

Collaboration + big data: The need for partnerships to influence policy and practice

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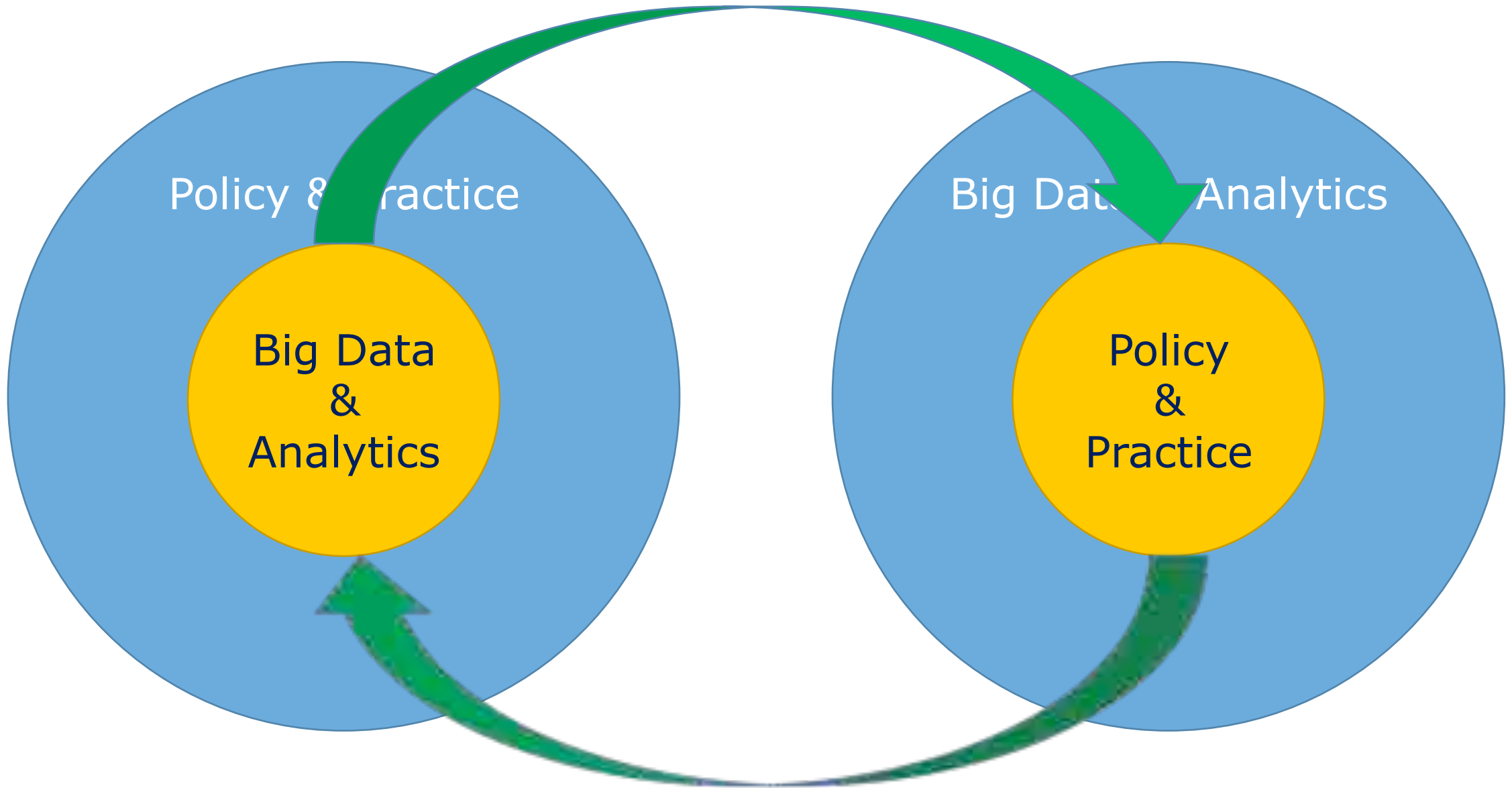
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Symposium Objectives

