Transportability across Populations

Amgen conference on July 25th

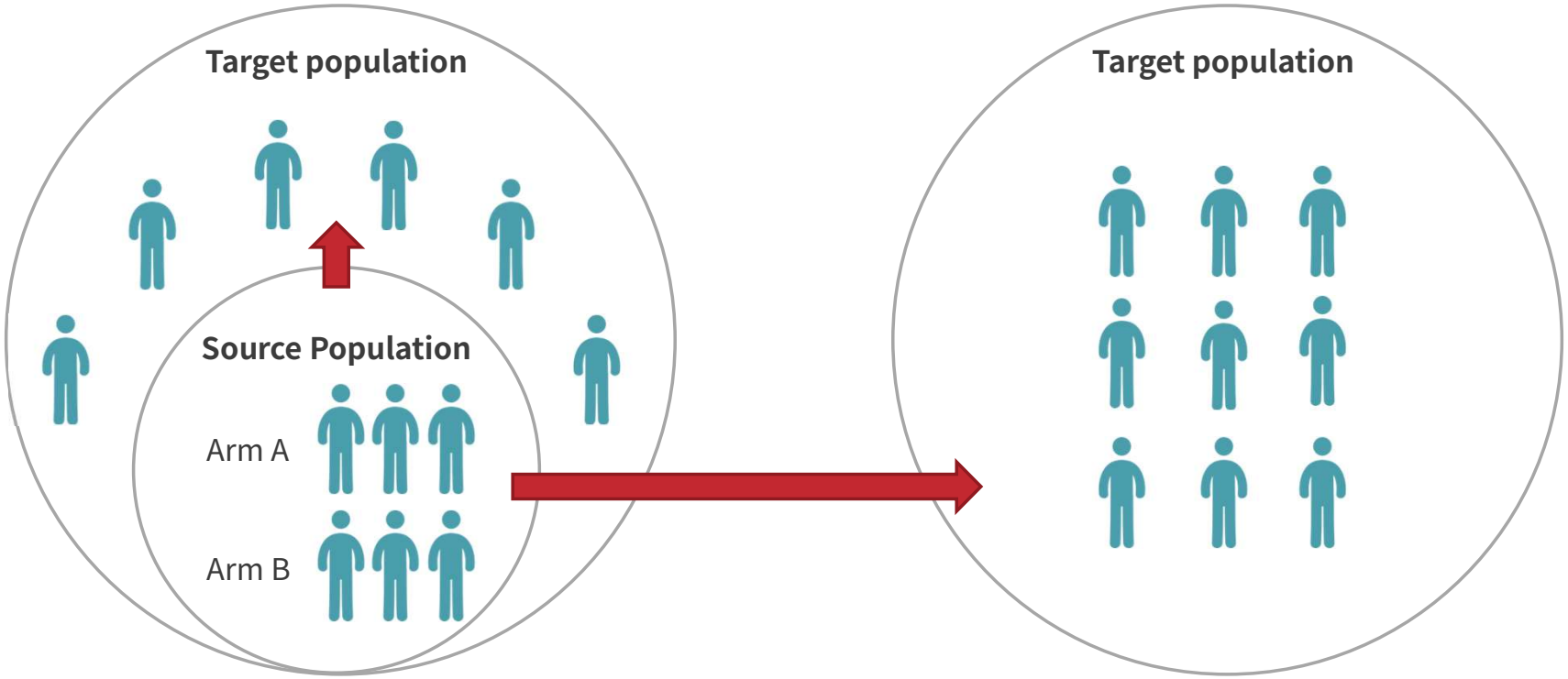
Brian Meng-Hsun Li

Population Heath Data Center NCKU
National Cheng Kung University

成功大學

成大群體健康數據中心
Population Health Data Center NCKU

Generalizability or Transportability



Generalizability

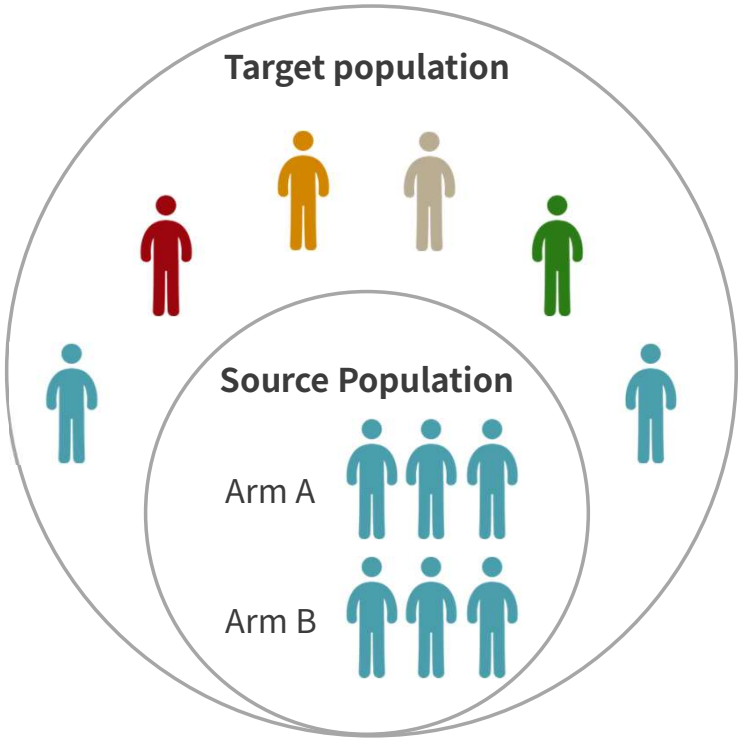
the source population is a *subset* of the target population

Transportability

the source population is *external* to the target population

Eur J Epidemiol. 2019;34(8):719-22.

Different Characteristics in Population



Generalizability

Transportability

Eur J Epidemiol. 2019;34(8):719-22.

Generalizability of RCT to Clinical Practice

2000s

External validity of randomised controlled trials: "To whom do the results of this trial apply?"

Lancet 2005; 365: 82–93 Peter M Rothwell

ORIGINAL INVESTIGATION

Are the Results of Randomized Controlled Trials on Anticoagulation in Patients With Atrial Fibrillation Generalizable to Clinical Practice?

Andrew Evans, MRCP; Lalit Kalra, PhD, FRCP *Arch Intern Med*. 2001;161(11):1443-1447.

Generalizability of Cancer Clinical Trial Results

Prognostic Differences between Participants and Nonparticipants

Cancer. 2006;106(11):2452-2458.

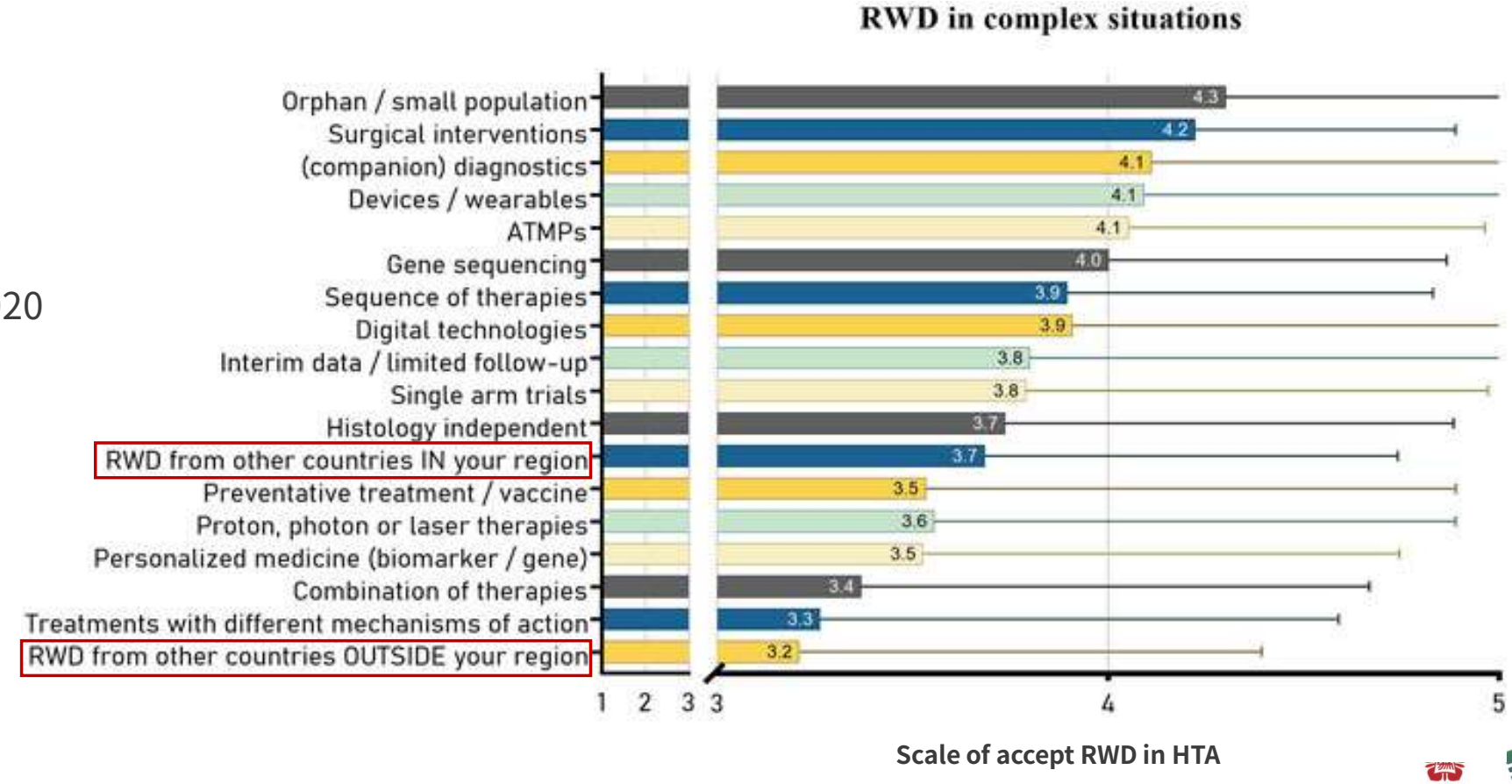
Linda S. Elting, Dr.P.H.[1]
Catherine Cooksley, Dr.P.H.[1]
B. Nebiyou Bekele, Ph.D.[1]
Michael Frumovitz, M.D.[2]
Elenir B. C. Avritscher, M.D.[1]
Charlotte Sun, Dr.P.H.[2]
Diane C. Bodurka, M.D.[2]

BACKGROUND. The generalizability of clinical trial results is questionable, because fewer than 5% of cancer patients participate. The authors examined the comparability of clinical trial participants and nonparticipants and the potential impact of differences.

