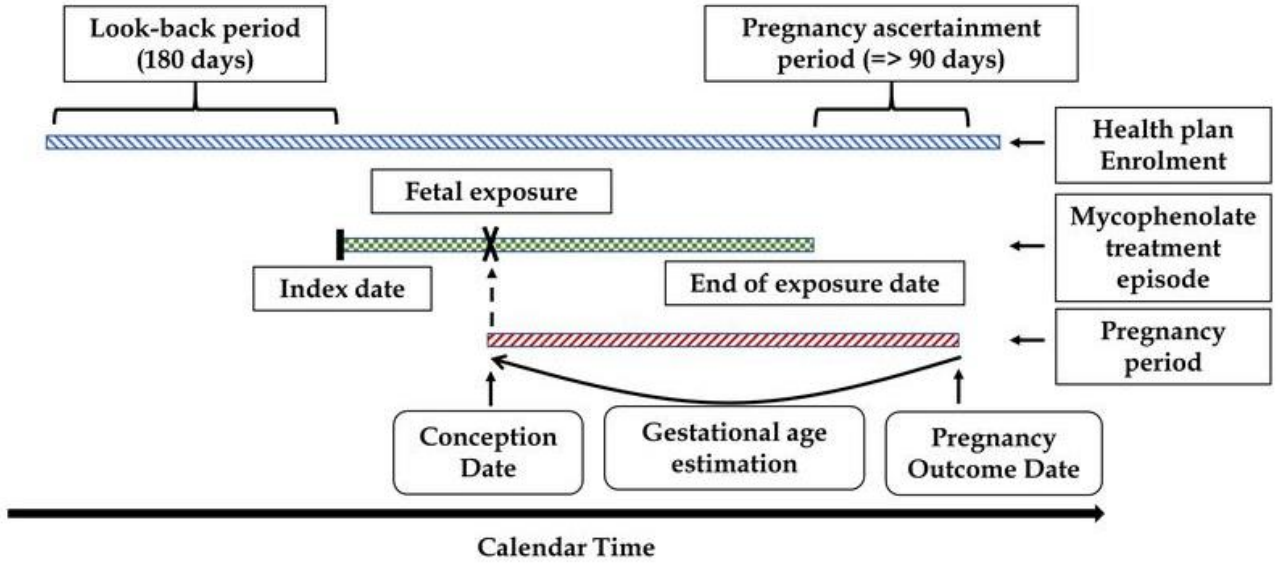


adjusted for age, indication, geographic region, clinical comorbidities

Results: Conception During Treatment

Study Period	Adjusted Incidence Rate per 1,000 years of treatment	Adjusted Rate Difference per 1,000 years of treatment	Adjusted Rate Ratio
REMS Period	12.5 (8.9 to 17.6)	−0.4 (−5.9 to 5.0)	0.97 (0.63 to 1.49)
Medication Guide Period	12.9 (9.9 to 16.9)	Reference	

C) Study design for Analysis 2 (Pregnancy occurrence during mycophenolate treatment episode)



Conclusion

- Pregnancy at initiation of mycophenolate was significantly decreased in the REMS period
- Conception during treatment was not significantly different in the REMS period compared to the medication guide period
- The REMS program appears to prevent pregnancies at treatment initiation, but fails to prevent conception during treatment

Case Study #3: Qsymia

Original Research | 21 March 2023

Assessment of the Risk Evaluation and Mitigation Strategy (REMS) for Phentermine–Topiramate to Prevent Exposure During Pregnancy

Authors: Amir Sarayani, PharmD, MPH, PhD, William Troy Donahoo, MD, Christian Hampp, PhD, Joshua D. Brown, PharmD, PhD, and Almut G. Winterstein, PhD | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 176, Number 4 • https://doi.org/10.7326/M22-1743

Background

- Qsymia is topiramate/phentermine and was approved as a combo drug in July 2012
- Indication is obesity
- Absolute contraindication in pregnancy
  - Main risk for topiramate is oral clefts

Qsymia REMS

- Established in July 2012 at drug approval
- REMS components at approval:
  - Patient: recommended pregnancy test prior to initiation, recommended effective contraception
  - Prescriber: optional online prescriber training module
  - Pharmacy: medication guide and patient education dispensed at each fill, dispensing only through specialty pharmacies that must be certified
- In 2022, the prescriber training component was discontinued

Study Design

- Data Source: MarketScan research databases (2012-2018)
- Population: Female patients 12-55 years old with at least 1 prescription fill of anti-obesity medications
- Outcomes measured: pregnancy at initiation, conception during treatment
- Comparison groups: patients using 3 groups of obesity medications:
  - Qsymia
  - Topiramate (with obesity diagnosis requirement and absence of epilepsy or migraines)
  - Anti-obesity medications: liraglutide, lorcaserin, bupropion/naltrexone

Results: Pregnancy at Initiation

Cohort	Prevalence per 1,000 treatment episodes		Prevalence Ratio	Prevalence Difference per 1,000 episodes
	Qsymia	Topiramate		
Qsymia vs. Topiramate	0.9 (0.5 to 1.4)	1.6 (1.3 to 2.0)	0.54 (0.31 to 0.95)	-0.7 (-1.3 to -0.2)
	Qsymia	Anti-Obesity		
Qsymia vs. Anti-Obesity	0.8 (0.5 to 1.3)	1.7 (1.4 to 2.0)	0.47 (0.27 to 0.81)	-0.9 (-1.4 to -0.4)
	Topiramate	Anti-Obesity		
Topiramate vs. Anti-Obesity	1.4 (1.1 to 1.8)	1.9 (1.6 to 2.3)	0.74 (0.55 to 1.01)	-0.5 (-1.0 to 0.0)

adjusted for age, indication, geographic region, clinical comorbidities

Results: Conception During Treatment

Cohort	Incidence Rate per 1,000 treatment episodes		Rate Ratio	Rate Difference per 1,000 episodes
	Qsymia	Topiramate		
Qsymia vs. Topiramate	9.1 (6.2 to 13.2)	15.0 (12.7 to 17.6)	0.61 (0.40 to 0.91)	-5.4 (-9.6 to -1.3)
	Qsymia	Anti-Obesity		
Qsymia vs. Anti-Obesity	8.4 (5.8 to 12.1)	15.1 (13.0 to 17.5)	0.56 (0.37 to 0.83)	-6.5 (-10.3 to -2.7)
	Topiramate	Anti-Obesity		
Topiramate vs. Anti-Obesity	13.7 (11.6 to 16.2)	16.7 (14.3 to 19.4)	0.83 (0.66 to 1.03)	-3.3 (-6.6 to 0.1)

adjusted for age, indication, geographic region, clinical comorbidities

Conclusion

- Qsymia REMS is effective at reducing prenatal exposure at initiation and during treatment
- The generic drug topiramate does not have any risk minimization and has prenatal exposure similar to other anti-obesity drugs

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Conclusions

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Conclusions

- Few studies have looked at the effectiveness of risk minimization strategies to prevent prenatal exposure
- Studies that have been conducted vary widely in outcome measures based on components of the REMS
- Mitigation of drug initiation during pregnancy appears somewhat more effective than prevention of conception during treatment
  - Differences may be due to prescriber and patient awareness
- Effectiveness varies by patient type and REMS may need to be tailored to more to specific patient groups and clinical scenarios

