

# Innovative Data Analytics To Inform Pharmacokinetics and Dosing in Pregnancy

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# Medication use in Pregnancy – Current Status

## Increasing medication use

- In the US, **9 out of 10** women take **medication** during **pregnancy**
- **80% of pregnant women** take **≥ 1** medication during first trimester

## Off-label use

- **90% of medications** approved do not have labeling for pregnant women
- After **PLLR implementation in 2015**, only **10%** have data for **pregnancy** from **human studies**

## Lack of pregnancy drug trials (PDT)

- Only **0.32%** of the active registered trials are PDT, in a 2014 global survey
- Among active PDTs, **only 4.4%** had **pharmacokinetic** evaluations
- Only **7%** of the active PDTs were funded by **pharmaceutical industry**

## PLLR: Pregnancy & Lactation Labeling Rule

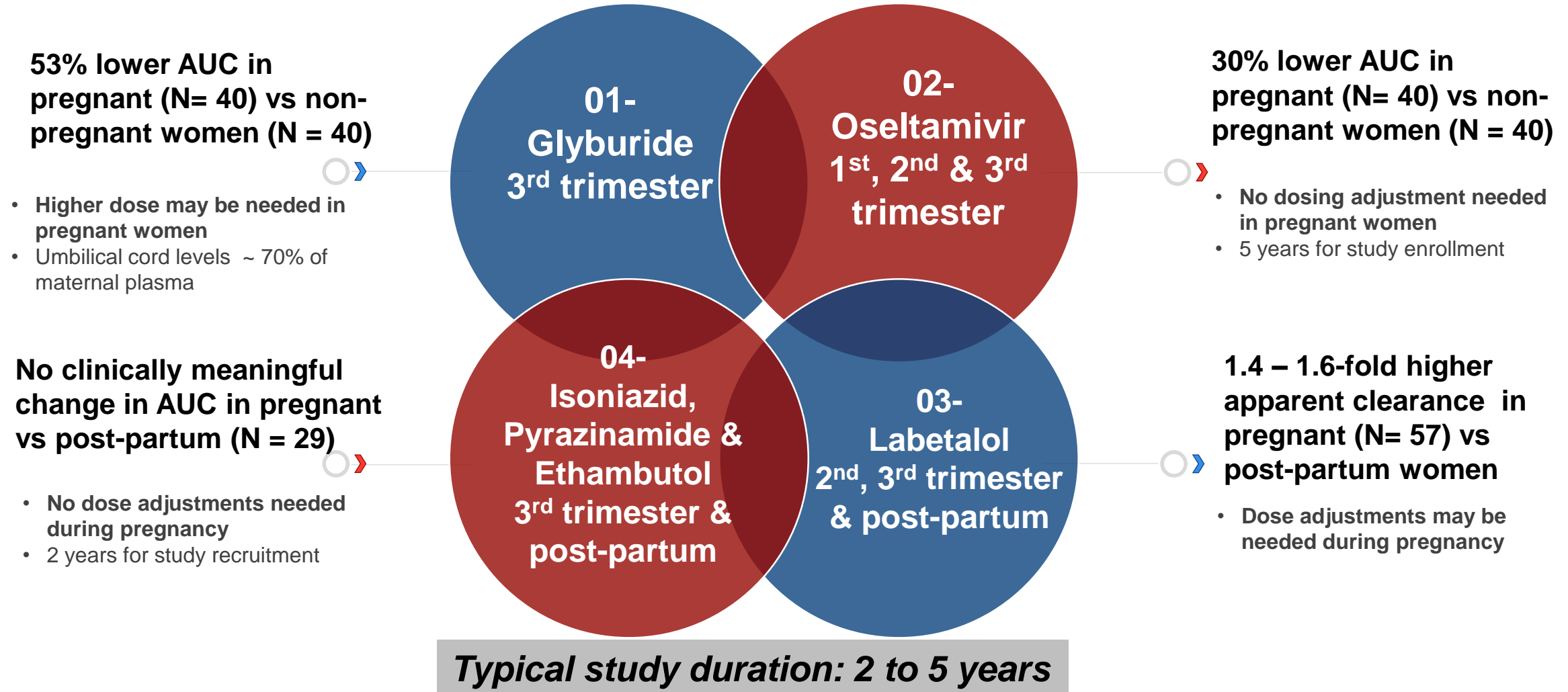
<https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html>

Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, van den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals.