METHODS. A retrospective cohort of 19,340 cancer patients who were diagnosed between January 1990 and December 1997 was characterized by trial participation. The distributions of prognostically important factors among trial participants were

Real World Data in Health Technology Assessment

2020



Front Pharmacol. 2022;13:837302.

Upcoming Methodology Article of Transportability

Now

TUTORIAL IN BIOSTATISTICS

WILEY Statistics in Medicine

Extending inferences from a randomized trial to a new target population

Issa J. Dahabreh[1,2,3,4] | Sarah E. Robertson[1,2] | Jon A. Steingrimsson[5] | Elizabeth A. Stuart[6] | Miguel A. Hernán[4,7,8]

Stat Med. 2020;39(14):1999-2014.

RESEARCH ARTICLE

Statistics in Medicine WILEY

A calibration approach to transportability and data-fusion with observational data

Kevin P. Josey[1] | Fan Yang[2] | Debashis Ghosh[2] | Sridharan Raghavan[3,4]

Stat Med. 2022;41(23):4511-4531..

RESEARCH ARTICLE

Statistics in Medicine WILEY

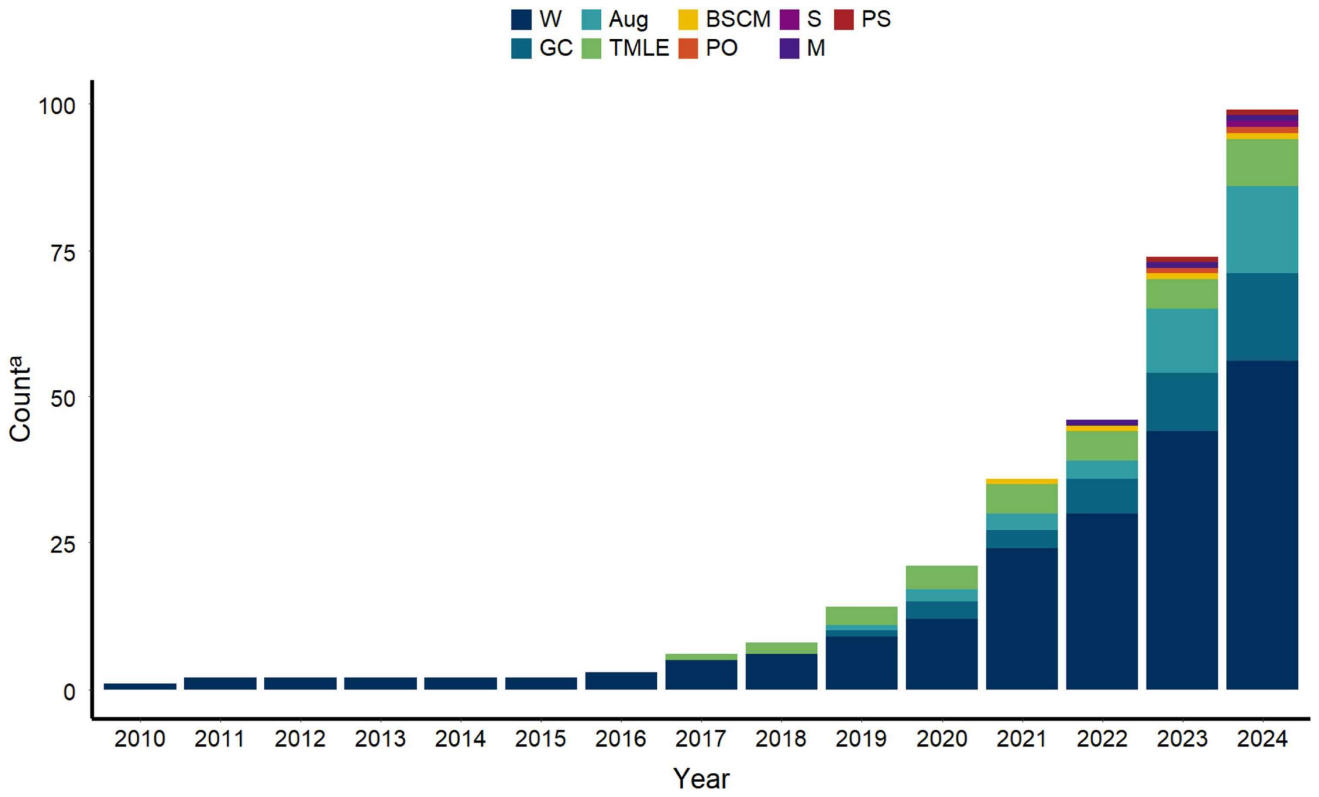
Sensitivity analysis using bias functions for studies extending inferences from a randomized trial to a target population

Issa J. Dahabreh[1,2,3] | James M. Robins[1,2,3] | Sebastien J.-P. A. Haneuse[2] | Iman Saeed[4] | Sarah E. Robertson[1,2] | Elizabeth A. Stuart[5] | Miguel A. Hernán[1,2,3,6]

Stat Med. 2023;42(13):2029-2043.

Upcoming Research Article of Transportability

Now



W: Weighting; GC: G-computation; Aug: Augmented; TMLE: Targeted maximum likelihood estimation; BSCM: Bayesian structural causal modelling; PO: Regression of pseudo-outcomes; S: Structural modelling and simulation; PS: Post-stratification.

Ann Epidemiol. 2025;104:61-70.

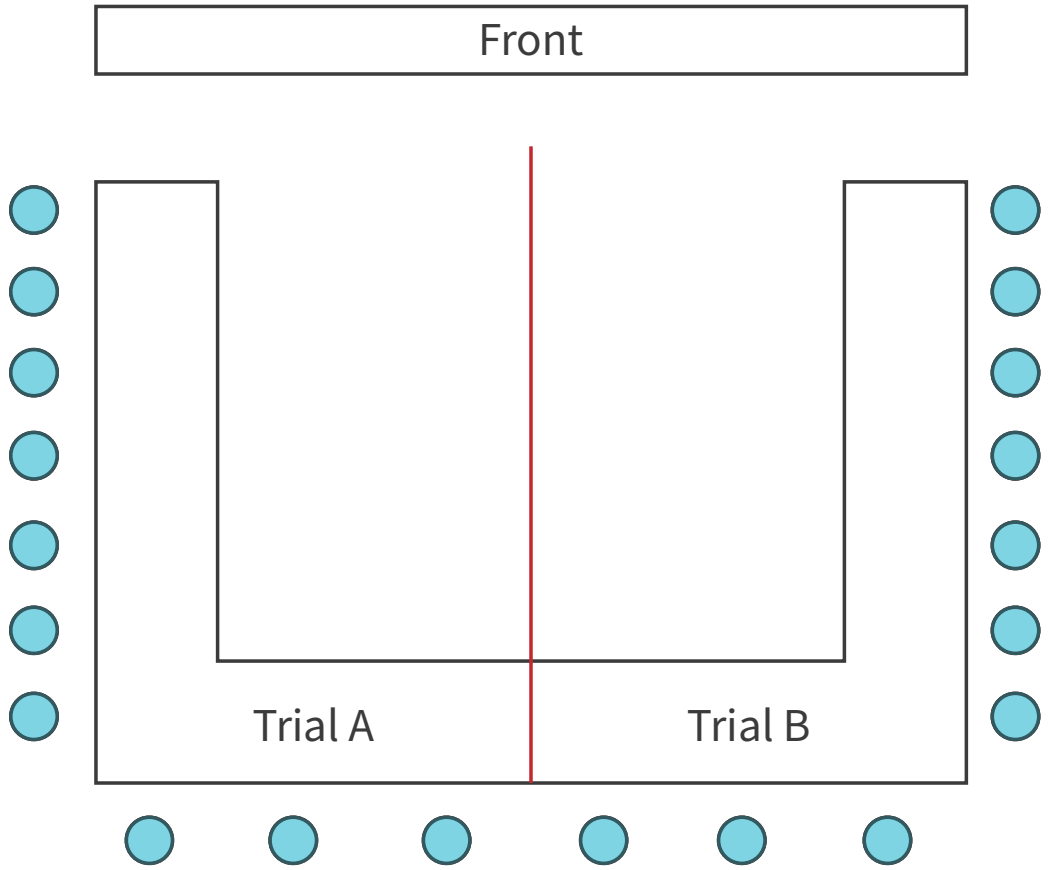
The Fortune Circle

Will the person assigned to circle win the game?