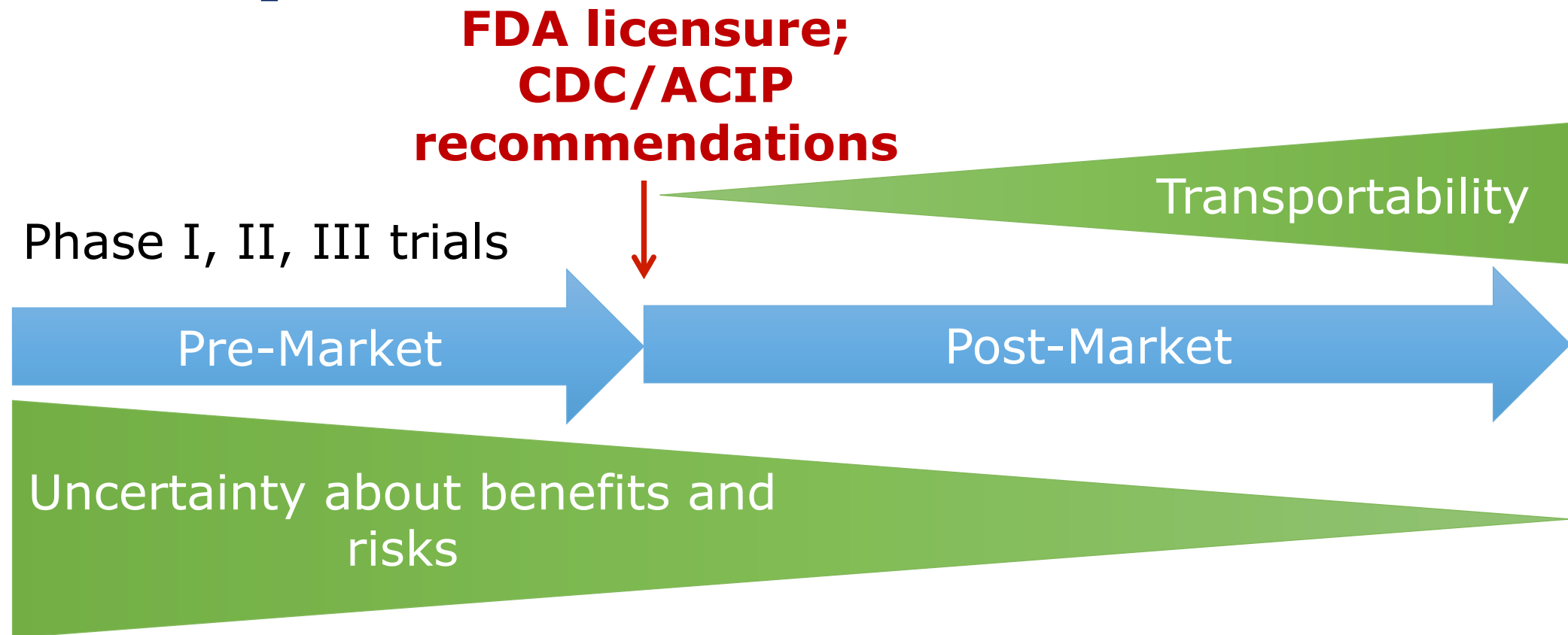
- 1) To bring together** scientists from diverse disciplines to discuss health research and methods that involve large health care data
- 3) To discuss** methodological challenges encountered in research, **share ideas for addressing them, and brainstorm future directions**