*American Journal of Obstetrics and Gynecology*. 2014;211(6):690.e1-690.e11.;Scaffidi J, Mol B, Keelan J. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2017;124(1):132-140.;Byrne JJ, Saucedo AM, Spong CY. Evaluation of Drug Labels Following the 2015 Pregnancy and Lactation Labeling Rule. *JAMA Network Open*. 2020;3(8):e2015094.

Ren Z, Bremer AA, Pawlyk AC. Drug development research in pregnant and lactating women. *American Journal of Obstetrics and Gynecology*. 2021;225(1):33-42. doi:[10.1016/j.ajog.2021.04.227](https://doi.org/10.1016/j.ajog.2021.04.227)

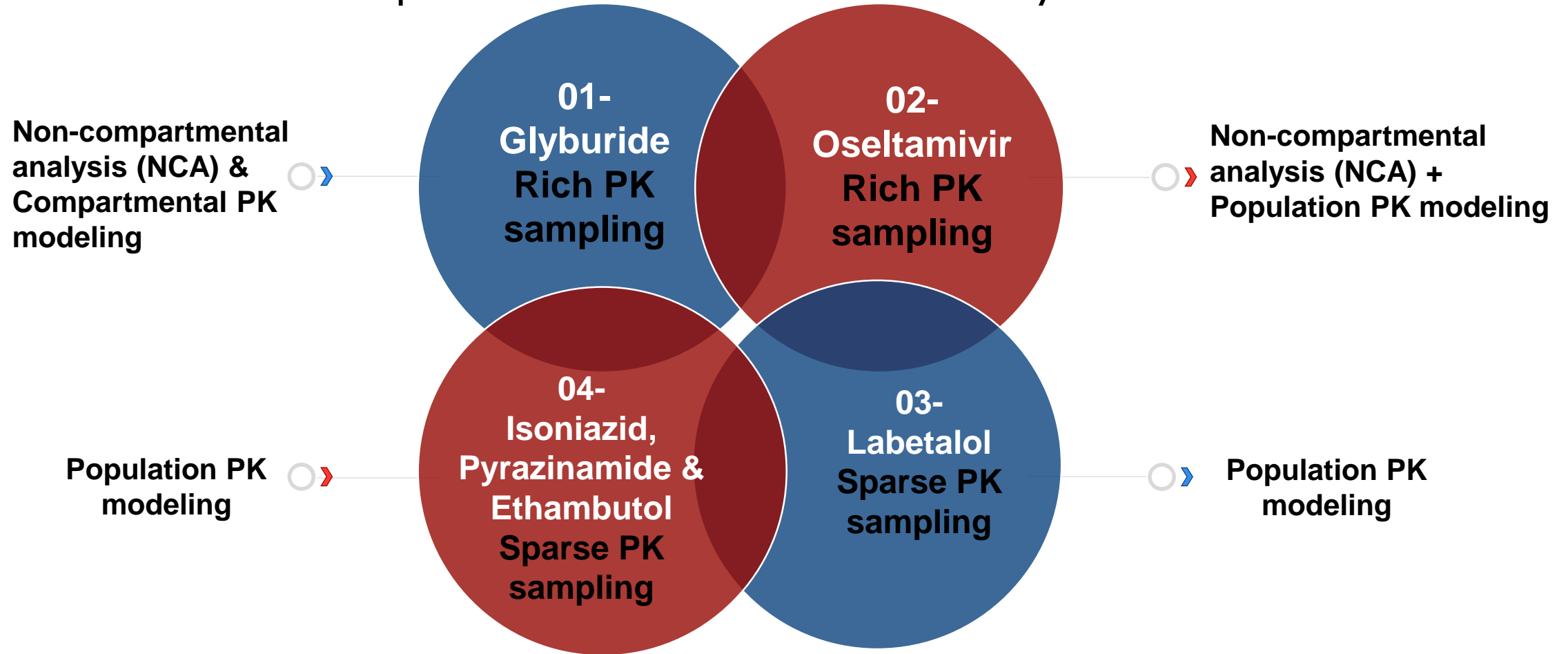
# Dedicated PK trials in pregnant women by NICHD – OPRCs and academic researchers has informed clinical practice



