

# Framing the Research Question

The 2026 APAC-VALUE Study Design

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# Speaker Profile

A Digital Health Expert Bridging Medicine, Management, and Data Science

## Jason C. Hsu, PhD



### Current Positions

- President, OHDSI Taiwan Society
- Professor, International PhD Program in Biotech and Healthcare Management, College of Management, TMU
- Director, Clinical Data Center, TMU
- Director, Research Center of Data Science on Healthcare Industry, College of Management, TMU



### Education

- Postdoctoral Fellow, Department of Population Medicine, Harvard Medical School, Harvard University, Boston, USA
- PhD, International Business, National Taiwan University
- M.S., Institute of Technology Management, National Tsing Hua University
- B.S., School of Pharmacy, Taipei Medical University



### Areas of Expertise

- Health Data Science
- Clinical Data Analysis
- Precision Pharmacotherapy
- Biotech and Healthcare Management



## The APAC-VALUE study: A global characterisation study of VALproate Utilisation and Exposure among men and women of childbearing age

- Valproate has long been an effective therapy for epilepsy, but growing global regulatory attention has highlighted the potential risks of neurodevelopmental disorders in children exposed *in utero*. While much of the focus has been on use in pregnancy, more **recently several, but not all**, regulatory agencies have issued safety warnings on the use of valproate in men prior to conception and **neurodevelopmental risk** (and other risks?) in offspring.
- **Aim:** to describe utilisation patterns, trends, and population characteristics to understand how safety warnings translate into real-world practice across different regulatory jurisdictions.

# The Double-Edged Sword: Sodium Valproate



**First-line for  
Generalized  
Epilepsy**

Unmatched efficacy



**Up to 10%  
Major Congenital  
Malformations**

Severe teratogenicity risk



A critical clinical dilemma: maternal seizure control vs. the long-term health of the next generation.

# Beyond Pregnancy: The Emerging Paternal Risk

KNOWN RISK:  
MATERNAL EXPOSURE  
DURING PREGNANCY



EMERGING RISK:  
PATERNAL EXPOSURE  
PRIOR TO CONCEPTION



JAMA  
Network | **Open**



Original Investigation | Neurology

## Paternal Valproate Use and Neurodevelopmental Disorder and Congenital Malformation Risk in Offspring

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### Abstract

**IMPORTANCE** Limited clinical evidence is available about the risk of neurodevelopmental disorders (NDD), including autism spectrum disorders and congenital malformations (CM), in offspring following paternal exposure to antiepileptic medications.

**OBJECTIVE** To investigate the risk of NDD (any subtype) and CM (major and/or minor) in offspring paternally exposed to valproate vs lamotrigine or levetiracetam monotherapy within 3 months prior to conception.

**DESIGN, SETTING, AND PARTICIPANTS** This observational, population-based, nationwide cohort study used Nordic registries data with family linkage (offspring born between 1997-2018 [Denmark], 2010-2019 [Norway], and 2007-2019 [Sweden]). Offspring born within the study period and paternally exposed to either (1) valproate or (2) lamotrigine or levetiracetam were identified and followed-up until 12 years or the end of the study period, whichever came first. Data were obtained from October 2020 (Denmark), June 2021 (Norway), and March 2021 in Sweden) and analyzed from October 2020 to July 2023.

**EXPOSURES** Paternal exposure to (1) valproate or (2) lamotrigine or levetiracetam during the spermatogenic risk window (derived from each National Prescription Registry).

### Key Points

**Question** Is paternal valproate vs lamotrigine or levetiracetam exposure associated with neurodevelopmental disorder or congenital malformation risk in children?

**Findings** In this cohort study of 5721 offspring in Denmark, Norway, and Sweden whose fathers were exposed to either (1) valproate or (2) lamotrigine or levetiracetam, paternal exposure to valproate within 3 months prior to conception was associated with significantly increased risk of neurodevelopmental disorders vs lamotrigine or levetiracetam. Risk of congenital malformations was not different between exposure groups, although estimates were heterogeneous.

# Bridging Science and Public Health Policy



**Scientific Evidence → Public Health Action**

# Deconstructing the Regulatory Response: 5W1H

An Overview of the Global Regulatory Facts.