Examples of Successful Partnerships in Vaccine Safety

Lifecycle Approach to Vaccine Safety



VSD and PRISM

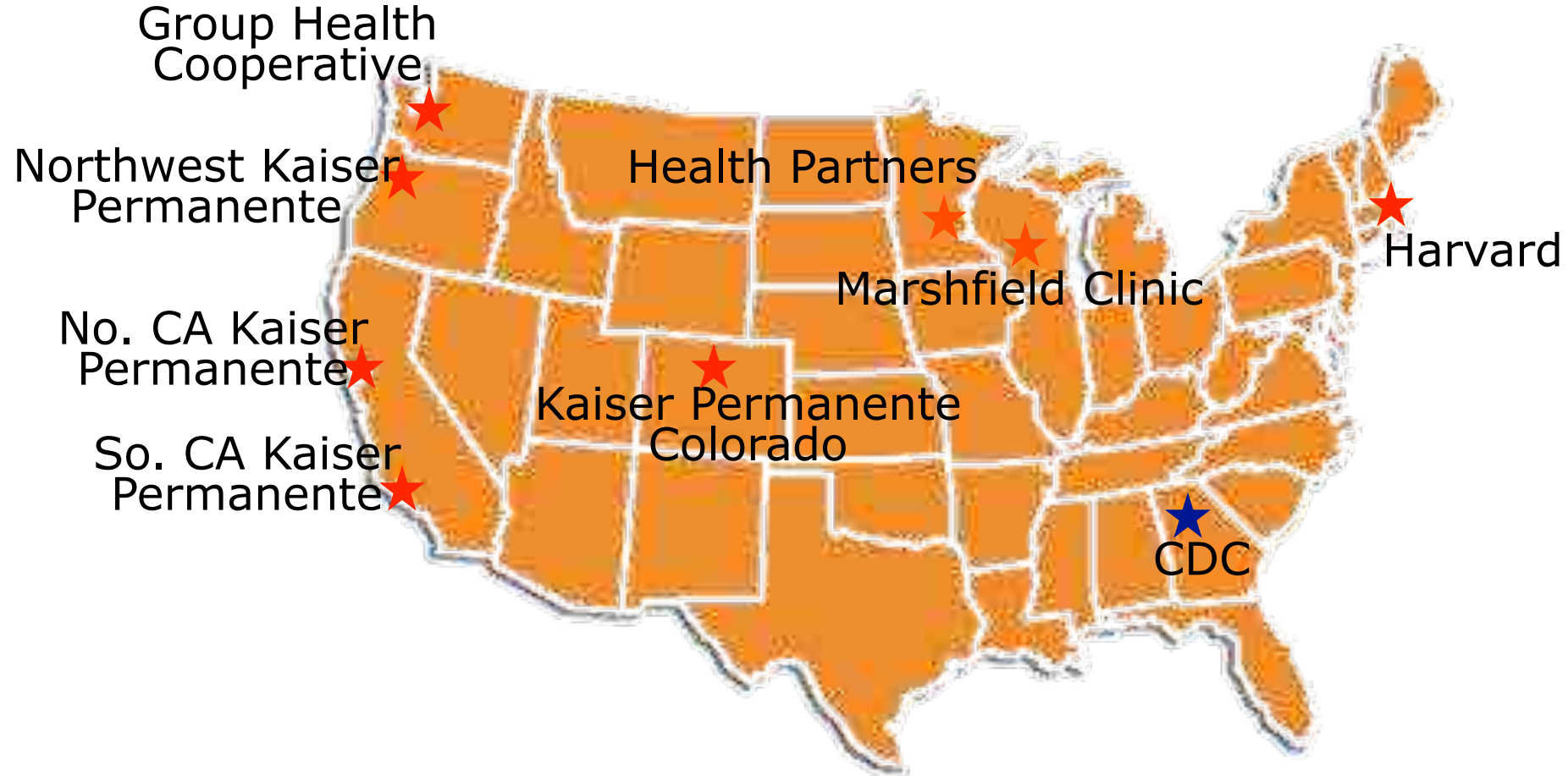
Vaccine Safety Datalink

- Established in 1990, funded by CDC
- 8 U.S. health plans
- ~9 million children and adults
- Rapid access to electronic health records, including immunization records

Post-licensure Rapid Immunization Safety Monitoring system

- Established in 2009, now part of FDA-funded Sentinel
- 4 national health insurers
- ~170 million children and adults
- Links health plan, state immunization registry and birth registry data