## OPRC – Obstetric-Fetal Pharmacology Research Center

Pillai VC, Han K, Beigi RH, et al. Population pharmacokinetics of oseltamivir in non-pregnant and pregnant women. *British Journal of Clinical Pharmacology*. 2015;80(5):1042-1050; Hebert MF, Ma X, Naraharisetti SB, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther*. 2009;85(6):607-614; Abdelwahab MT, Leisegang R, Dooley KE, et al. Population Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Pregnant South African Women with Tuberculosis and HIV. *Antimicrob Agents Chemother*. 2020;64(3):e01978-19; Fischer JH, Sarto GE, Hardman J, et al. Influence of Gestational Age and Body Weight on the Pharmacokinetics of Labetalol in Pregnancy. *Clin Pharmacokinet*. 2014;53(4):373-383.

# Type of study design dictates the type of pharmacokinetic analysis



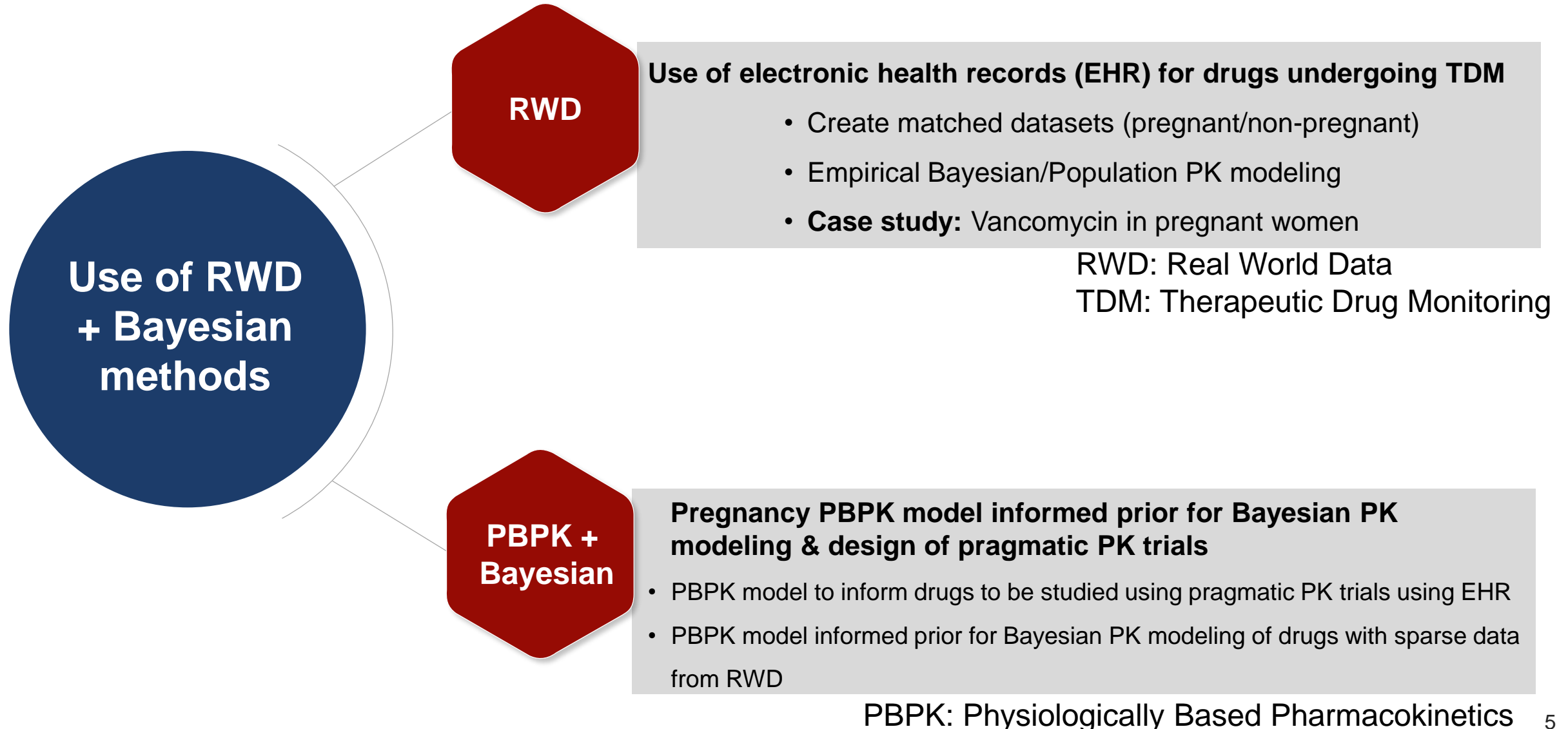
**Recommendations on dosing adjustments may be needed**