Randomized assignment

- Circle at the bottom of the beverage (intervention group)
- No circle at the bottom of the beverage (reference group)

The Fortune Circle



The Fortune Circle

Front

Trial A:

RR of having fortune

1.25

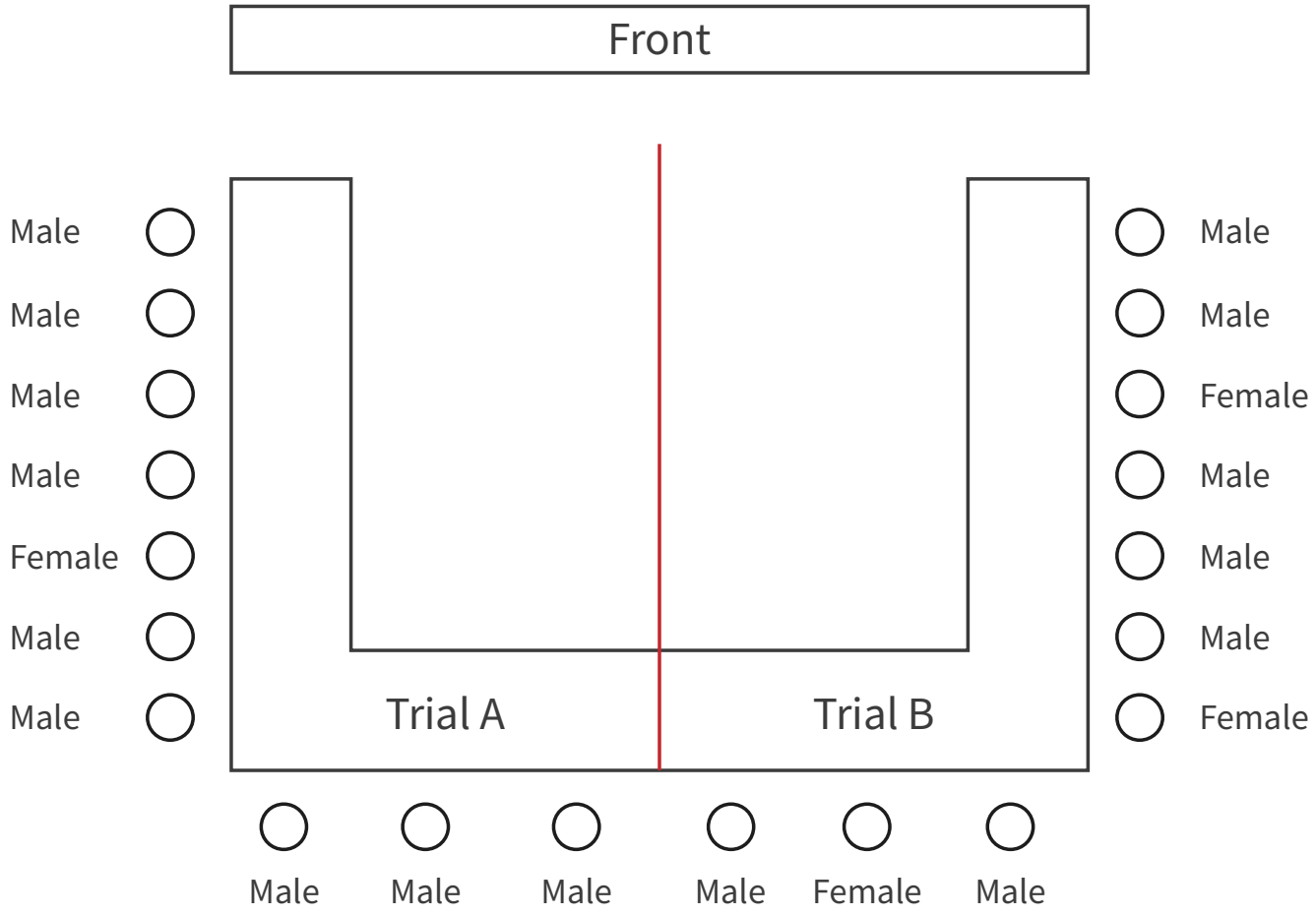
Trial B:

RR of having fortune

0.80

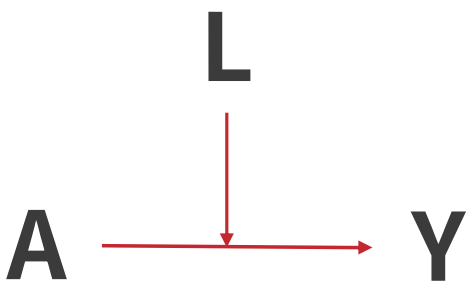
Different results in Trial A and Trial B despite randomization

Oops! The Effect Modifiers



Sex as Effect Modifiers

Bonus chance of winning the game if a male is randomly assigned to the circle



L=1, male

A=1, circle

Y=1, win the game

Different Distribution of Effect Modifiers

Front

Trial A:

RR of having fortune

1.25

9 Males
1 Females

Trial B:

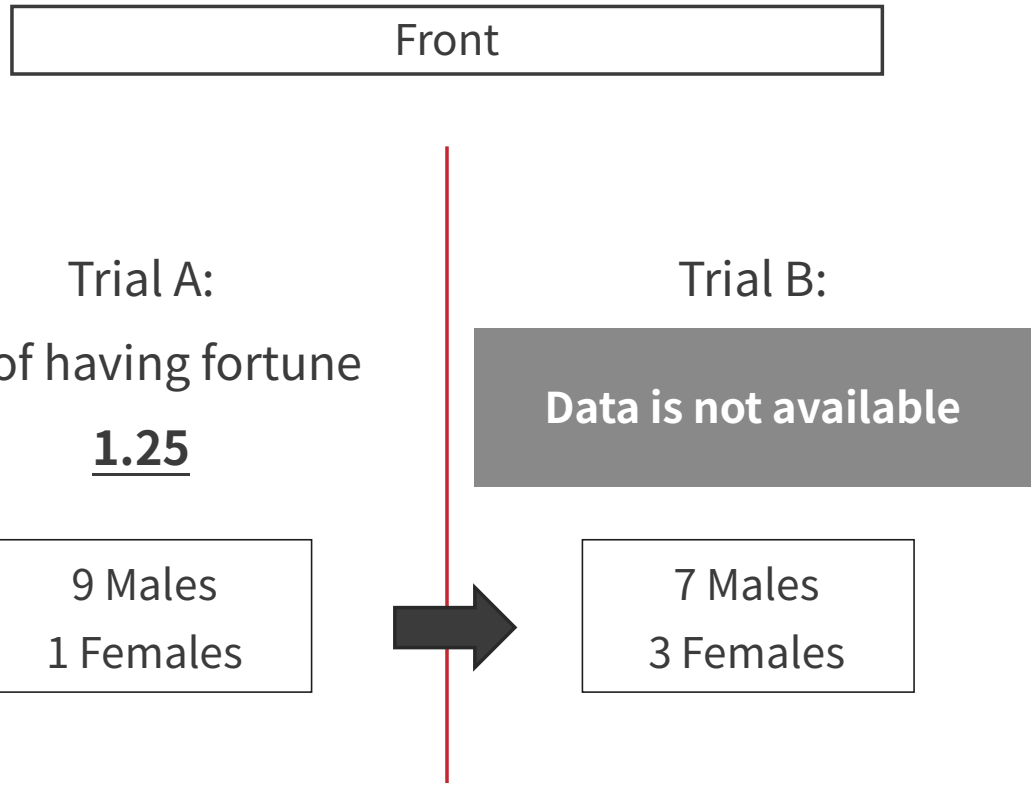
RR of having fortune

0.80

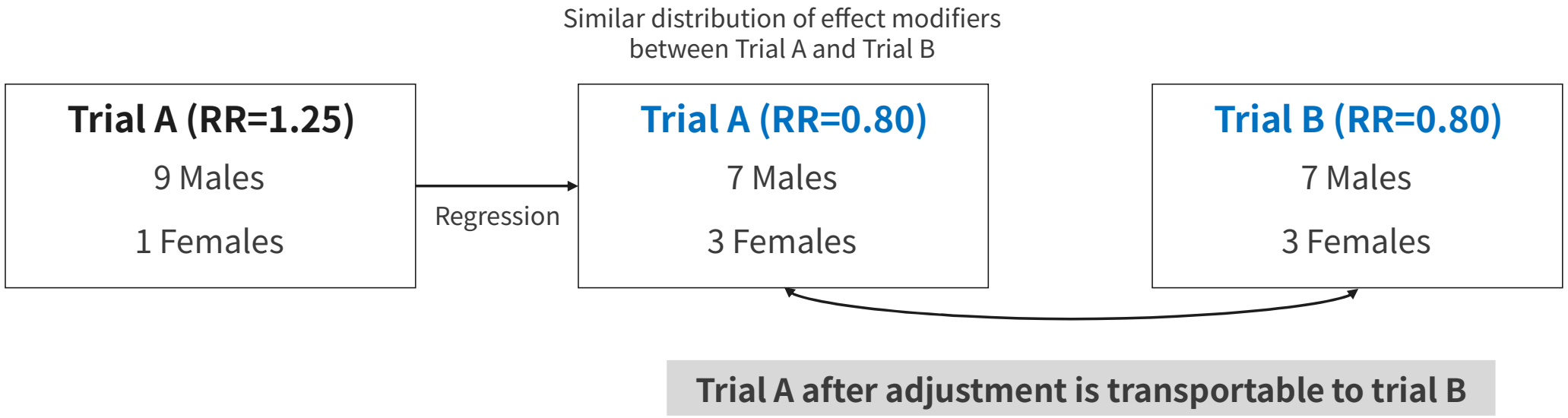
7 Males
3 Females

Trial A and B are not transportable

How to Achieve the Transportability



Achieve Transportability through Regression



Trial A after adjustment is transportable to trial B

Outcome regression

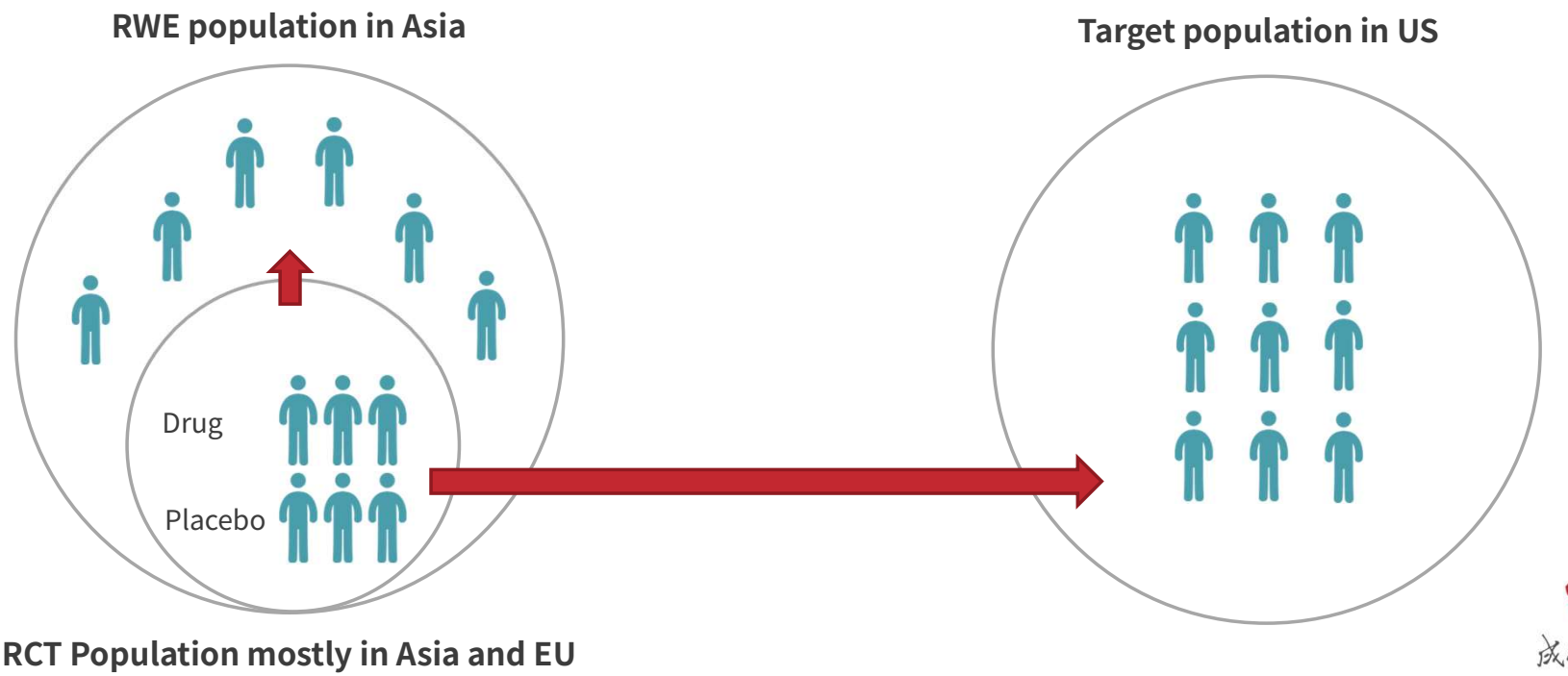
$$\text{logit}(P[Y=1]) = \beta_0 + \beta_1 A + \beta_2 L + \beta_3 (A \times L) + \beta_4 C$$

0 0 -1.39 2.77

When Should We Consider Transportability

Scenario 1 – Applying RCTs in the real world

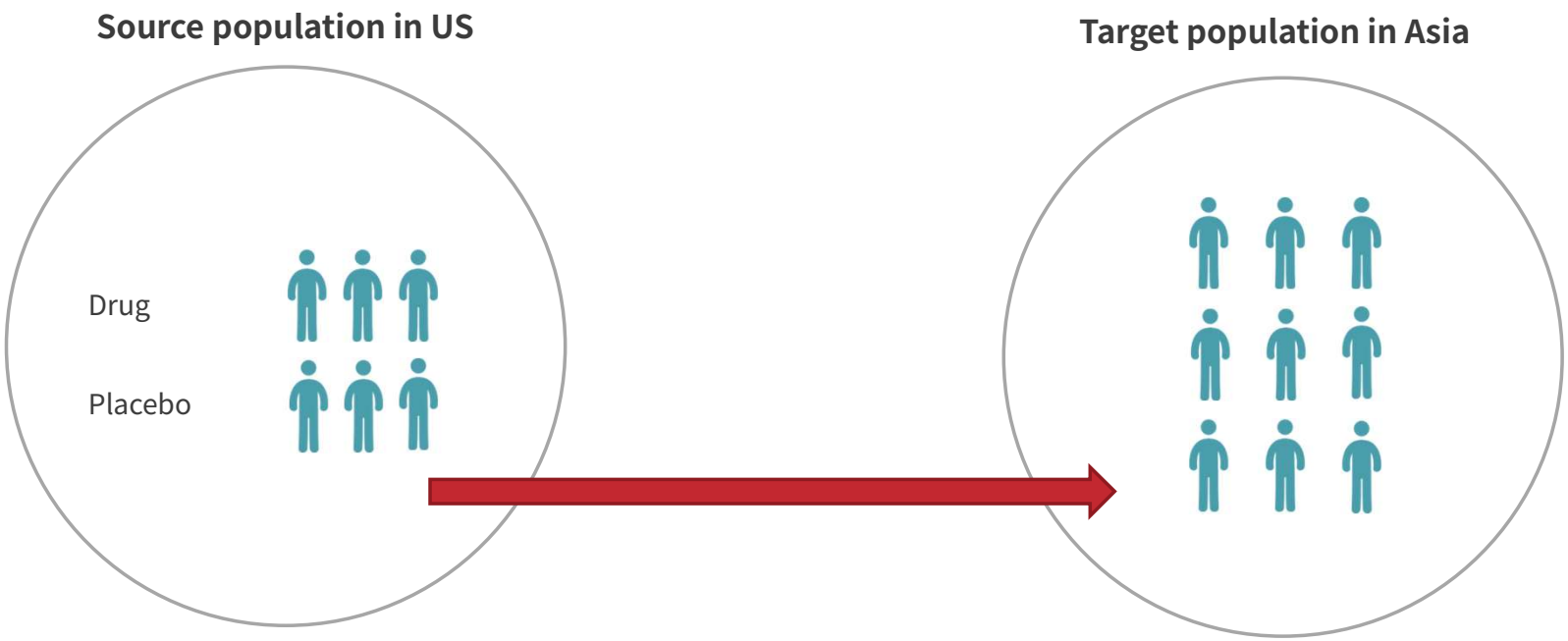
Example: Inebilizumab-cdon was newly approved for IgG4-related disease in the US since 2025.



When Should We Consider Transportability

Scenario 2 – Applying RWEs in the different countries

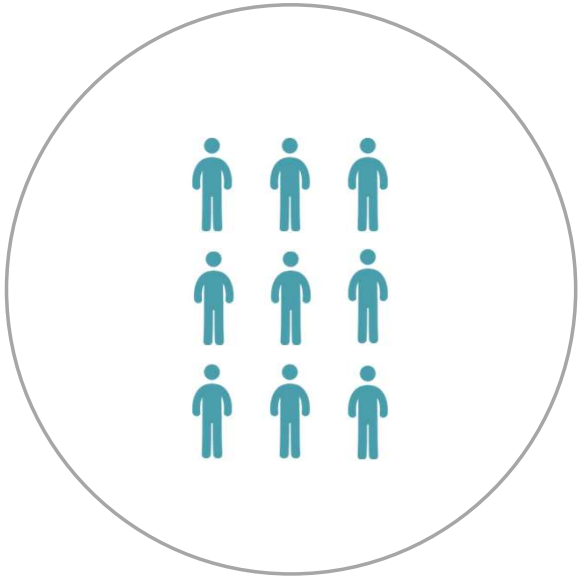
Example: Tirzepatide was approved in the US since 2022 and was newly approved in Taiwan since 2024.



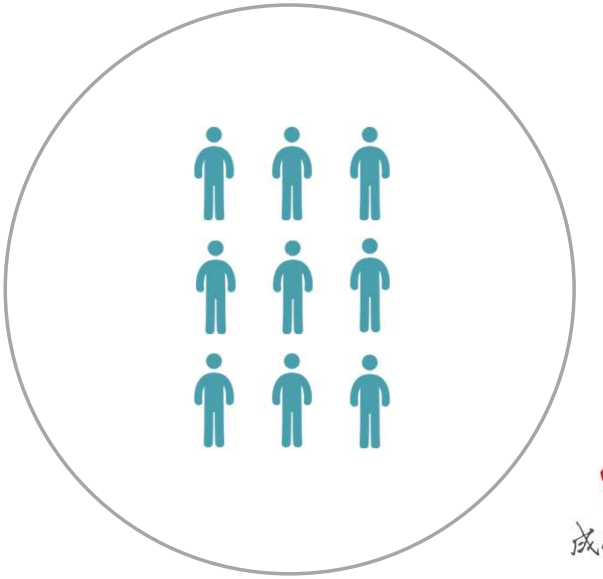
Key Assumptions of Transportability

Causal assumptions
1. Conditional exchangeability for treatment assignment 2. Positivity of treatment assignment 3. Stable unit treatment value assumption for treatment assignment