# Why: The Driven Force Behind Guideline Shifts



Maternal Utero Exposure



Paternal Pre-conception Risk



Signal expansion from maternal utero exposure to paternal pre-conception risk.

# Who: Expanding the Regulatory Shield

<b>Why</b> 	<b>Who</b> 	<b>What</b> 
<b>Where</b> 	<b>When</b> 	<b>How</b> 



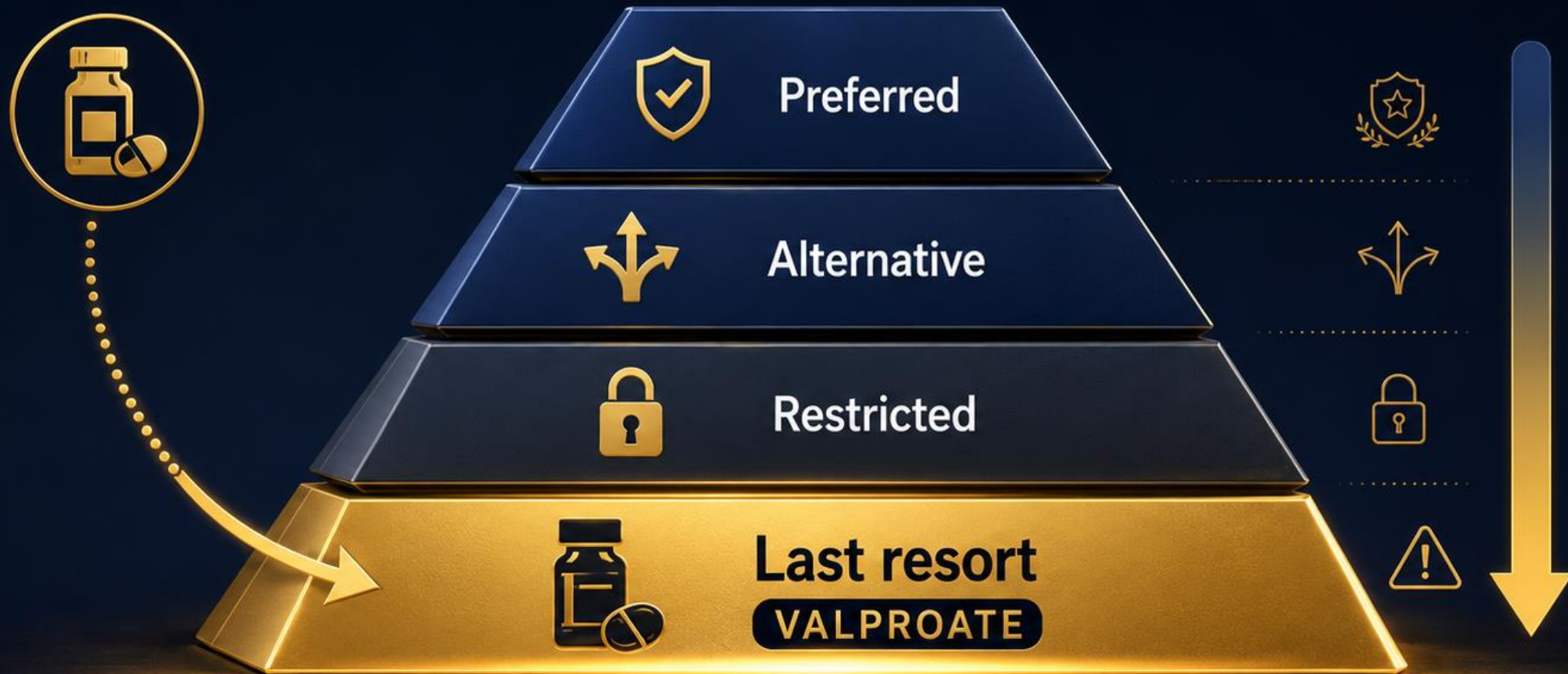
Maternal Protection



Paternal Risk Exposure

 Transition from Maternal Protection to Paternal Risk Exposure.

# What: The Restriction of Valproate



Reclassified from a first-line anchor to a last-resort alternative.