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Thank you

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Teratogenic Risk Impact Mitigation:
How to Prioritize Teratogenic Medications for REMS

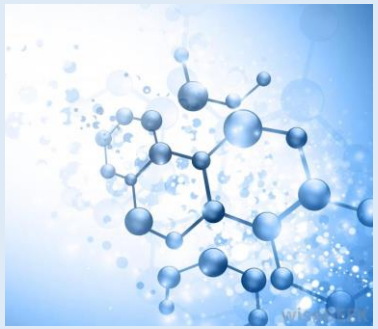
37th Annual OTIS Education Meeting
June 30th, 2025

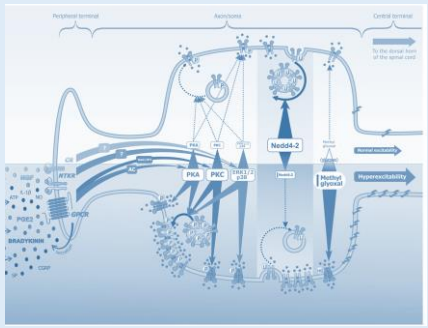
Almut G Winterstein, PharmD, PhD, FISPE
Pharmaceutical Outcomes & Policy, College of Pharmacy
Epidemiology, Colleges of Public Health & Professions and Medicine
Center for Drug Evaluation and Safety
University of Florida

Disclosures

- Funding related to pregnancy from NIH, FDA, CDC, Bill Gates Foundation.
- Consulting fees from Lykos, Syneos, Ipsen, Bayer, Novo Nordisk, Merck, all unrelated to this work.

Why TRIM?





REMS or no REMS?

Label Warnings	
Generic Name	**Drug Approval Year**
Methotrexate	1953
Warfarin	1954
Valproic acid	1978
Lisinopril	1987
Simvastatin	1991
Paroxetine	1992
Ribavirin	1998
Vismodegib	2012

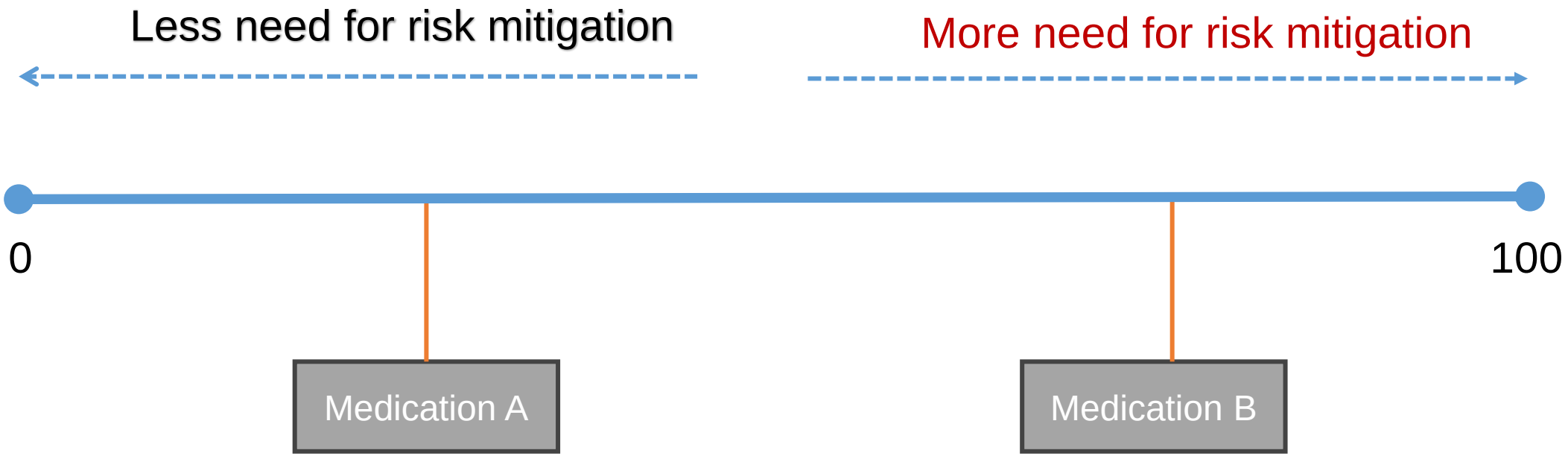
REMS	
Generic Name	**Drug Approval Year**
Isotretinoin*	1982
Mycophenolate	1995
Thalidomide*	1998
Bosentan*	2001
Lenalidomide*	2005
Ambrisentan@*	2007
Telavancin@	2009
Fingolimod@	2010
Phentermine/Topiramate	2012
Pomalidomide	2013
Riociguat	2013
Macitentan@	2013

*These agents had RiskMAP programs before REMS were enacted in 2007.
@ REMS released several years after approval.

TRIM Vision

Teratogenic Risk Impact and Mitigation (TRIM)

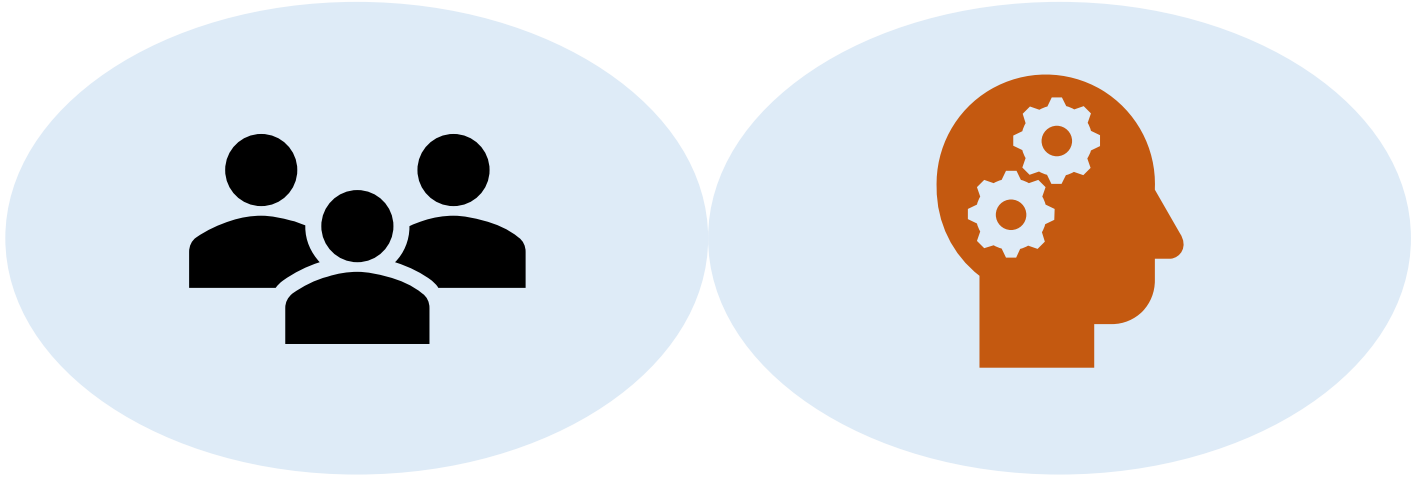
Develop a quantitative tool (TRIM) that consists of explicit, measurable criteria that can assist in the decision making regarding the need for a REMS for medications with teratogenic effects.