Vaccine Safety Datalink Partners



Sentinel (PRISM) Partners

HPHC Institute



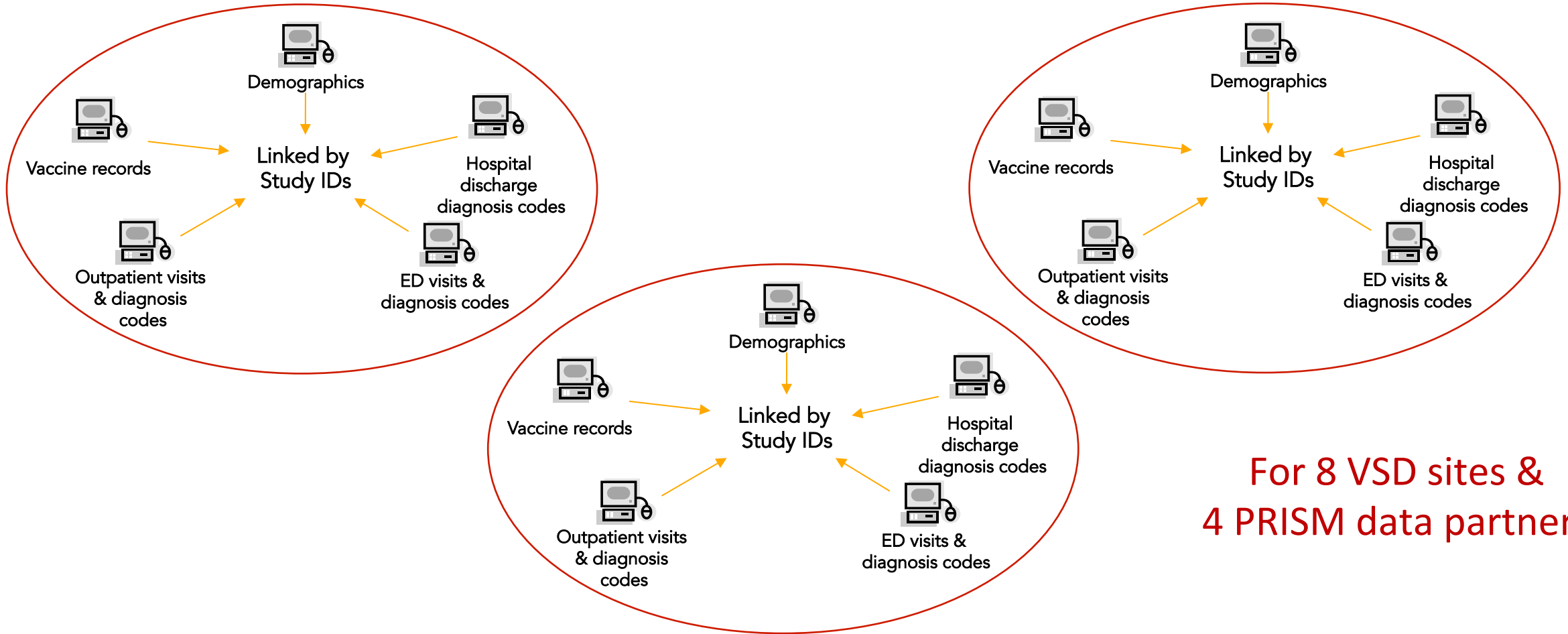
Data and scientific partners



Scientific partners



VSD and PRISM: Person-Level Files at Multiple Sites



For 8 VSD sites &
4 PRISM data partners

Distributed Data Model for Confidentiality

Individual
health plans

Updates person-level files
on vaccine exposure
and outcomes (e.g. weekly, monthly)

Coordinating
Center

Submits programs to each site
to provide aggregate counts of
vaccines and health outcomes
without person-level identifiers