# Where: High Policy Heterogeneity across APAC



Mandatory pregnancy prevention programs vs. passive label modifications.

# When: The Staggered Chronological Timeline

Why Who What Where **When** How

## Wave 1

Maternal Exposure  
Old Warnings



## Wave 2

Paternal Pre-conception Risk  
New Policies



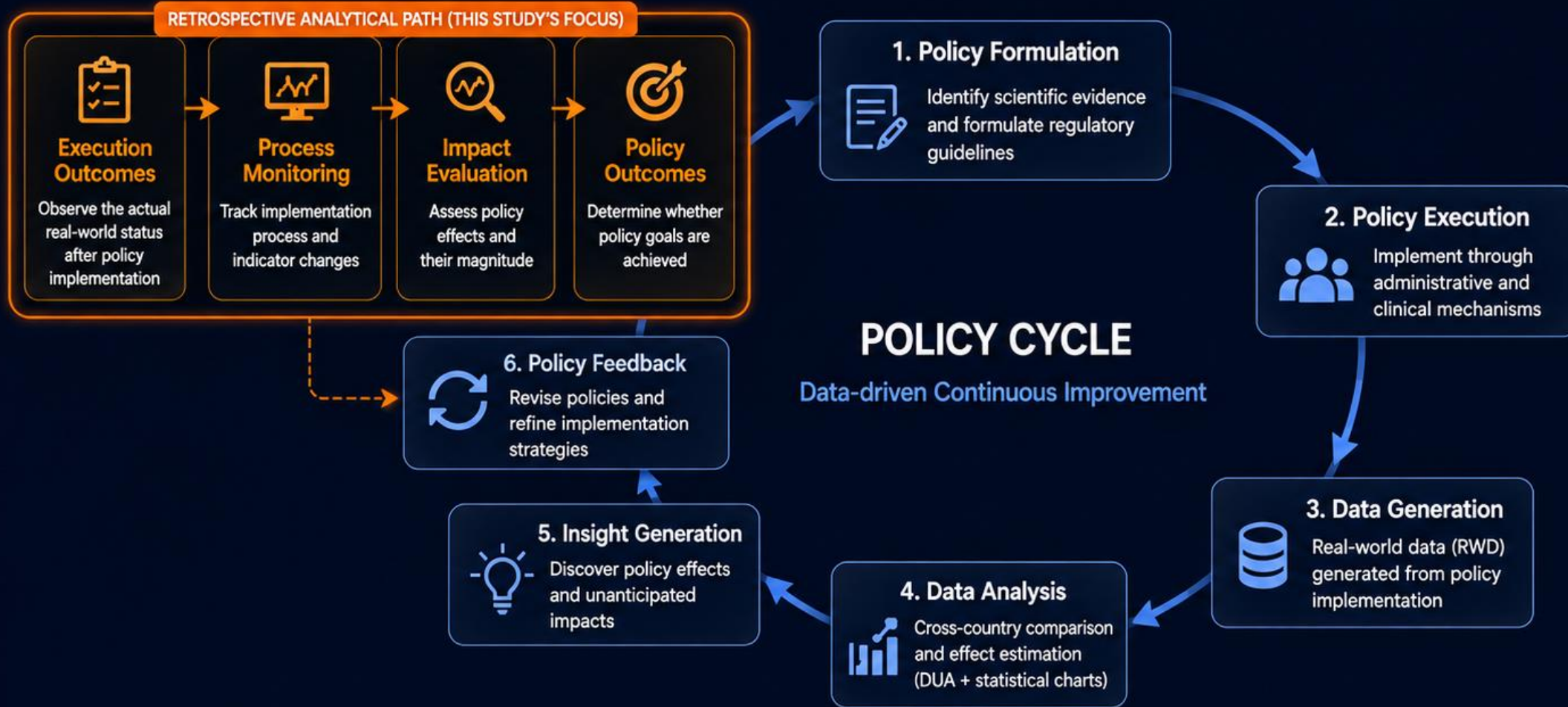
 Staggered chronological shocks make fixed calendar indices impossible.