TRIM Approach

Development of TRIM tool

Epidemiology meets Decision Sciences



Criteria
Modified Delphi Study

Metrics
Delphi Study

Weights
Discrete Choice Experiment

Scores
Evidence syntheses & RWD analyses

Winterstein et al, *Drug Safety* 2025

TRIM Expert Panel

Panel Member (Academia)	Affiliation
Sonia Hernandez-Diaz	Harvard
Janine E Polifka	UW / TERIS
Katherine L Wisner	George Washington University
Dikea Roussos-Ross	UF Psych
Brian Bateman	Stanford
Sharon Voyer Lavigne	UConn Health
Jeanne Sheffield	Hopkins
Sarah G. Običan	USF
Reem S. Abu-Rustum	UF
Anthony R. Scialli	Independent
Peter Kaboli	VA Internal Medicine
Michael F. Greene	Harvard
Denise J. Jamieson	University of Iowa
Anick Bérard	Univ of Montreal
Beth Choby	Independent
Ellen Zimmermann	UF
Beth Conover	Univ. of Nebraska
Christina D. Chambers	UCSD
Michael S. Wolf	Northwestern Medicine
Kathleen Hoeger	Univ of Rochester

Panel Member (Industry)	Affiliation
Rachel Sobel	Regeneron
Christian Hampp	Regeneron
Anthony M DeLise	Novartis
Susan Bielmeier Laffan	Amgen
Kristine Shields	Independent
Janet Hardy	Independent
Melissa Tassinari	Independent
Caitlin Knox	Regeneron
Alicia Gilsenan	RTI
Meredith Smith	Evidera/ USC
Tarek Hammad	Takeda
Amir Sarayani	Janssen
(Government)	Affiliation
Margaret (Peggy) Honein	CDC
Cindy Moore	Former CDC/ Contractor
(Patient Representative)	Affiliation
Adrienne Griffen	Maternal Mental Health Leadership Alliance
Mariah Leach	Patient Representative

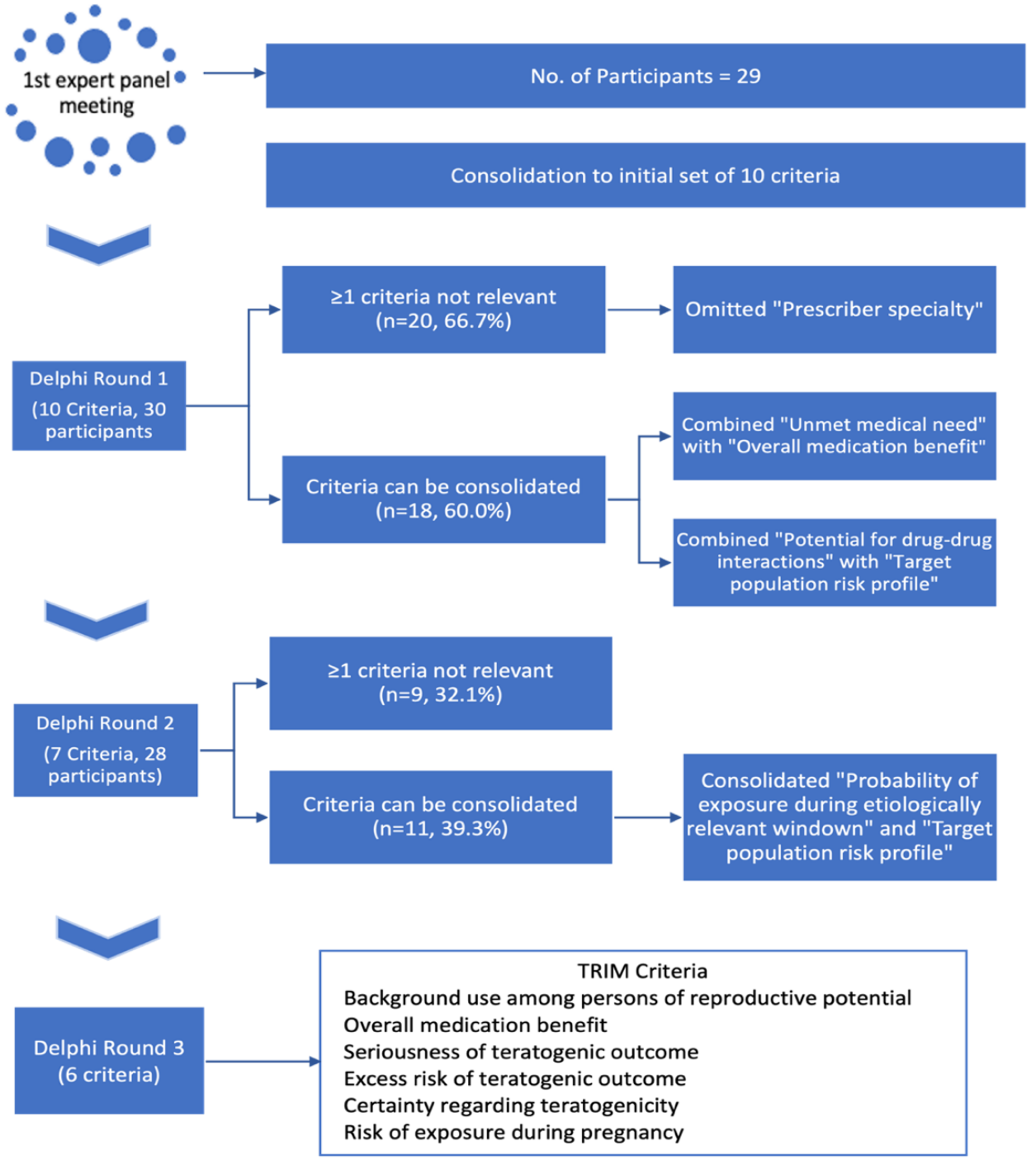
Criterion development

Modified Delphi Design (Delphi process supplemented with initial focus groups)

- Broad brainstorming to develop exhaustive list of candidate criteria
- Delphi process (virtual): panel members asked to evaluate criteria for completeness, relevance, and distinctiveness
- Responses collected informed subsequent revisions
- Consensus defined as >80% agreement

Initial set of unique criteria (from 36)
1. Prevalence of drug use
2. Overall drug benefit
3. Unmet medical need
4. Seriousness of adverse effect
5. Frequency of the adverse effects
6. Certainty regarding teratogenicity
7. Drug-drug interactions
8. Target population risk profile
9. Specialty of prescribers
10. Probability of exposure during etiologically relevant window