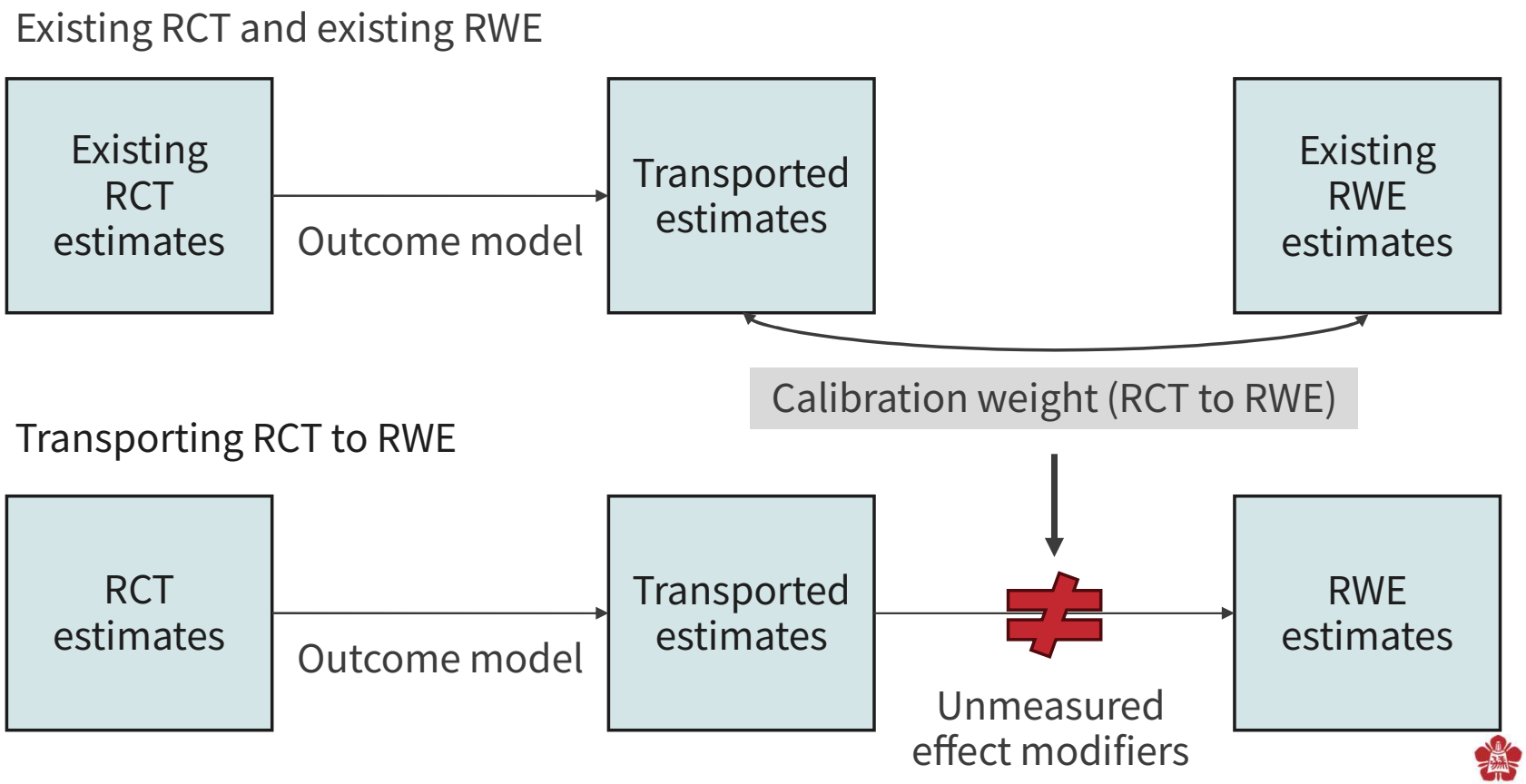
Source population in US



Target population in Asia



Transportability Framework



When Are Calibration Weights Applicable?

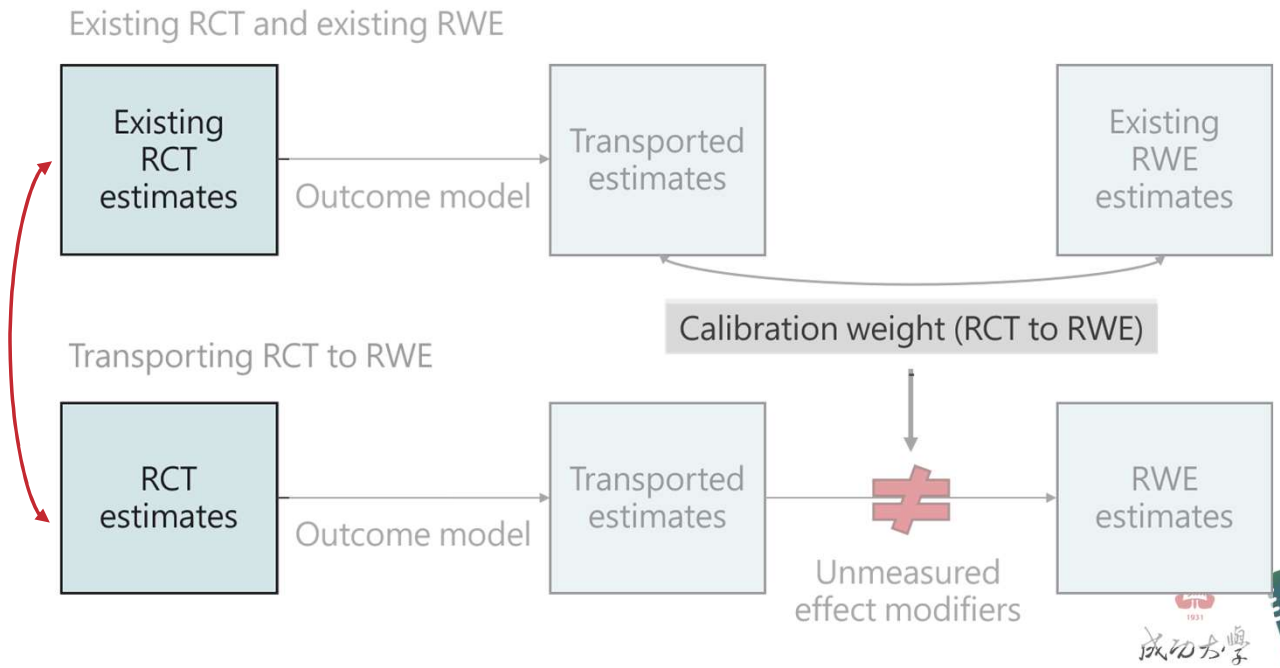
Scenario 1 – Applying RCTs in the real world

Example: Inebilizumab-cdon was newly approved for IgG4-related disease in the US since 2025.