# How: Administrative Enforcement Mechanisms



• Active digital restrictions vs. passive risk communication. •

# Policy Cycle: Moving from Execution to Evaluation



**DUA and charts are Just expression tools.  
Answering the “So What?” is the goal.**



# Research Question 1: Did the policy effectively deter utilization?



## Did the policy effectively deter utilization?

*Population-level overall effect*



Measuring the Macro Population Shift

Tool: Longitudinal Trends (by Sex)



# RQ1 Policy Implications: Deterrence & Spillover Effects



**Policy Makers  
(Policy Penetration)**



**Does passive  
communication  
work?**

Assess whether early warnings and public messages effectively deter utilization at the population level.



**Epidemiologists  
(International Spillover)**



**Does male  
prescription drop  
before local  
mandates?**

Detect temporal lead (or lag) across countries to evaluate international spillover and cross-border influence.



Answering RQ1 reveals whether the policy **truly deterred utilization** and whether its effects extend beyond borders.



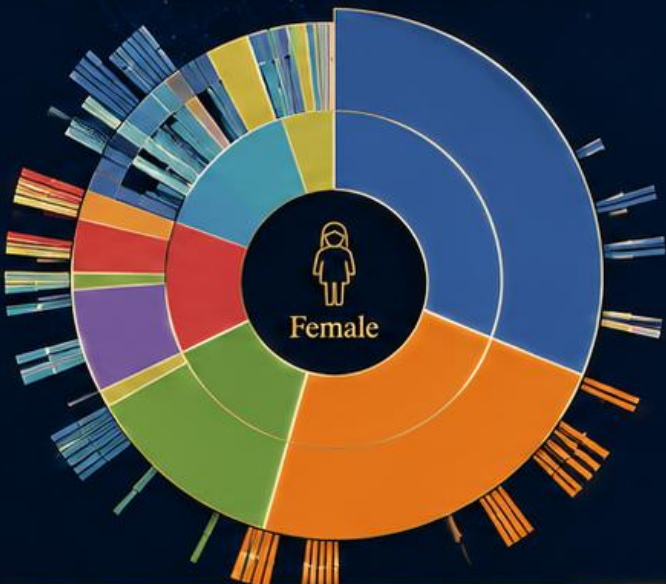
# Research Question 2: Where did clinicians and patients switch to?

## Where did clinicians and patients switch to?

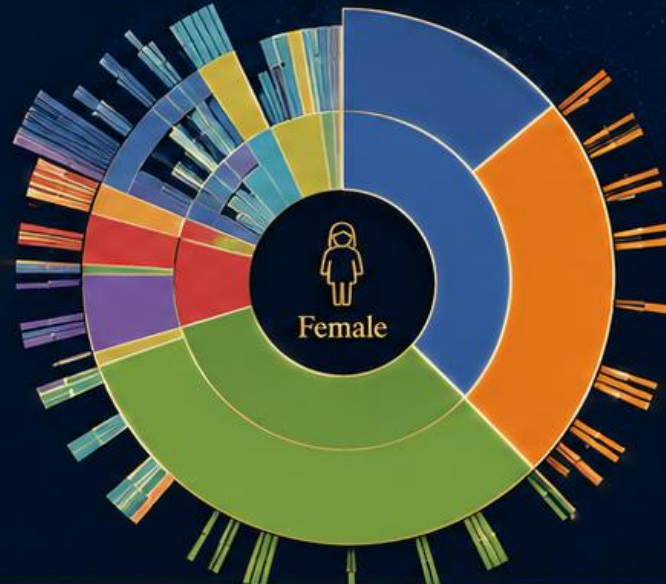
*Individual-level switching behavior*



Pre-Policy (Before Decline)



Post-Policy (After Decline)



**Treatment Pathways (Examples)**

- Carbamazepine
- Lamotrigine
- Levetirecetam
- Topiramate
- Other Anti-seizure Medications
- Benzodiazepines
- Polytherapy Combinations
- Non-Pharmacologic / Other
- Other Pathways