Summary Criterion development



Final TRIM Criteria

Criterion	Description	Rationale	Examples
1. Background use among persons of reproductive potential	Characterizes population size potentially impacted by teratogenic effect, i.e., women of reproductive potential who use the medication (label and off-label) and their offspring.	A larger user population translates into a larger public health impact.	• Thalidomide has small user population; • Isotretinoin has large user population; • Topiramate has large user population due to off label use.
2. Overall medication benefit among persons of reproductive potential	Characterizes medication benefit considering seriousness of the indication, medication efficacy and availability of alternatives (label or off-label) for women of reproductive potential or during pregnancy (e.g., risk to the mother/infant if the condition is left untreated or treated with less effective or safe alternative).	REMS can improve medication safety and hence improve a medication's benefit risk ratio.	• Isotretinoin is more effective than alternatives, but risk of acne if left untreated is generally low; • Valproic acid has several alternatives for treatment of seizures; • Dual endothelin receptor antagonists (e.g., bosentan) are more effective than alternatives and risk if untreated is high.
3. Seriousness of teratogenic outcome	Characterizes seriousness of teratogenic effects considering severity, chronicity, reversibility, availability & type/invasiveness of treatment.	A more serious teratogenic effect translates into a more serious public health impact.	• Isotretinoin causes life-threatening brain/heart defects; • Topiramate causes cleft lip/palate with effects that can be mitigated

Final TRIM criteria (continued)

Criterion	Description	Rationale	Examples
4. Excess risk of teratogenic outcome	Characterizes the frequency of the of the teratogenic effect.	Greater frequency of adverse effects translates into a greater public health impact.	• An excess of 25 pregnancy losses per 100 pregnancies among individuals exposed to mycophenolate
5. Certainty regarding terato-genicity	Characterizes the level of certainty considering available evidence, biological plausibility and other factors in assessing the probability for teratogenicity	Stronger evidence allows for more certainty regarding the magnitude of risk.	• High-quality observational studies have consistently described teratogenic risk of valproic acid resulting in high level of certainty; • Striking temporal association between thalidomide approval and excess unusual limb malformations, which was replicated in animal studies, resulting in a high level of certainty; • Animal studies and mechanism of action suggest tobramycin ototoxic effects but only one case series in humans with limited detail is available, resulting in moderate level of certainty
6. Risk of exposure during pregnancy	Characterizes risk for exposure during etiologically relevant pregnancy window, considering risk of unintended pregnancy due to noncompliance with safe use behaviors, duration and timing of use, medication half-life, and decreased hormonal contraceptive effectiveness due to drug-drug interactions	Higher risk for prenatal exposure translates into higher public health impact	• Higher risk-taking among teenagers leads to unintended pregnancy; • Carbamazepine reduces hormonal contraceptive effectiveness; some biologics have multi-months half-life; • Consistent chronic use of valproate versus short-term use of SMP/TMX[a] translates in different risk for prenatal exposure; • ACE-I likely not problematic during first trimester when risk for accidental exposure is highest

Initial metrics proposed

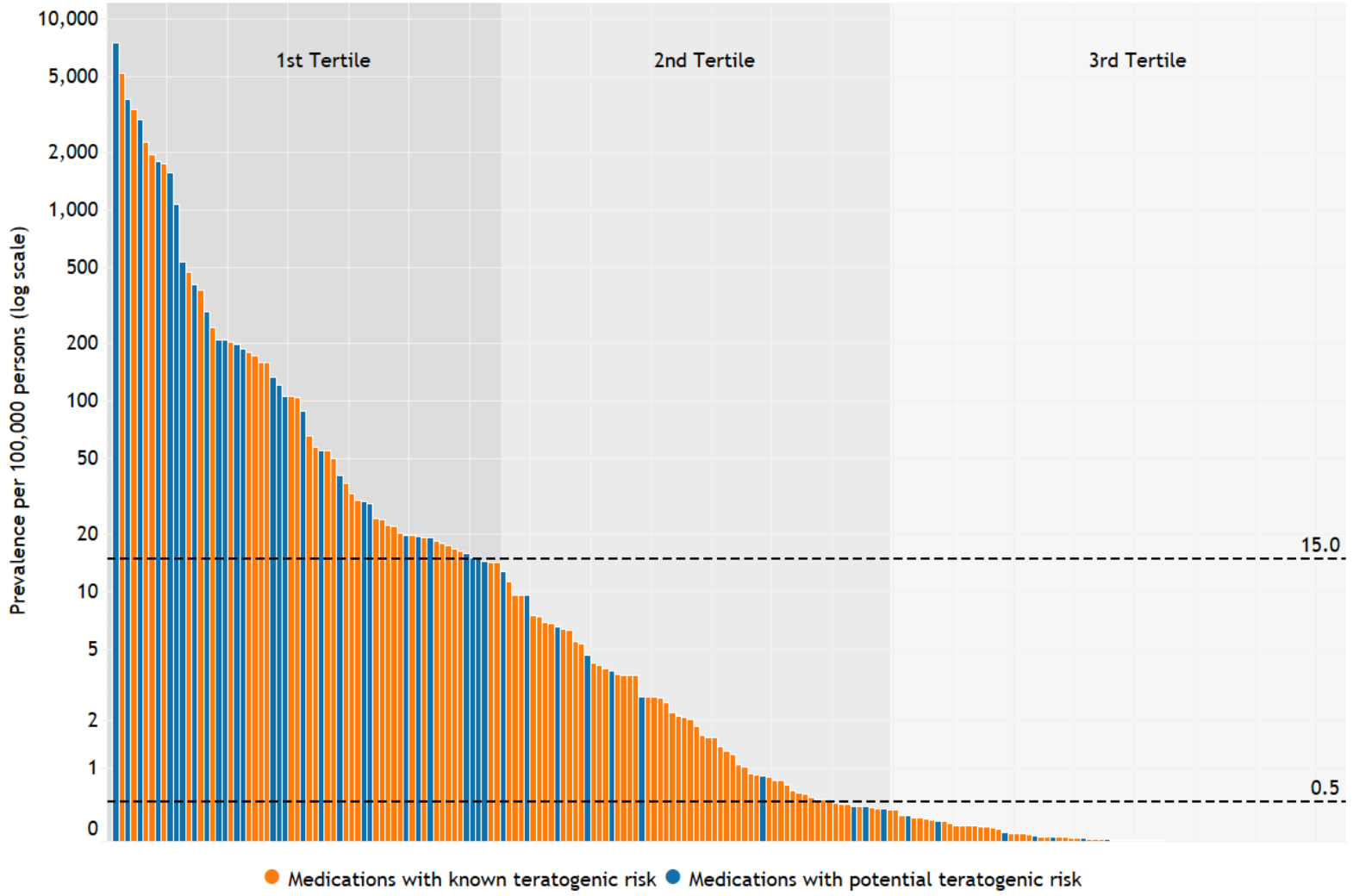
Criterion	Metrics
1. Prevalence of medication use	Annual prevalence of medication use among women of childbearing age 1. High: ≥10 per 100,000 women of childbearing age 2. Moderate: 1 to 10 per 100,000 women of childbearing age 3. Low: <1 per 100,000 women of childbearing age
2. Overall medication benefit	Medication is used for a condition which is: 1. Serious *without* alternative treatments available 2. Less serious *without* alternative treatment 3. Serious *with* alternative treatment 4. Less serious *with* alternative treatment
3. Seriousness of teratogenic effect	1. Death: includes pregnancy loss or infant death 2. Lifelong consequences: significant adverse infant outcomes with lifelong consequences that cannot be mitigated 3. Treatable: significant adverse outcomes that may be mitigated through treatment
4. Excess risk of teratogenic effect	Estimated attributable risk (AR) comparing risk among exposed and non-exposed (or exposed to active comparator) AR = $Risk_{exposed} - Risk_{unexposed}$ 1. High: >5% 2. Moderate: 1 to 5% 3. Low: <1%