Fold change:  $\frac{AUC_{\text{pregnant}}}{AUC_{\text{nonpregnant}}} \geq 2$  times lower

**Recommendations on no dosing adjustments needed**

Fold change:  $\frac{AUC_{\text{pregnant}}}{AUC_{\text{nonpregnant}}} < 2$  times lower

# Alternate strategies to inform PK & dosing in pregnancy with potential to move from “Off-patent to Approval”



# Use of electronic medical records for drugs undergoing TDM – Vancomycin case study

## Decision

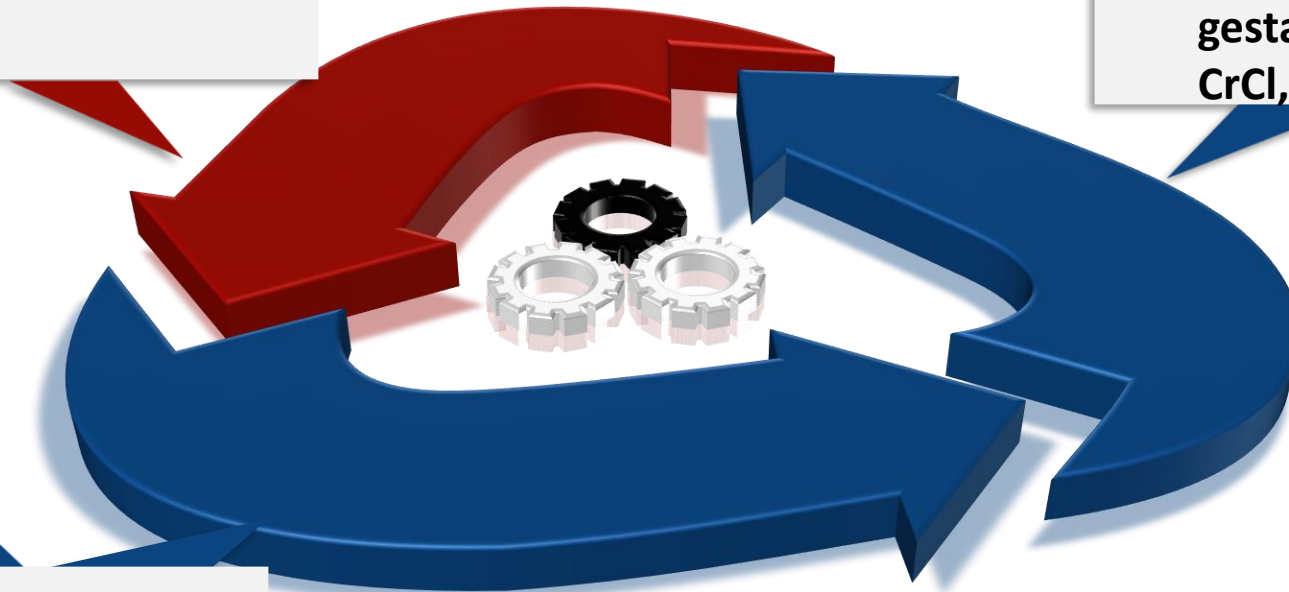
- Is there a need to adjust vancomycin dosing in pregnant women?