Inner Ring: Broad Class  
Outer Ring: Specific Pathways

# RQ2 Clinical Implications: Substitution Safety

Answering RQ2: **Where did clinicians and patients switch to?**



## Safe, Gradual Switching (Cross-tapering)

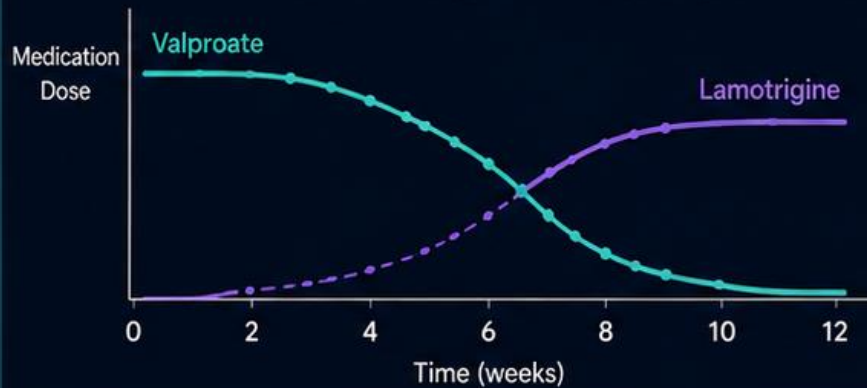


### Are alternatives safer?

Does a gradual switch reduce relapse risk?

### Example: Cross-tapering Pathway

Valproate → Lamotrigine (Cross-tapering over weeks)



**Clinical Benefit**  
Maintains seizure control while transitioning to a safer alternative.



Lower risk of seizure relapse and adverse events.

VS.



## Dangerous, Abrupt Cessation

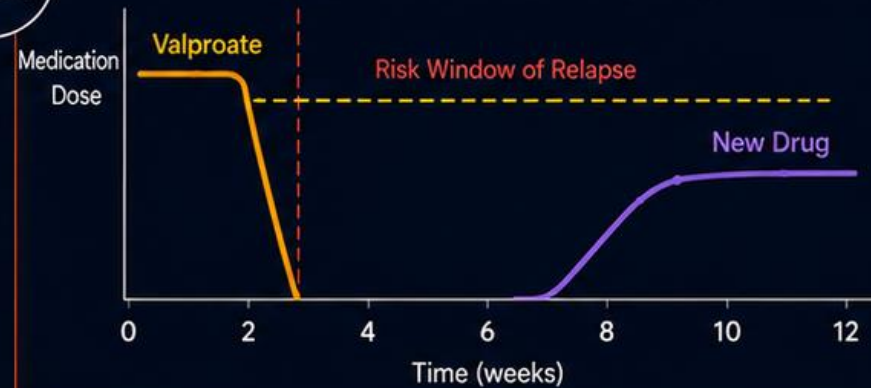


### Does rapid switching trigger seizure relapse?

Is abrupt discontinuation associated with harm?

### Example: Abrupt Discontinuation Pathway

Valproate → No Overlap (Abrupt Stop) → New Drug



**Clinical Risk**  
Gap in therapy increases risk of seizure relapse and emergencies.



Higher risk of seizure relapse, ED visits, and hospitalizations.