Real-world data

Considers indication seriousness & availability of alternatives

Considers range of risk differences in clinical teratogenicity studies

Criterion 1 Background use prevalence (averaged across Medicaid & MarketScan 2018)



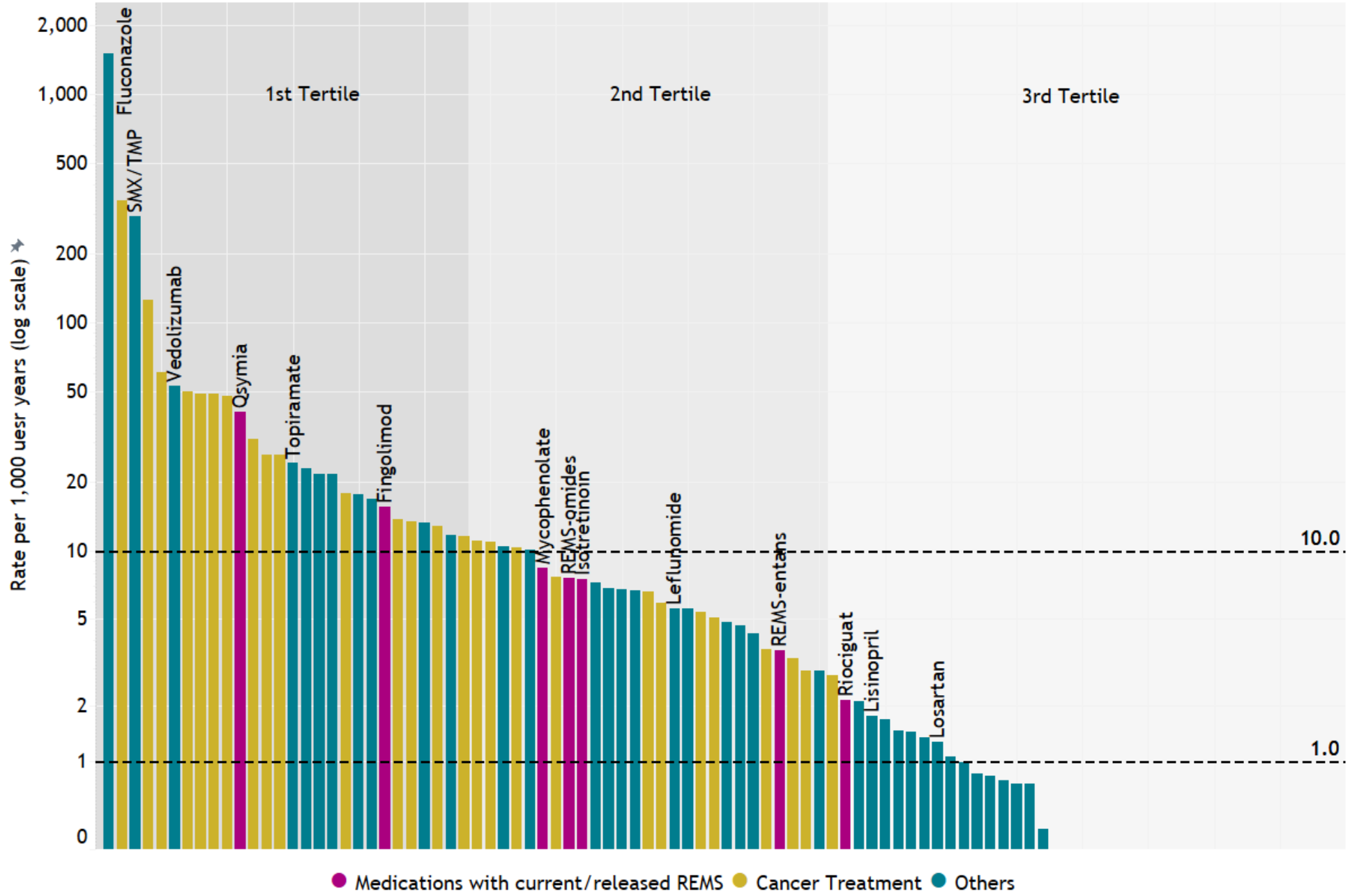
Initial metrics proposed

Criterion	Metrics
5. Level of certainty regarding teratogenicity	1. High – teratogenicity is close to certain This might be concluded based on consistent evidence from ≥ 2 high quality, controlled studies (RCT or observational including strong ecologic studies) with no major biases. 2. Moderate – teratogenicity if more likely than not This might be concluded based on a high-quality controlled study (RCT or observational) or strong evidence from case series (e.g., well described cases and rare exposure paired with rare effect) combined with high biologic plausibility (e.g., animal studies, class effects) 3. Limited – teratogenicity might exist This might be concluded based on weak or inconsistent evidence from c controlled studies with moderate-to-high risk of bias, or animal stu
6. Risk of prenatal exposure	Incidence of prenatal exposure among medication users: 1. High: ≥10 per 1000 user-years 2. Moderate: 1 to 10 per 1000 user-years 3. Low: <1 per 1000 user-years