## Information

- Retrospective electronic medical records of pregnant women
- At least 2 concentrations, dose, gestational age, bodyweight, CrCl, fat free mass

## Analysis

- Population PK model modeling – prior vancomycin models used as a starting point



*Rahul Goyal, Brady Moffett, Joga Gobburu et al, 2022 – Under consideration for publication: Population Pharmacokinetics of Vancomycin in Pregnant Women*

# Vancomycin case study

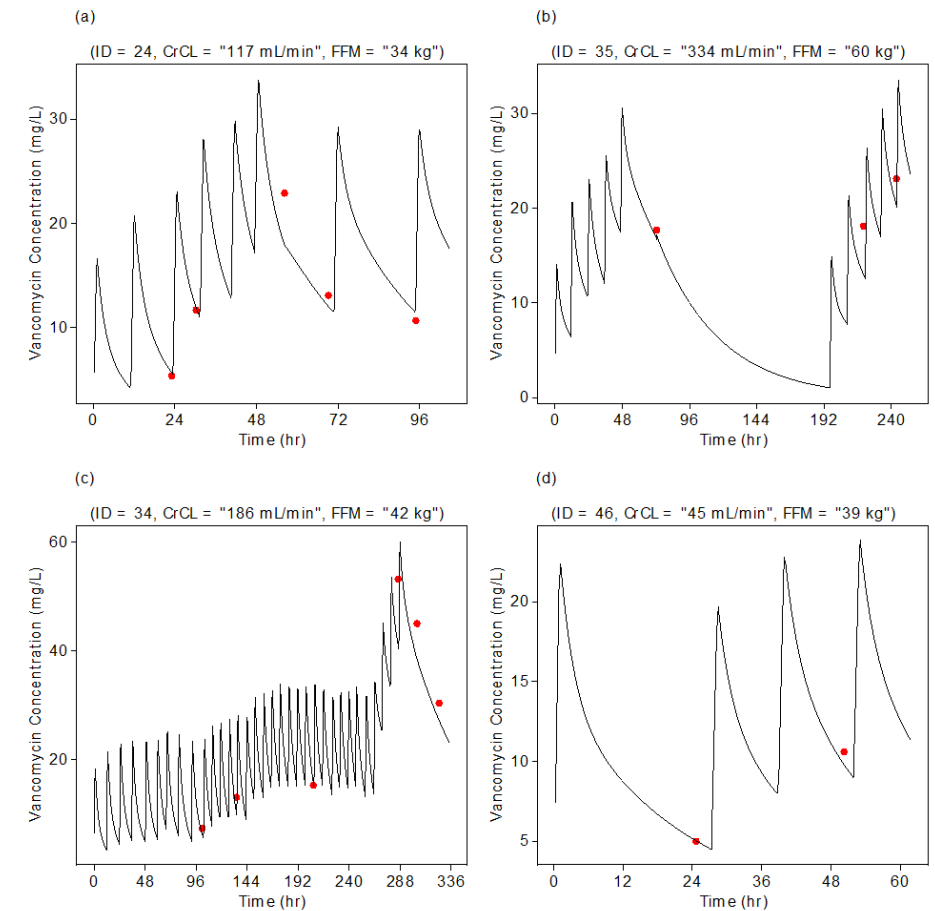
Variable	Value
Number of patients	34
Age (years)	28 (17-38)
Height (cm)	163 (147-173)
Total body weight (kg)	74 (43-157)
Gestational age (weeks)	27 (7-40)
Serum creatinine (mg/dl)	0.56 (0.27-1.97)
Creatinine clearance <sup>2</sup> (ml/min)	176 (43-389)
Fat-free mass <sup>3</sup> (kg)	45 (30-60)
Body mass index (kg/m <sup>2</sup> )	28 (19-70)

## Population PK model

- Two Compartmental PK model
- Peripheral volume and inter-compartmental clearance fixed based on prior literature