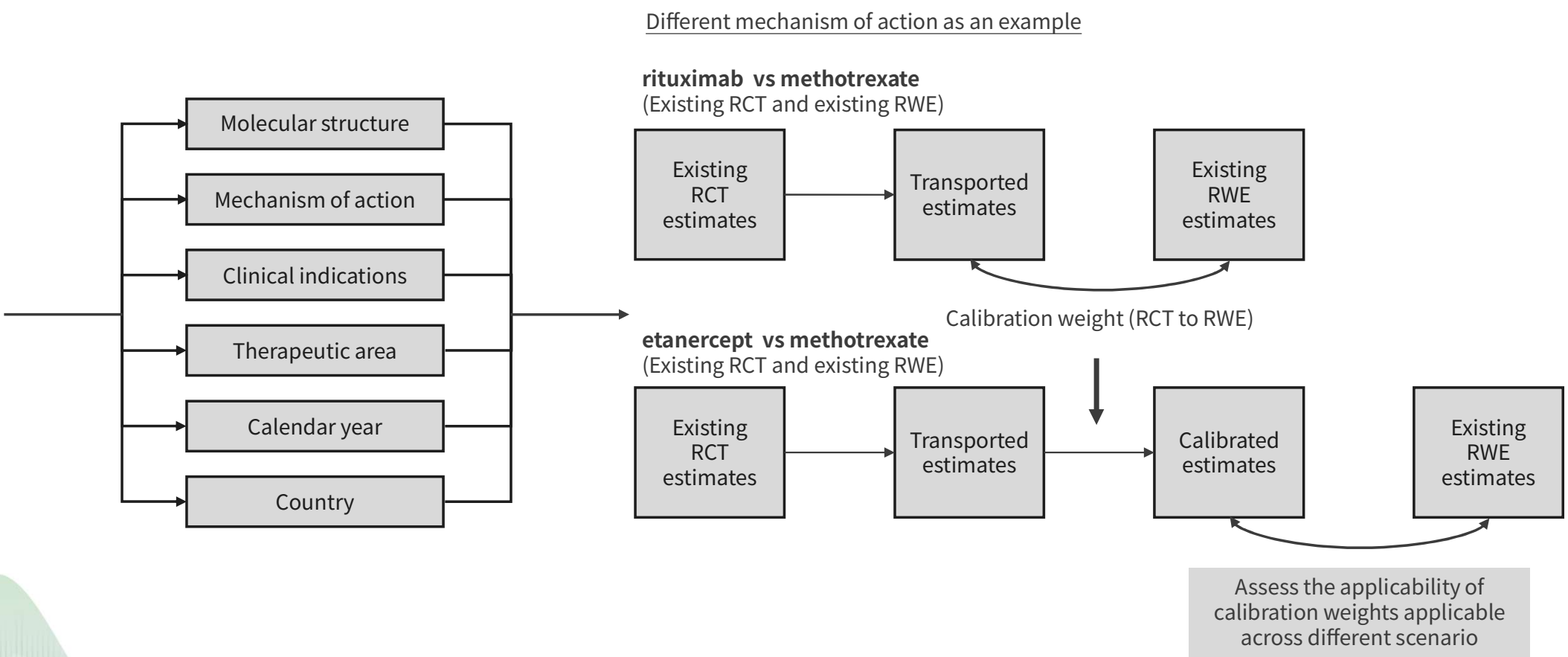
Rituximab
vs
Placebo

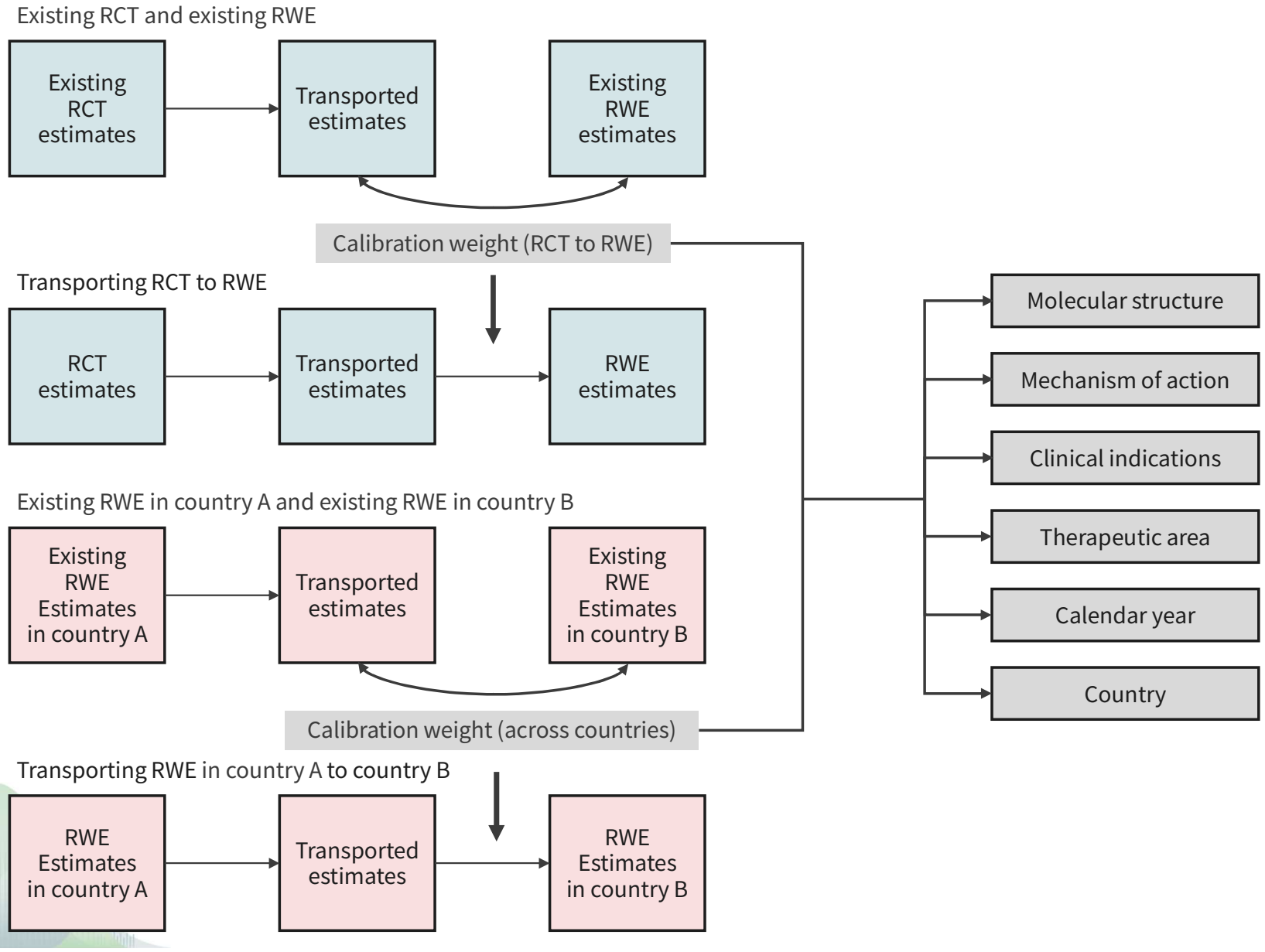
Different mechanism of action

Inebilizumab-cdon
vs
Placebo

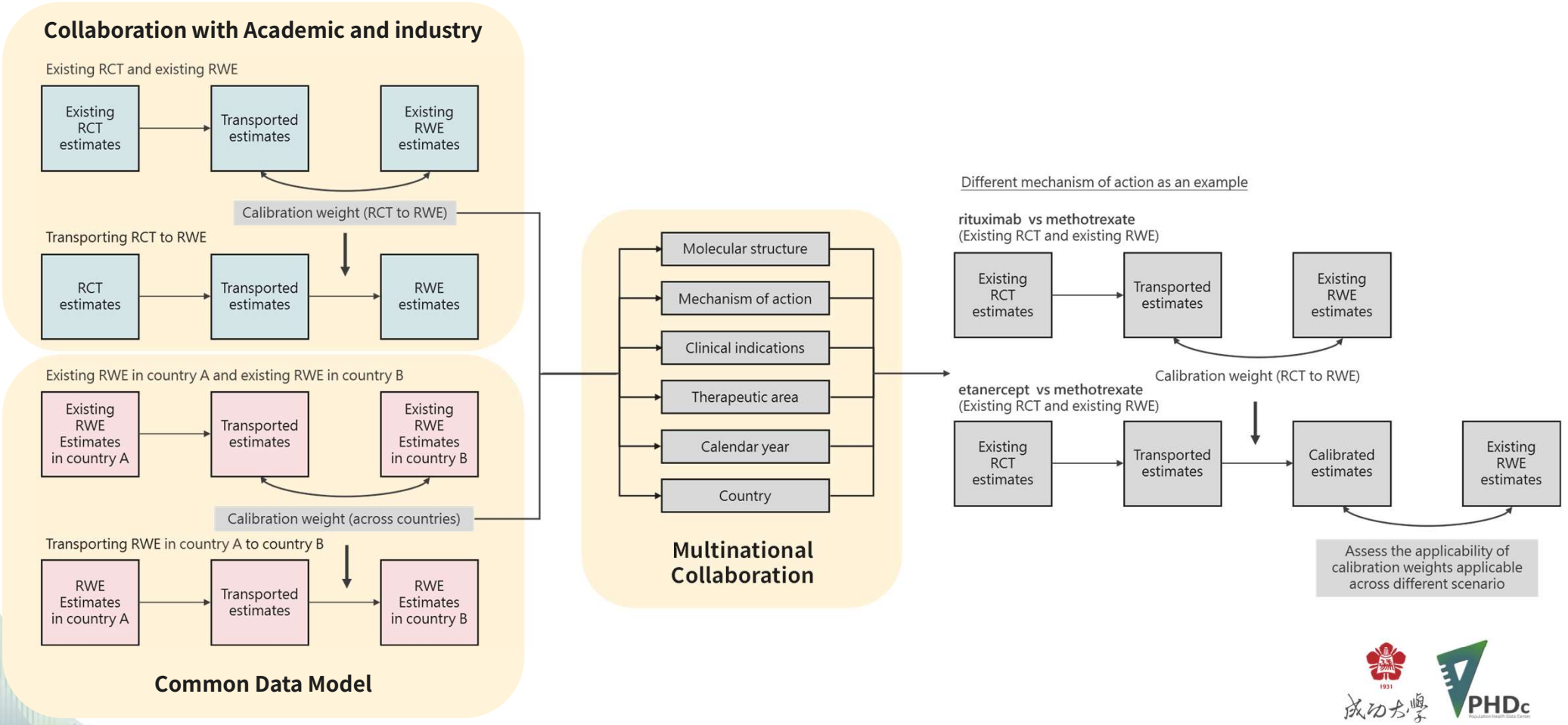


Applicable Scenario of Calibration Weight

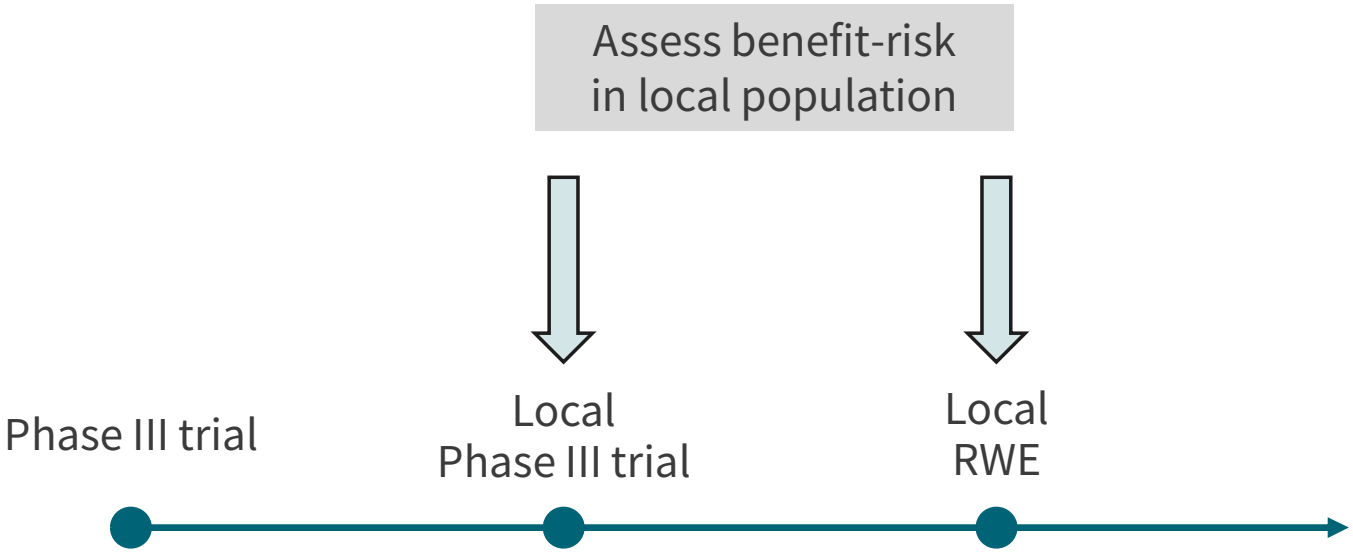



Existing RCT and existing RWE
Existing RCT estimates
Transported estimates
Existing RWE estimates
Calibration weight (RCT to RWE)
Transporting RCT to RWE
RCT estimates
Transported estimates
RWE estimates
Existing RWE in country A and existing RWE in country B
Existing RWE Estimates in country A
Transported estimates
Existing RWE Estimates in country B
Calibration weight (across countries)
Transporting RWE in country A to country B
RWE Estimates in country A
Transported estimates
RWE Estimates in country B
Molecular structure
Mechanism of action
Clinical indications
Therapeutic area
Calendar year
Country

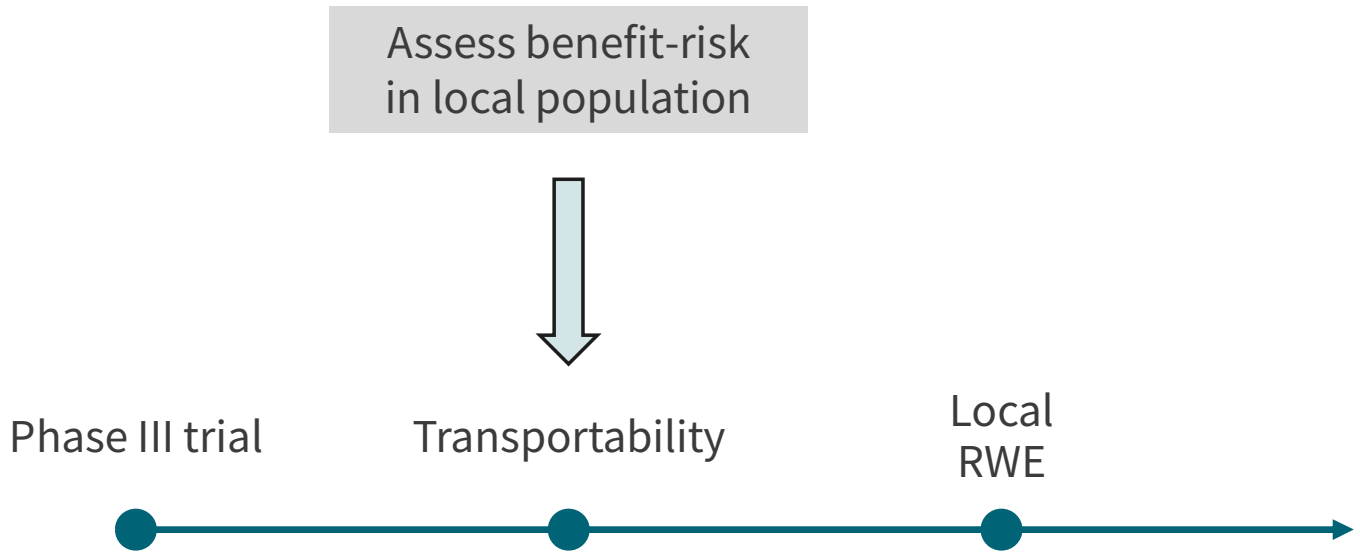
Establish a Transportability Framework based on IMPRESIVE project



Impact and Value of Transportability

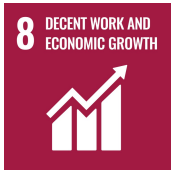


Impact and Value of Transportability



Impact and Value of Transportability

Expand applicability of real-world evidence to improve health outcomes



Reduce costs and save time in medical research

Facilitate innovation by bridging academic, industry, and government

Reduce health disparities of underrepresented populations

Thank You

Brian Meng-Hsun Li

brianli6699@gmail.com

Foundational Elements of Transportability

Engage Provide information to support drug approval 2021 Prolia project	**Collaborate** Taiwan, South Korea, Hong Kong, Japan 2022 IMPRESIVE 1.0
Standardize Prepare cohorts in common data model 2023 IMPRESIVE 2.0	**Visualize** Display evidence through interactive dashboards 2024 IMPRESIVE 3.0

IMPRESIVE 4.0 - Transportability

Build multinational transportability framework based on common data model

Transportability – Aim 1

- We aim to validate and calibrate transportability across these countries.