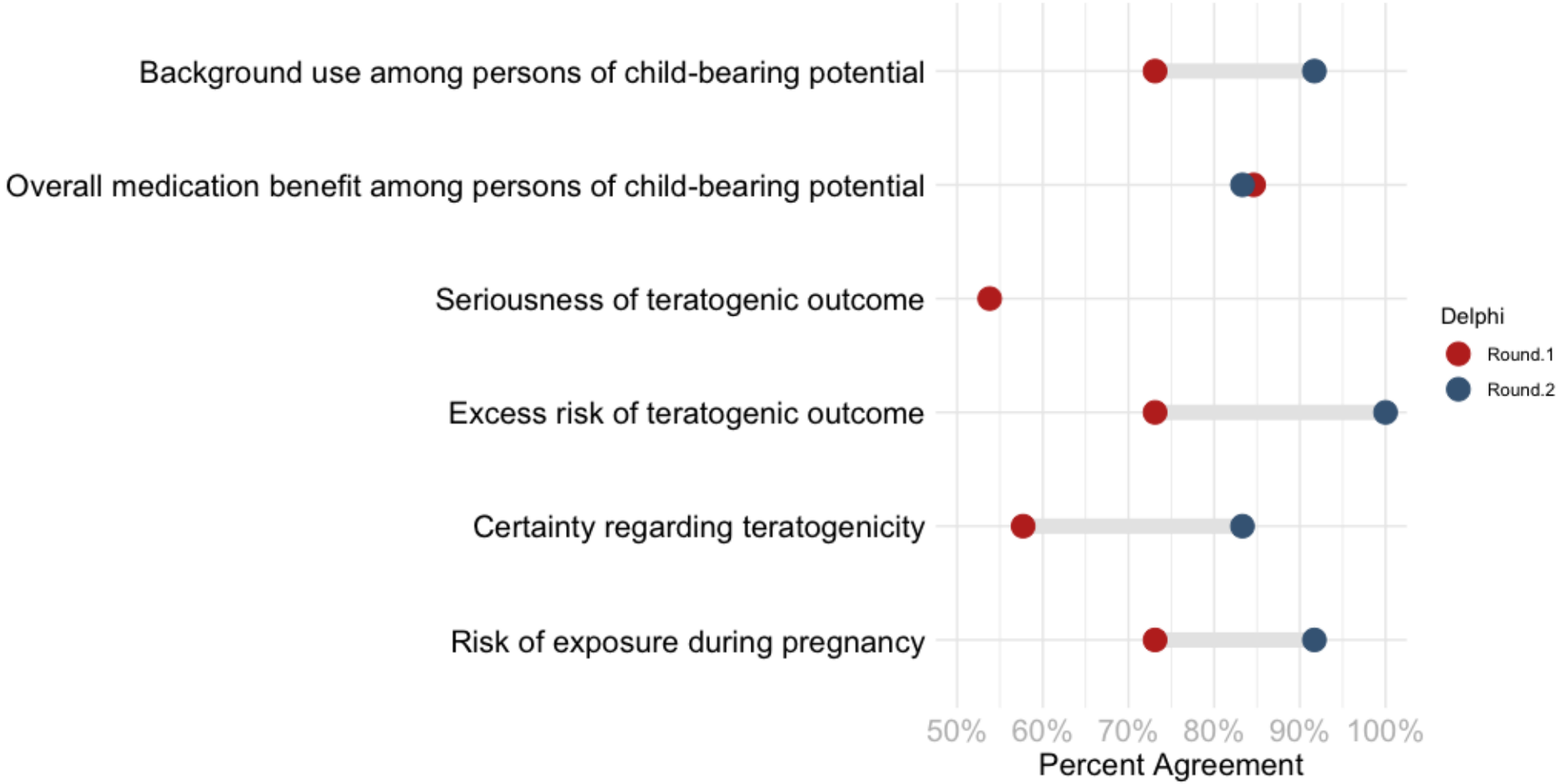
Considers study quality, consistency, and biological plausibility

Real-world data - reflects duration of use, initiation during pregnancy & conception during treatment, user population risk profile

Criterion 6 Incidence rate of prenatal exposure (averaged across Medicaid and MarketScan, 2014-2018)



Metrics development - Delphi rounds



Note: Panel members were asked to rank outcomes for criterion 3 “Seriousness of teratogenic outcome” in Delphi Round 2

Final Metrics

Criterion	Levels and definitions		
1. Background use	High	Tertiles of teratogenic medication use prevalences averaged across publicly and privately insured women of reproductive age	
	Moderate		
	Low		
2. Overall medication benefit		Type of condition treated	Availability of effective/safe alternatives
	High	Serious	No
	Moderate	Serious	Yes
		Less serious	No
	Low	Less serious	Yes
3. Seriousness of teratogenic outcome	Very serious	Stillbirth/ infant death/ serious lifelong consequences	
	Moderately serious	Miscarriage/ treatable serious outcomes	
4. Risk of teratogenic outcome	High	Risk difference > 5 per 100 pregnancies	
	Moderate	0.5 - 5 per 100 pregnancies	
	Low	< 0.5 per 100 pregnancies	
5. Certainty about teratogenicity	High	Teratogenicity is highly likely	
	Moderate	Teratogenicity is more likely than not	
	Low	Potential for teratogenicity	
6. Risk of exposure during pregnancy	High	Tertiles of prenatal exposure incidences to teratogenic medications averaged across publicly and privately insured women of reproductive age	
	Moderate		
	Low		

Development of scoring weights

- Discrete choice experiment design:
  - 36 choice sets (2 sets of 18) of hypothetical drug pairs with varying TRIM criteria levels
    - Combination of choice sets created using input from existing teratogenic medications
- Analysis and calculation
  - Weights derived via conditional logit model with robust standard errors to account for preference heterogeneity and correlation of choice tasks between raters

Scenario 1: Review the following scenario of information available for 2 hypothetical drugs

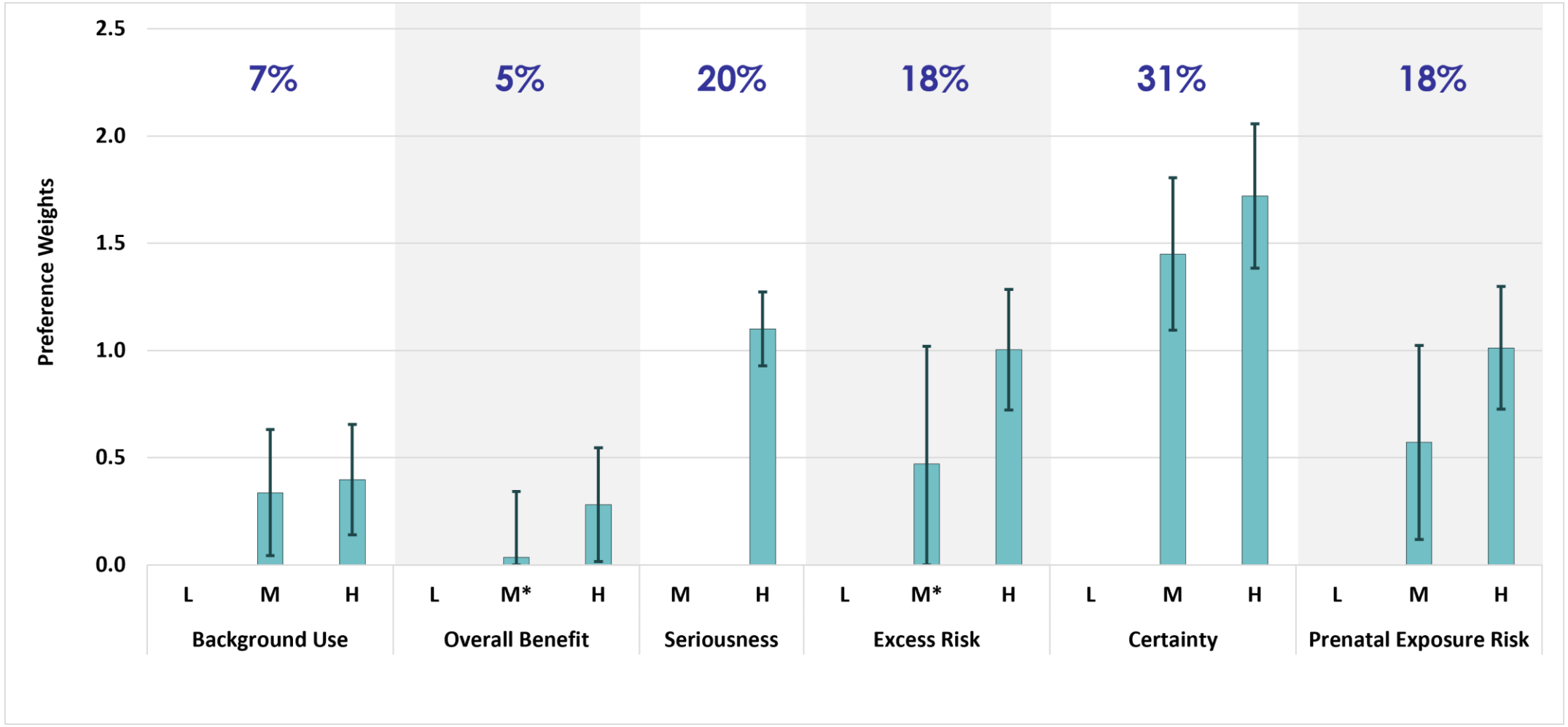
	Medication A	Medication B
Background use among persons of child-bearing potential	Low	High
Overall medication benefit among persons of child-bearing potential	High	Low
Seriousness of teratogenic outcome	Moderately Serious	Very Serious
Excess risk of teratogenic outcome	High	Low
Certainty regarding teratogenicity	Low	High
Risk of exposure during pregnancy	Moderate	High