Scientific
Partners

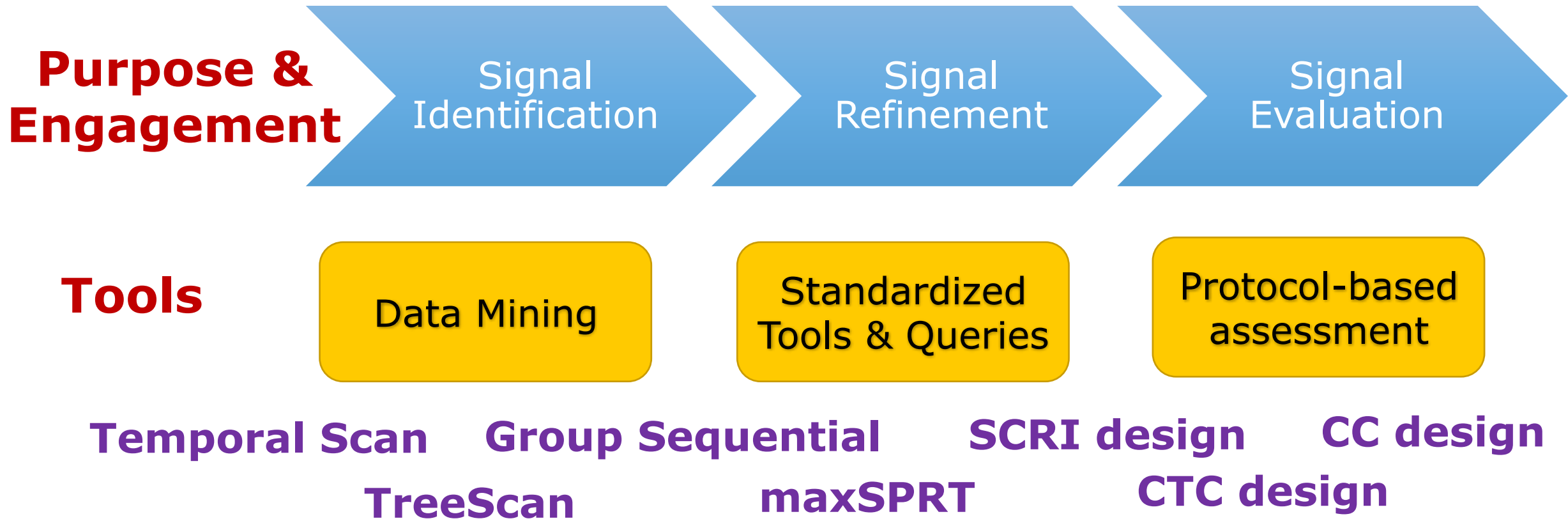
Conduct analyses



Communicate

Policy
makers

Framework & Tools (VSD & PRISM)



Collaboration to Generate Evidence for Decision-Making in 2 Systems

- Rotavirus Vaccine and Intussusception (PRISM)
 - Rare outcome
 - Conflicting findings
 - Power needed
- Inactivated Influenza Vaccine and Febrile Seizures (VSD)
 - Common outcome
 - New finding
 - Timeliness needed
- Getting the right data to the right people at the right time and in the right format

Rotavirus Vaccine & Intussusception – Conflicting Evidence

- 1999-RotaShield withdrawn <1 year post-licensure for excess risk of IS (10-20 cases per 100,000)
- RotaTeq (2006) and Rotarix (2008) licensed for use after Phase III trials with >70,000 and >60,000 infants - no increased risk of IS found
- Post-licensure studies had conflicting findings*
- PRISM asked to evaluate risk for IS in a **large population** of infants

Rotavirus and IS Protocol

- Partnership with 3 national insurers, academia and FDA
 - Epidemiologists, Biostatisticians, Clinicians, Regulatory Decision-makers, Project Managers, Programmer Analysts, Medical Record Review Teams
- 560,000 infants given ~1.4 million doses
- Self Controlled Risk Interval design used, adjusting for time-varying risk of IS
- Medical record review to validate exposures and outcomes

The NEW ENGLAND
JOURNAL of MEDICINE

- RotaTeq Dose 1 was associated with an increased risk of IS in U.S.
- Temporal cluster on Days 3-7
- Attributable risk ranged from 0.2-3.2 excess cases/100,000 doses for first dose vaccinees
- "FDA has approved required revisions to the Prescribing Information and Patient Information for RotaTeq as a result of the new safety data from this Mini-Sentinel PRISM study."