Proof-of-concept Study Based on CDM

- A proof-of-concept study to test if the transported estimates are transportable to the true estimates
  - Population: hospitalized patients with ASCVD
  - Intervention: prasugrel
  - Comparison: clopidogrel
  - Outcomes: myocardial infarction and major bleeding
- Four emulation of the target trial using four databases (NHIRD, NHIS, CDARS, DeSC)

Four Studies Emulating the TRITON-TIMI 38 Trial

Protocol component	Modified TRITON-TIMI 38 trial	Emulation of the target trial using four databases (NHIRD, NHIS, CDARS, DeSC)
Eligibility criteria	Inclusion criteria • Aged >= 18 years • Patients with unstable angina or non–ST-elevation myocardial infarction within 72 hours and TIMI risk score of 3 or more • Patients with ST-segment elevation myocardial infarction within 12 hours with primary PCI • Patients with ST-segment elevation myocardial infarction after 12 hours to 14 days without primary PCI Exclusion criteria • Contraindicated for prasugrel or clopidogrel	Same as the target trial; We assumed that receiving prasugrel and clopidogrel indicates there was a determination of no contraindications.
Treatment strategies	(1) Initially receiving prasugrel (2) Initially receiving clopidogrel	Same as the target trial
Treatment assignment	Randomly assigned to a strategy	Same as the target trial; We assumed eligible patients are randomly assigned to a strategy by propensity score with fine stratification weighting to generate a study population with balance characteristics

Identify Measured Effect Modifiers

Effect modifiers	Clopidogrel	Prasugrel
Variables for clinical indications		
High baseline bleeding risk (age ≥ 75 y, CKD, prior GI bleeding)	V	V
High baseline thrombotic risk (STEMI vs NSTEMI, diabetes, PAD)	V	V
Concomitant oral anticoagulant therapy	V	V
TIMI Risk Score for NSTEMI	V	V
Time to medication	V	V
Time to PCI	V	V
Variables for drug class		
No NSAID interaction	V	V
Variables for mechanism of action		
No impact of CYP2C19-LOF genotype		V
No PPI interaction		V

Specify the Outcome Model by Cox Regession

$$h(t \mid A,L)=h_0(t) \times \exp(\beta_1 A+\beta_2 L+\beta_3(A \times L))$$

- We specify the outcome model with indicators for treatment and effect modifiers with their product term.
- We assess model specification by comparing:
  - parametrical survival curve by the outcome model
  - non-parametrical survival curve by the Kaplan-Meier estimator

The Transported Estimates

Observed estimates

Population A using data from country A

Transported estimates

Population B using data from country A

Outcome model

$$h(t \mid A,L)=h_0(t) \times \exp(\beta_1 A+\beta_2 L+\beta_3 (A \times L))$$

Calibrate the Transported Estimates

Transported estimates

Population B using data from country A

≠

True estimates

Population B using data from country B

Unmeasured effect modifiers
(e.g., social determinants of health)

$$Calibration\ Weights = \frac{Transported\ Estimates}{True\ Estimates}$$

6 calibration weights on social determinants of health (SDOH)

TW KR	KR JP
TW HK	KR HK
TW JP	KR JP

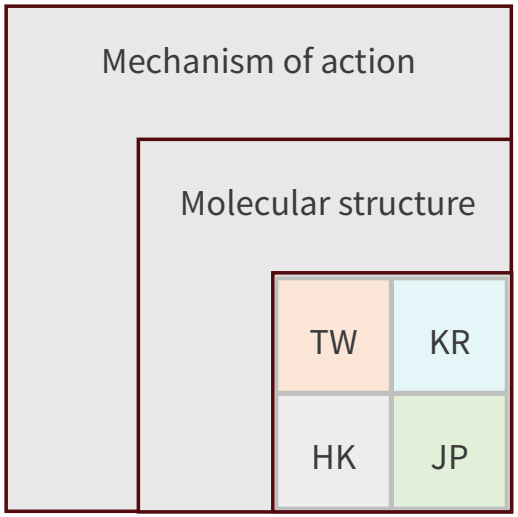
Application of Transportability Calibration

- Applying the inverse of calibration weights to transported estimates could enhance their transportability.

$$Transported\ Estimates \times \frac{1}{Calibration\ weights} = True\ Estimates$$

Transportability – Aim 2

- We aim to identify scenarios where transportability calibration is appropriate (i.e., no residual effect modifiers after applying calibration)



Transportability Calibration

P2Y12 inhibitors → COX inhibitors (e.g., aspirin)

Aromatic thienopyridine → Triazolopyrimidine (e.g., ticagrelor)

Two Proof-of-concept Study Based on CDM

- A proof-of-concept study to test if the transported estimates **with calibration** are transportable to the true estimates in the scenario when intervention with **different molecular structure**
  - Population: hospitalized patients with ASCVD
  - Intervention: ticagrelor
  - Comparison: clopidogrel
  - Outcomes: myocardial infarction and major bleeding

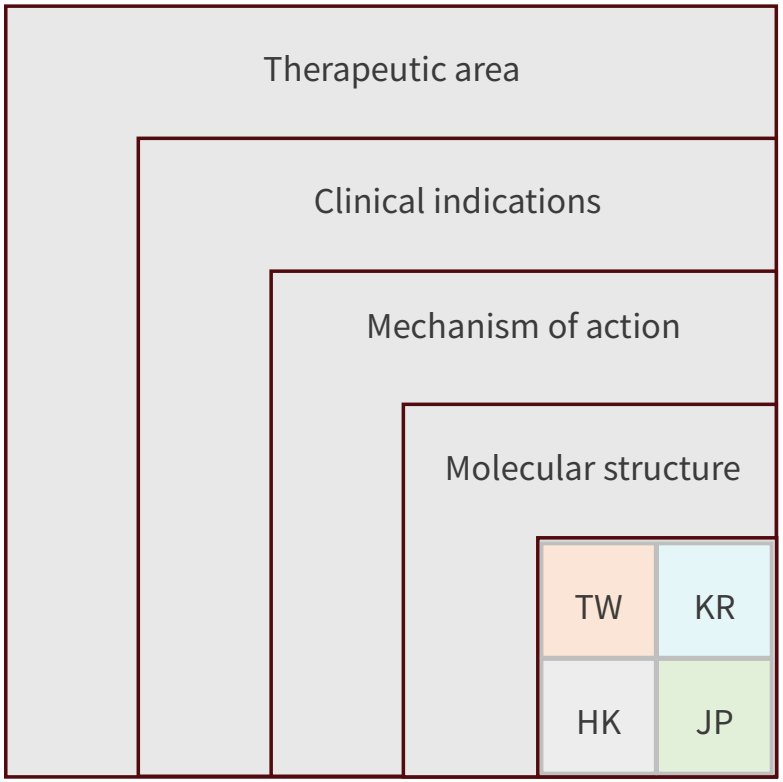
Two Proof-of-concept Study Based on CDM

- A proof-of-concept study to test if the transported estimates **with calibration** are transportable to the true estimates in the scenario when intervention with **different mechanism of action**
  - Population: hospitalized patients with ACS
  - Intervention: clopidogrel
  - Comparison: aspirin
  - Outcomes: myocardial infarction and major bleeding

Transportability Calibration: A Practical Perspective

- Transported estimates with calibration can provide information about the local population to stakeholders
- Calibration weights is useful in particular situation (e.g., different molecular structure)
- Calibration weights need to be used with caution in particular situation (e.g., different mechanism of action)