Based on the information provided, which medication would you prioritize for consideration for a REMS?

○ Medication A

○ Medication B

TRIM scoring weights



TRIM Results

Selection of study medications

Medications with active or released REMS	Medications without REMS
1. Fingolimod	1. Topiramate
2. Isotretinoin	2. Sulfamethoxazole + Trimethoprim
3. Mycophenolate	3. Fluconazole
4. Thalidomide	4. Lisinopril
5. Pomalidomide	5. Carbamazepine
6. Lenalidomide	6. Valproate
7. Ambrisentan	7. Warfarin
8. Macitentan	8. Vedolizumab
9. Bosentan	9. Phenytoin
10. Riociguat	10. Sirolimus
11. Televancin	11. Amiodarone
12. Phentermine + Topiramate	12. Hydroxyurea
	13. Leflunomide

Input values and levels

TRIM Criterion	Approach
1. Prevalence of medication use among persons of childbearing potential	Mean of Medicaid and MarketScan prevalences assigned to tertile-based predefined bin
2. Overall medication benefit	Clinical expert panel assessment (2 physicians, 3 pharmacists) of indications and treatment options
3. Seriousness of teratogenic effect	Extracted from studies with highest certainty
4. Excess risk of teratogenic effect	Extracted from studies with highest certainty
5. Level of certainty regarding teratogenicity	Evidence synthesis & bias assessment & assessment of biological plausibility (team consensus)
6. Risk of prenatal exposure	Rates for medications with known teratogenic risk across Medicaid and MarketScan populations with ≥ 10,000 at-risk days

- Scores for each medication calculated by summing the estimated preference weights (regression coefficients) of the respective metric levels
- Calculated scores then scaled from 0 to 100 using min-max normalization, anchored by two hypothetical medications representing the lowest and highest need for risk mitigation.

Input values for non-REMS medications

	Criterion 1. Background use	Criterion 2. Overall medication benefit	Criterion 3. Seriousness of teratogenic effect	Criterion 4. Excess risk	Criterion 5. Level of certainty	Criterion 6. Prenatal exposure risk
	Prevalence per 100,000 women	Indication	Teratogenic Outcome(s)	Attributable Risk	Evidence	Incidence per 1,000 user-years
Sulfamethoxazole + Trimethoprim	5248.7	Urinary tract infection	Major malformations (e.g., neural tube defects)	1.10%	Inconsistent evidence from ≥2 high quality studies	294.7
Fluconazole	7530.4	Candidiasis	Major malformations	1.10%	Consistent evidence from ≥2 high quality studies	1511.5
Lisinopril	3406.4	Hypertension	ACE-inhibitor fetopathy	1.70%	Consistent evidence from ≥2 high quality studies	1.8
Carbamazepine	181.6	Seizures	Infant death, cognitive dysfunction	0.69%	Consistent evidence from ≥2 high quality studies	22.0
Valproate	477.7	Seizures	Neural tube defects	6.00%	Consistent evidence from ≥2 high quality studies	17.0
Warfarin	161.4	Thromboembolism	Stillbirth	2.80%	Controlled studies including ecologic studies	13.4
Vedolizumab	19.5	Inflammatory bowel disease	Spontaneous abortion	3.30%	Consistent evidence from ≥2 high quality but underpowered studies	53.1
Phenytoin	66.4	Seizures	Major malformations	1.70%	Consistent evidence from ≥2 high quality studies	17.9
Sirolimus	7.6	Post transplant rejection prophylaxis	Spontaneous abortion	4.0%	Weak/inconsistent evidence from case series	6.8
Amiodarone	17.8	Arrhythmia, heart failure	Infant death	5.14%	Weak/inconsistent evidence from case series	5.6
Hydroxyurea	22.2	Sickle cell disease	Spontaneous abortion	4.81%	Controlled studies with moderate-to-high risk of bias	31.3
Leflunomide	55.2	Rheumatoid Arthritis	Spontaneous abortion	0.31%	Consistent evidence from ≥2 high quality studies	5.6

Input values for REMS medications

	Criterion 1. Background use	Criterion 2. Overall medication benefit	Criterion 3. Seriousness of teratogenic effect	Criterion 4. Excess risk	Criterion 5. Level of certainty	Criterion 6. Prenatal exposure risk
	Prevalence per 100,000 women	Indication	Teratogenic Outcome(s)	Attributable Risk	Evidence	Incidence per 1,000 user-years
Fingolimod	19.7	Relapsing multiple sclerosis	Spontaneous abortion/miscarriage	1.40%	Controlled studies with moderate-to-high risk of bias	15.8
Isotretinoin	206.03	Severe acne	Major malformations (e.g., CNS and CV defects)	42.70%	Controlled studies including ecologic studies	7.5
Mycophenolate	104.9	Post-transplant	Cardiovascular defects	8.70%	Controlled studies including ecologic studies	8.5
Thalidomide and analogues	3.9	Multiple myeloma	Phocomelia	27.90%	Controlled studies including ecologic studies	7.6
Topiramate + Phentermine	16.9	Obesity	Major malformations	0.80%	Consistent evidence from ≥2 high quality studies	40.7
Topiramate	1751.8	Seizures	Major malformations	0.80%	Consistent evidence from ≥2 high quality studies	24.6
Bosentan/ambrisentan/ macitentan	7.5	Pulmonary hypertension	Pregnancy loss (spontaneous abortion)	10.20%	Strong evidence from case series with high biological plausibility	3.6
Riociguat	1.2	Pulmonary hypertension	Major malformations	0.90%	Animal data	2.1