## Covariate model

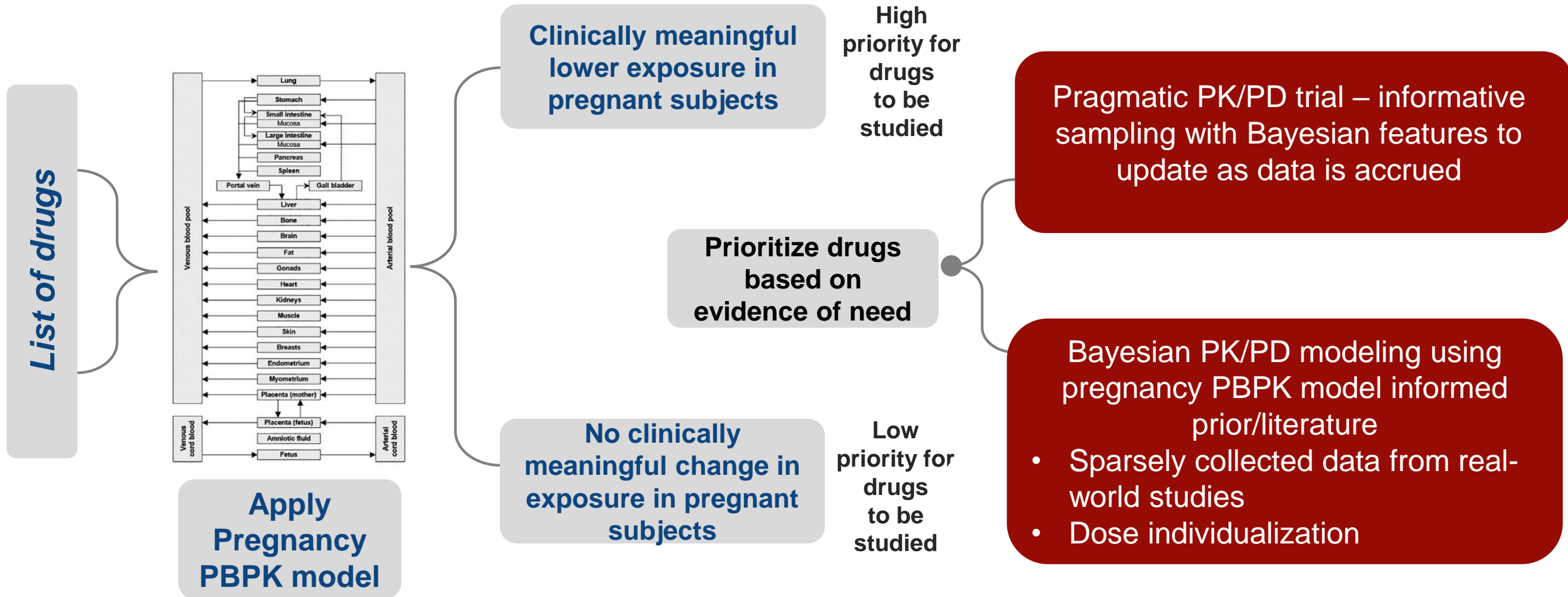
- Creatinine clearance and fat-free mass on clearance
- Fat-free mass on volume