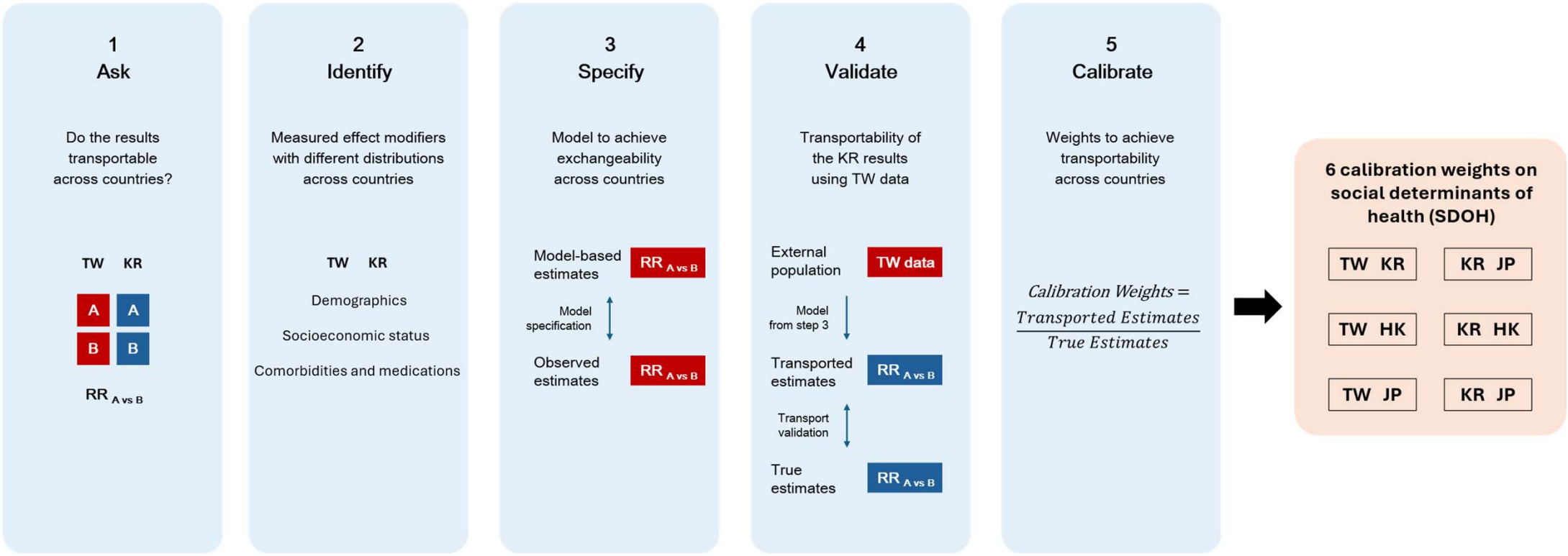
Further Research Interests



Transportability Calibration

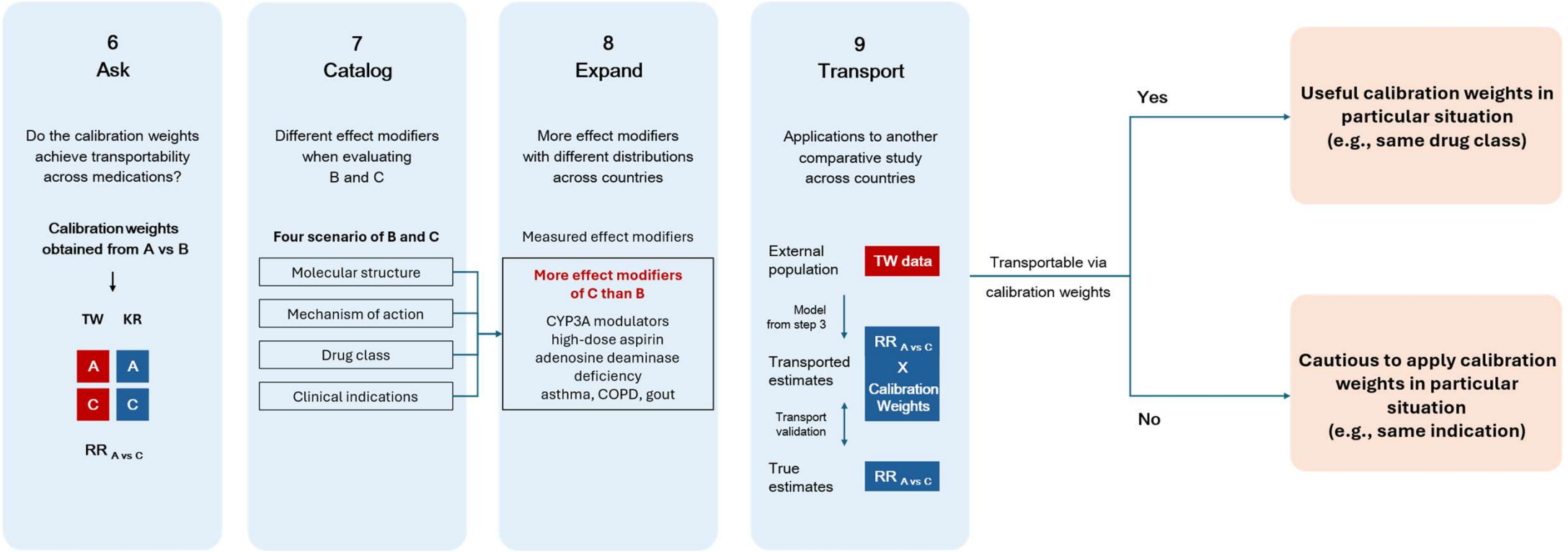
Cardiology	→	Endocrinology (e.g., diabetes)
Atherosclerosis	→	Atrial fibrillation
P2Y12 inhibitors	→	COX inhibitors (e.g., aspirin)
Aromatic thienopyridine	→	Triazolopyrimidine (e.g., ticagrelor)

Transportability Calibration across Countries



TW, Taiwan; KR, South Korea; HK, Hong Kong; JP, Japan

Scenario for Applying Transportability Calibration



IMPRESIVE 4.0 Timeline

	7	8	9	10	11	12	1	2	3	4	5	6	7
Kick-off conference	■												
Study document													
Protocol development	■	■											
Protocol circulation		■	■										
SAP development			■	■									
Data analysis in local population													
Cohort identification					■	■	■						
Baseline characteristics						■	■	■					
Outcome model specification						■	■	■	■	■			
Transported estimates							■	■	■	■	■		
Reporting visualization											■	■	
Meeting	▲			▲	(Discussions with each site as needed)						▲		▲

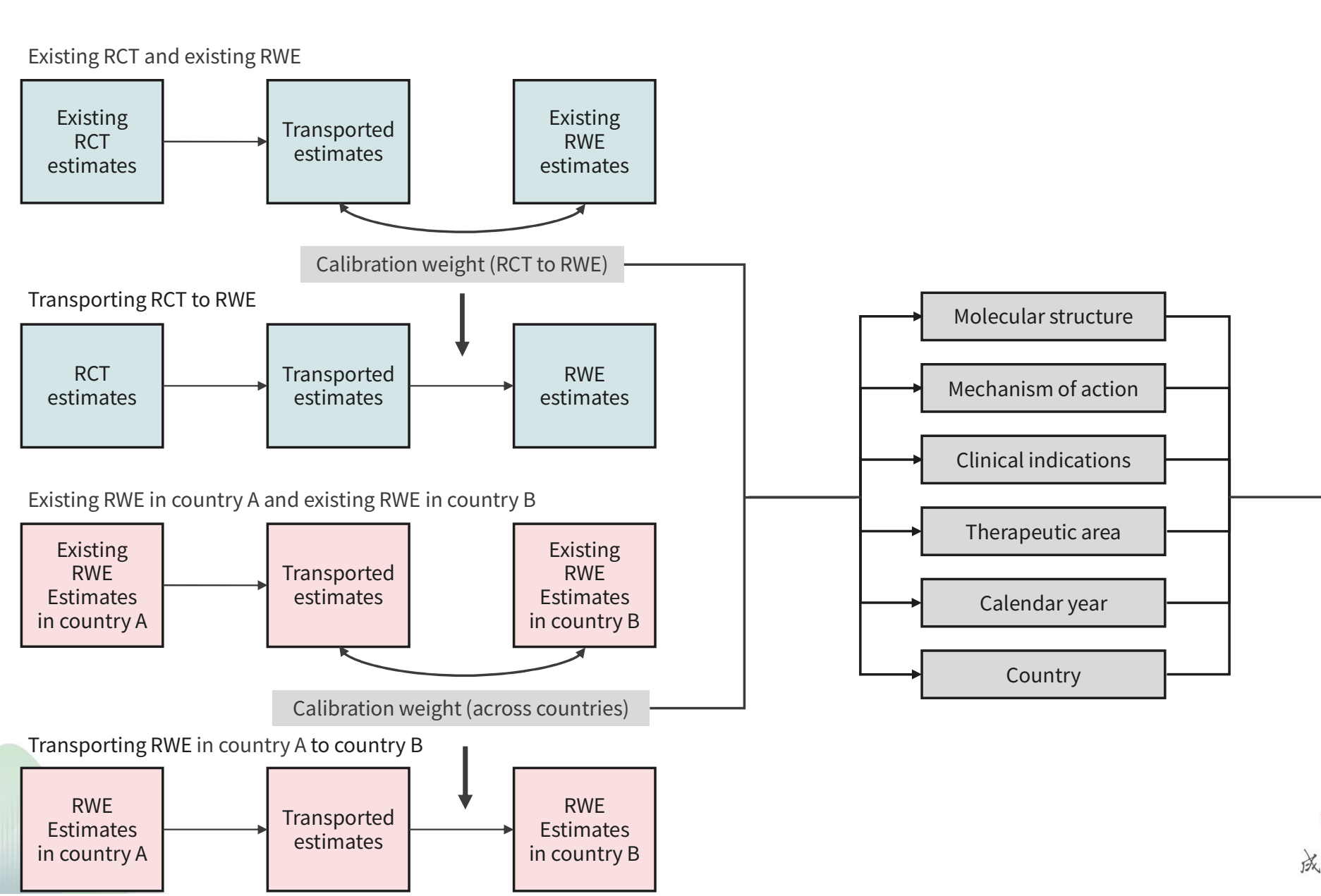
Thank You

Brian Meng-Hsun Li

brianli6699@gmail.com

Identify Measured Effect Modifiers

Potential effect modifiers	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Variables for indication				
High baseline bleeding risk (age ≥ 75 y, CKD, prior GI bleeding)	V	V	V	V
High baseline thrombotic risk (STEMI vs NSTEMI, diabetes, PAD)	V	V	V	V
Concomitant oral anticoagulant therapy	V	V	V	V
TIMI Risk Score for NSTEMI	V	V	V	V
Time to medication	V	V	V	V
Time to PCI	V	V	V	V
Variables for mechanism of action				
No NSAID interaction		V	V	V
Variables for irreversible/ reversible P2Y12 inhibitor				
No impact of CYP2C19-LOF genotype			V	V
No PPI interaction			V	V
Variables for active pharmaceutical ingredient				
Adenosine deaminase deficiency (RA, SLE, SS, AOSD)				V
Exacerbation of AE to discontinuation (asthma, COPD, gout)				V
CYP3A modulators				V
High-dose aspirin (>100 mg) activate PGI_2				V



Different mechanism of a

rituximab vs methotrex
(Existing RCT and existing

Existing RCT estimates

etanercept vs methotre
(Existing RCT and existing

Existing RCT estimates