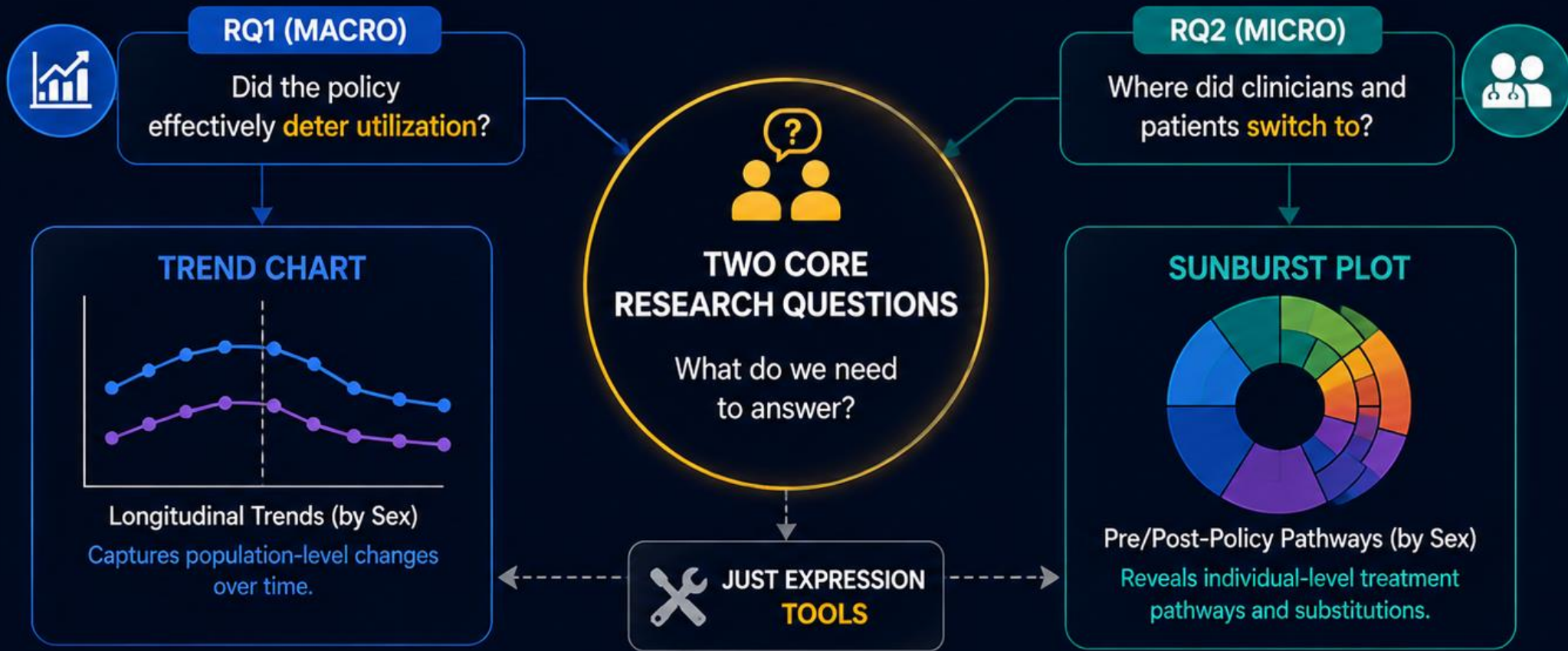


## So What?

Understanding substitution patterns helps ensure **safer transitions**, **avoid harmful disruptions**, and **protect against seizure relapse**.