Criterion levels for non- REMS medications

	1. Background use	2. Overall benefit	3. Seriousness of effect	4. Excess risk	5. Certainty	6. Prenatal exposure risk
Sulfamethoxazole + trimethoprim	High	Moderate	Very serious	Moderate	Moderate	High
Fluconazole (≥450mg during pregnancy)	High	Moderate	Very serious	Moderate	High	High
Lisinopril	High	Moderate	Very serious	Moderate	High	Moderate
Carbamazepine	High	Moderate	Very serious	Moderate	High	High
Valproate	High	Moderate	Very serious	High	High	High
Warfarin	High	Moderate	Very serious	Moderate	High	High
Vedolizumab	High	Moderate	Moderately serious	Moderate	Moderate	High
Phenytoin	High	Moderate	Very serious	Moderate	High	High
Sirolimus	Moderate	Moderate	Moderately serious	Moderate	Low	Moderate
Amiodarone	High	Moderate	Very serious	High	Low	Moderate
Hydroxyurea	High	High	Moderately serious	Moderate	Low	High
Leflunomide	High	Moderate	Moderately serious	Low	High	Moderate

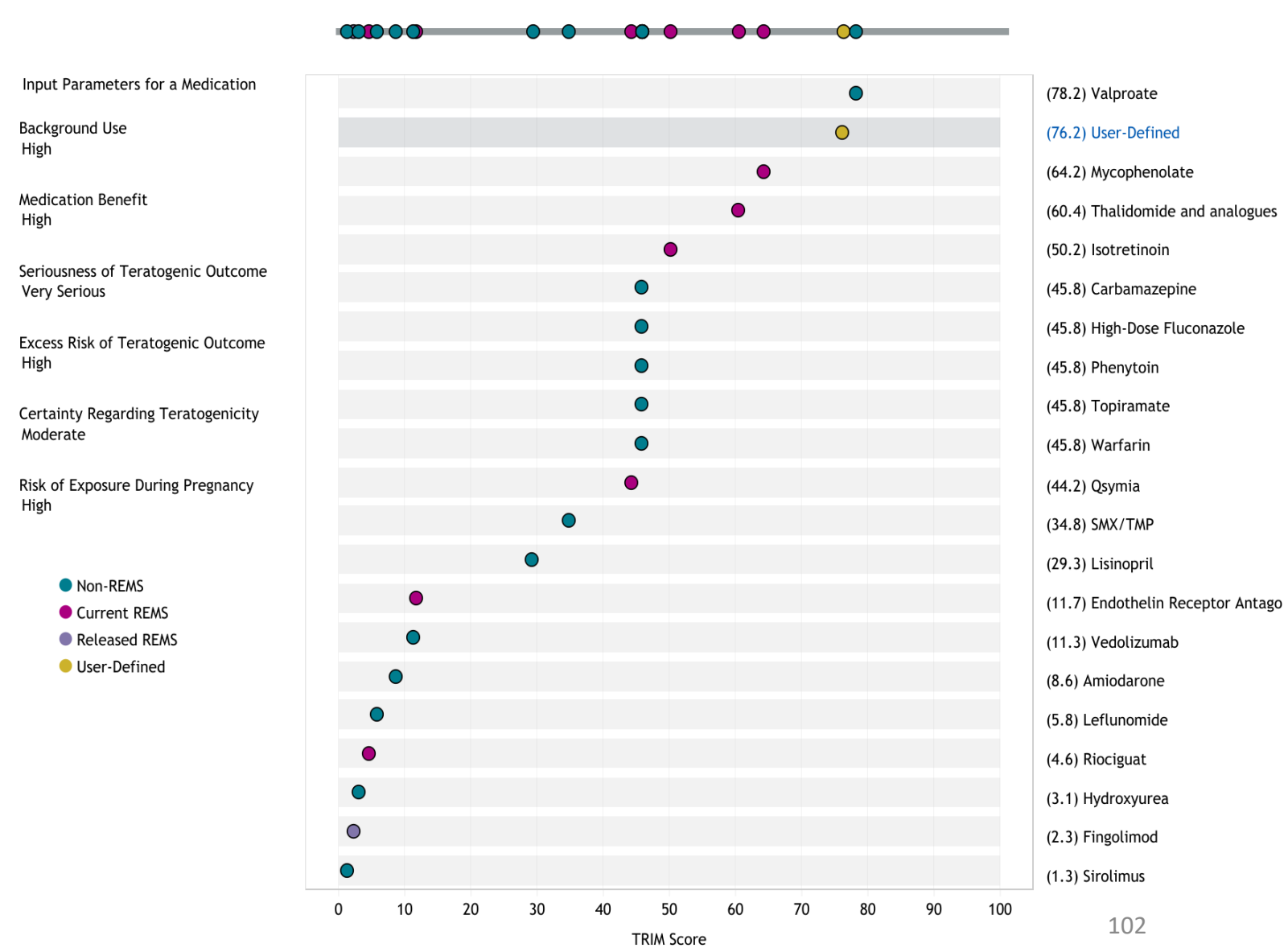
Criterion levels for REMS medications

	1. Background use	2. Overall benefit	3. Seriousness of effect	4. Excess risk	5. Certainty	6. Prenatal exposure risk
Fingolimod	High	Moderate	Moderately serious	Moderate	Low	High
Isotretinoin	High	Moderate	Very serious	High	High	Moderate
Mycophenolate	High	High	Very serious	High	High	Moderate
Thalidomide and analogues	Moderate	High	Very serious	High	High	Moderate
Topiramate	High	Moderate	Very serious	Moderate	High	High
Qsymia	High	Low	Very serious	Moderate	High	High
Bosentan/ambrisentan/macitentan	Moderate	Moderate	Moderately serious	High	Moderate	Moderate
Riociguat	Moderate	Moderate	Very serious	Moderate	Low	Moderate

Aim 3 Final TRIM Scores

https://tabsoft.co/3PIlLnL

Medication	Score
High	100.0
Valproate	78.2
Mycophenolate	64.2
Thalidomide and analogues	60.4
Isotretinoin	50.2
Warfarin	45.8
Carbamazepine	45.8
Fluconazole	45.8
Phenytoin	45.8
Topiramate	45.8
Qsymia	44.2
Sulfamethoxazole/ Trimethoprim	34.8
Lisinopril	29.3
Endothelin Receptor Antagonists	11.7
Vedolizumab	11.3
Amiodarone	8.6
Leflunomide	5.8
Riociguat	4.6
Hydroxyurea	3.1
Fingolimod	2.3
Sirolimus	1.3
Low	0.0



Key take aways

- Created a tool that can prioritize medications for risk mitigation
  - Comprehensive set of criteria with weights
  - Does purposely NOT include burden, because burden is REMS specific while the need for risk mitigation is not
  - Flags medications where “something” more than standard needs to be done
- Created metrics that are transparent and reproducible and were able to generate input values for all study drugs
  - Allows flexibility when different indications or outcome are considered
  - Interactive tool also allows “sensitivity analysis” to evaluate impact of varying input levels
- Results provides benchmarks for new drugs or re-evaluation of other drugs (with or without REMS) as evidence evolves
  - TRIM scores position several non-REMS drugs at similar priority as current REMS drugs
- Example of evidence-based regulatory decision-making illustrating an advancement in regulatory science and innovation; hoping for future use in enhancing Safe Use of Medications.

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Thank you!

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