## Decision

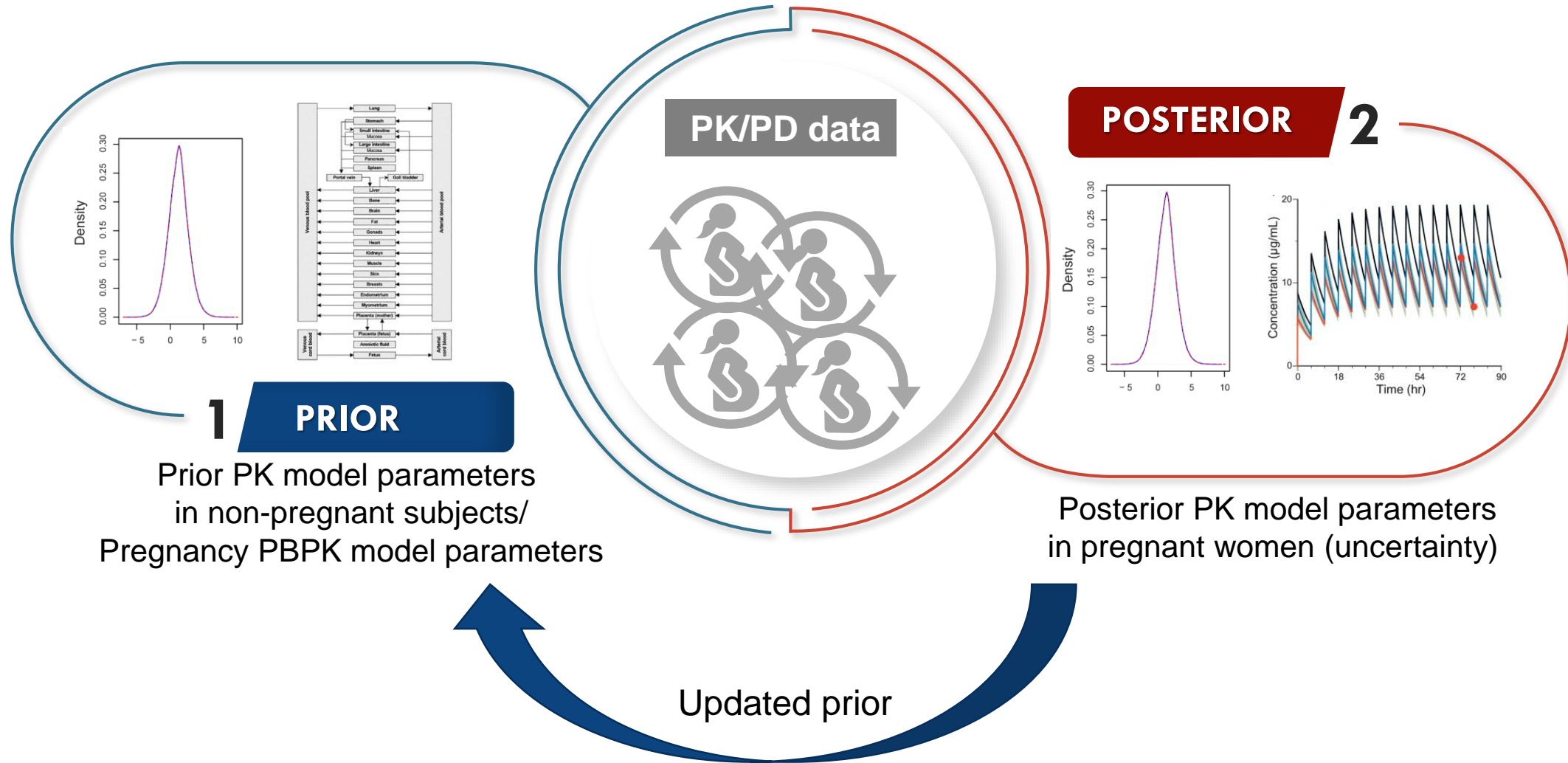
- Is there a need to adjust vancomycin dosing in pregnant women?
  - No dosing adjustments needed. AUC was similar between pregnant and non-pregnant subjects