# Aligning the Analytical Soul before Coding



**DUA**  
is the method.



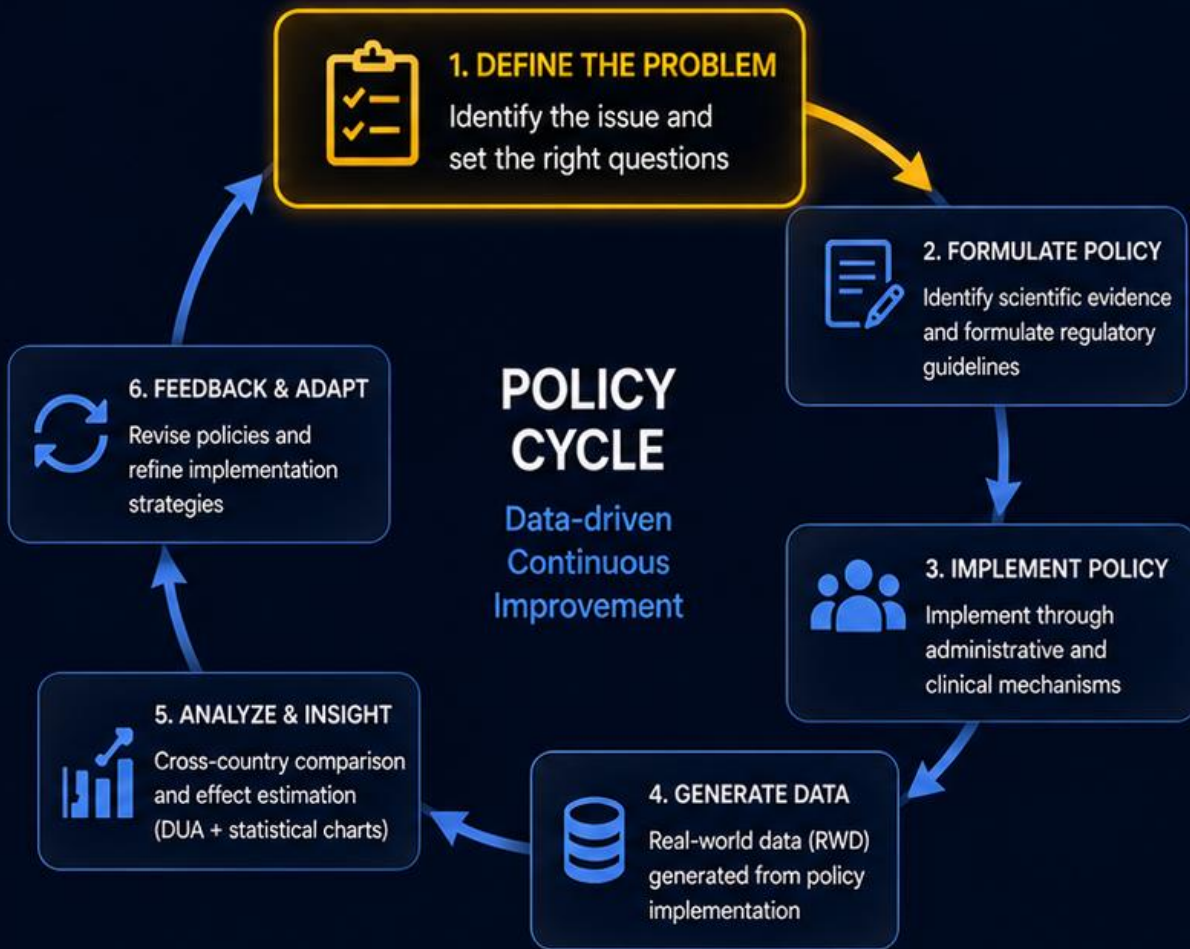
**Charts**  
are the expression.



**Answering the questions**  
is the **soul**.

*Clarity in the question. Rigor in the method. Impact in the answer.*

# Framing the Core Gap: From 5W1H to Data Logic



## THE GAP WE MUST BRIDGE



PAPER-BASED  
NOTICES ISSUED

VS.



UNCERTAIN  
COMPLIANCE &  
CLINICAL ANXIETY  
IN CLINICS

## ANALYTICAL THREE ARROWS



**1. REALLY?**  
Is the policy effective?  
(Evidence)



**2. ROOT CAUSE?**  
Why does it happen?  
Where does the problem lie?  
(Mechanism)



**3. SO WHAT?**  
What are the real-world implications? How should we respond?  
(Impact)



Every parameter we set in the data is to **cross this blind spot.**



Clear the question. Define the logic. Then the data will lead us to **the truth.**

# The Path: Parameter Consensus for Characterization Study



## Our Goal

Build a clean, comparable, and clinically meaningful cohort to characterize Valproate substitution pathways.



## 3 CORE ACTIONS

Define the study design in three key dimensions



## Why These Actions Matter

- ✓ Ensure cohort purity and analytic validity
- ✓ Capture meaningful population at risk
- ✓ Accurately observe substitution behavior



### Action 1 Clean Target (Exclude Bipolar/Migraine)

Maintain Table 1 purity by excluding psychiatric and headache indications that confound epilepsy treatment.



### Action 2 Demographics (< 55 Years?)

Consider relaxing the age cap to capture male patients at risk while balancing validity and feasibility.



### Action 3 Overlap Window

Define the pre/post observation window to identify true substitution events and ensure temporal clarity.

## KEY PARAMETER OPTIONS

### 1. Indication Filter

Exclude:

- Bipolar disorder
- Migraine / Headache
- Other non-epilepsy uses



Keep Table 1  
Epilepsy-pure

### 2. Age Range

Option A: 0 – 54 years  
(Conservative)  
Option B: 0 – 64 years  
(Expanded for male risk)



Balance validity  
vs. inclusiveness

### 3. Sex Stratification

- Analyze by Sex
- Report Sex-specific results
- Explore Sex × Policy interaction



Capture potential  
sex differences

### 4. Pre-Policy Window

Options:

- 6 months
- 12 months
- 24 months



Ensure baseline  
stability

### 5. Post-Policy Window

Options:

- 6 months
- 12 months
- 24 months



Capture substitution  
outcomes

### 6. Minimum Overlap

Options:

- ≥ 0 days
- ≥ 3 days
- ≥ 7 days



Ensure continuous  
care context

### 7. Index Definition

Valproate New-User  
(No use in baseline  
window)



Standardize  
index events



## The Path to Consensus



Agree on the **logic**  
behind each parameter.

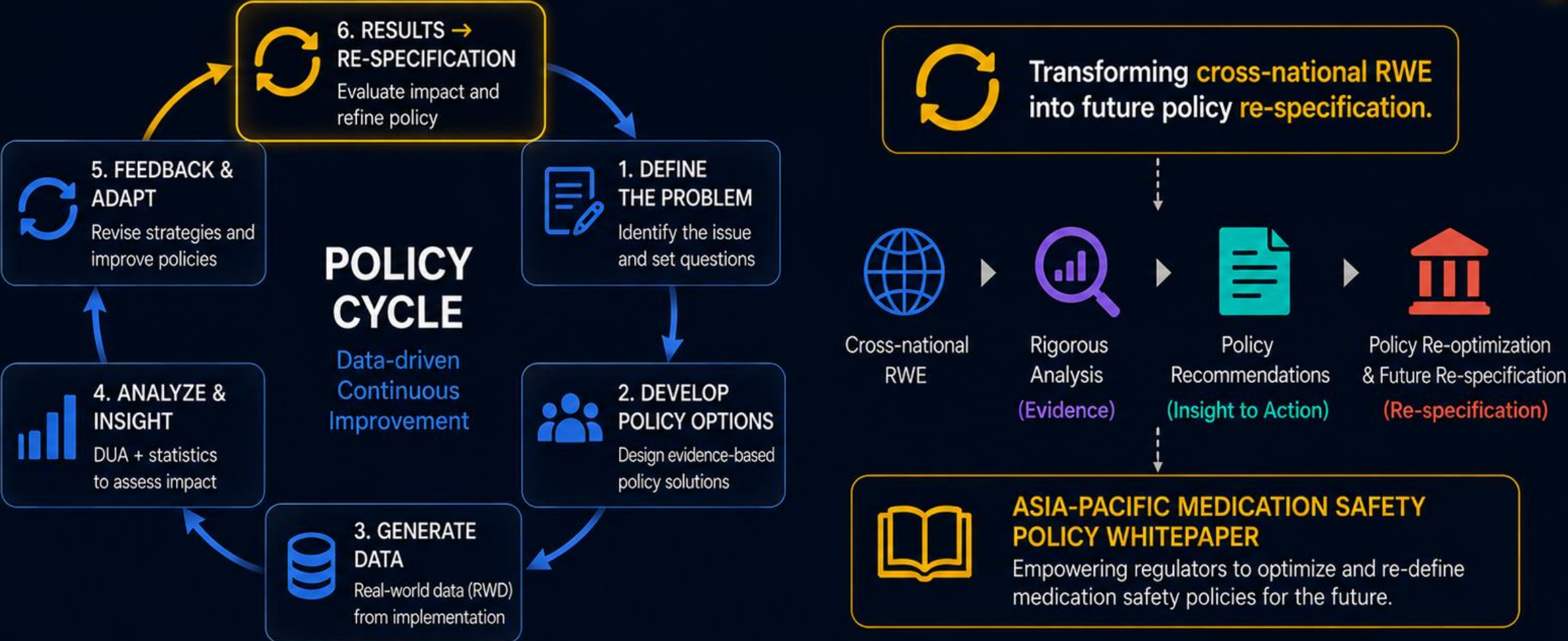


Align parameter  
settings across sites.



Enable reliable, comparable,  
and **actionable** results.

# Closing the Loop: Toward a Policy Whitepaper



- Evidence-Driven**  
Validate policy impact with RWE
- Improve Patient Safety**  
Reduce inappropriate use and risks
- Strengthen Collaboration**  
Share methods, standards, and results
- Continuous Learning**  
Enable ongoing policy evolution



# Thank You

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