# Pregnancy PBPK model informed Bayesian framework to prioritize study of drugs, design and analysis

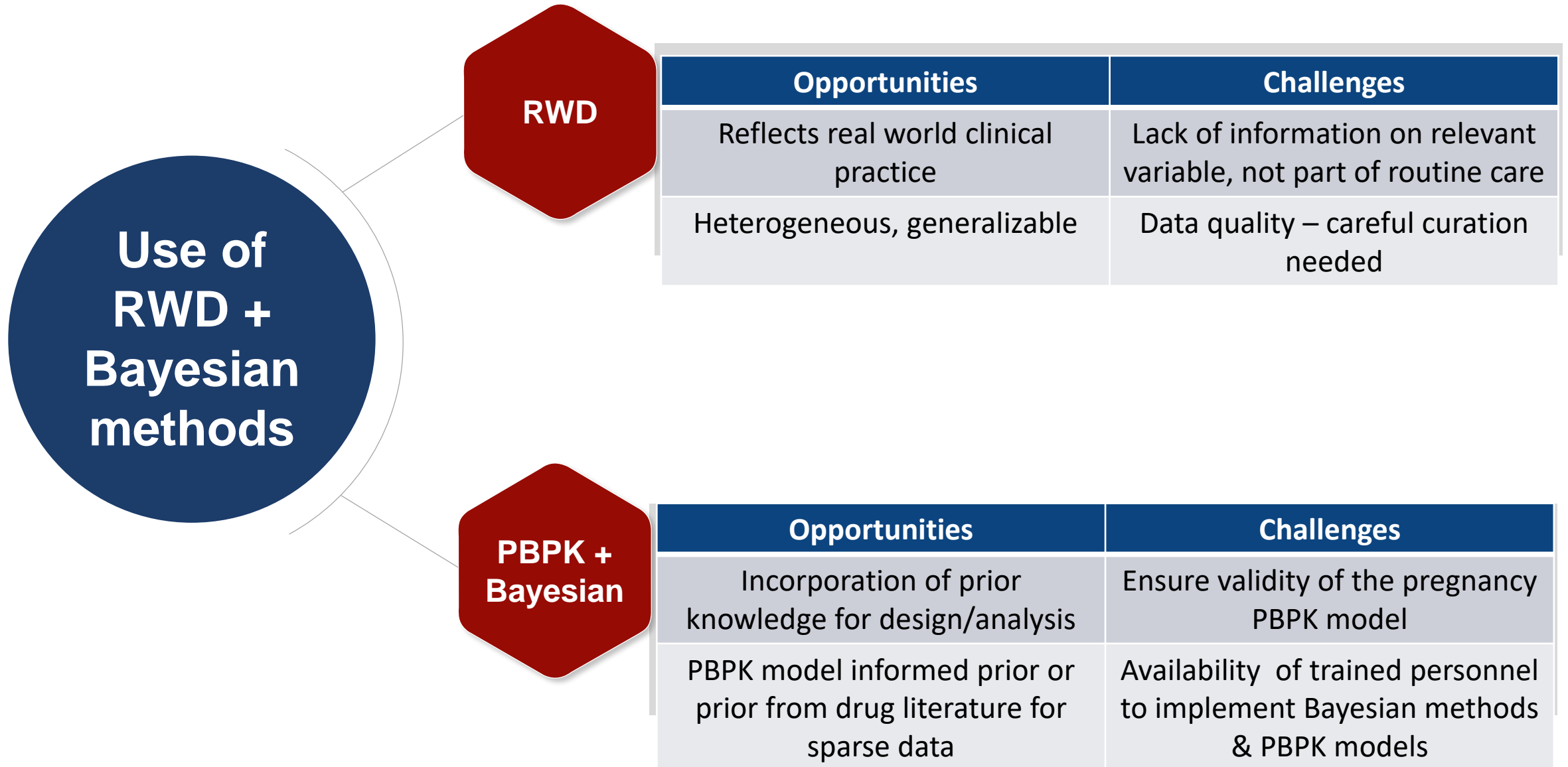




# Bayesian PK/PD modeling framework



# Opportunities & Challenges





# Consortium of multiple stake holders (academia, OPRCs, FDA, pregnancy community) needed to promote “Off-label to approval” pipeline



## Goal

By 2030, aspire to renew labeling information of 10 priority off-patent medications used in pregnancy



1

### CALL TO ACTION

Establish the collaboration between stakeholders & pregnancy community

2

### PILOT PROJECT

Demonstrate the process from inception to approval for 2 drug products

3

### REVIEW

Evaluate results of pilot product to ensure that a repeatable process is feasible

4

### FACILITATE SCALE UP

Finalize the systematic, reproducible process to achieve pregnancy labeling

5

### PROMOTE

Offer training to encourage other clinical pharmacology fellows to undertake such projects