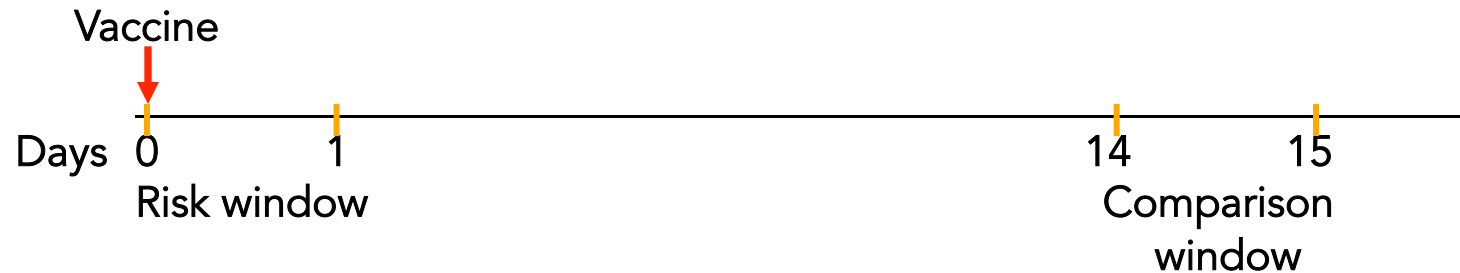
ABSTRACT

Febrile Seizures in Australia– New finding

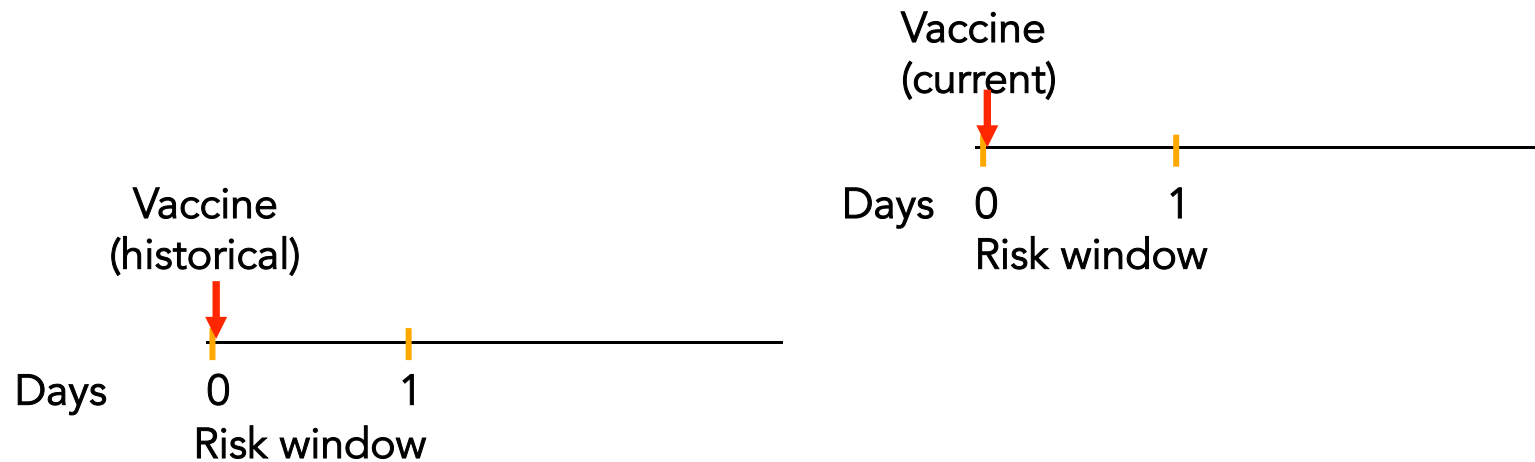
- Increased risk of FS in children <5 years following trivalent inactivated influenza vaccine (TIV) in the Summer of 2010
 - Rate of FS 9x higher than expected (~900 per 100,000 doses) in 1 vaccine manufacturer
 - No elevated risk seen for other TIV products
- Use of CSL vaccine was suspended for young children in both Australia and the U.S.
- VSD asked to conduct **near real-time surveillance** for FS during the 2010-11 season

Signal Identification – Tools available

- Primary approach: Self controlled risk interval design (SCRI)



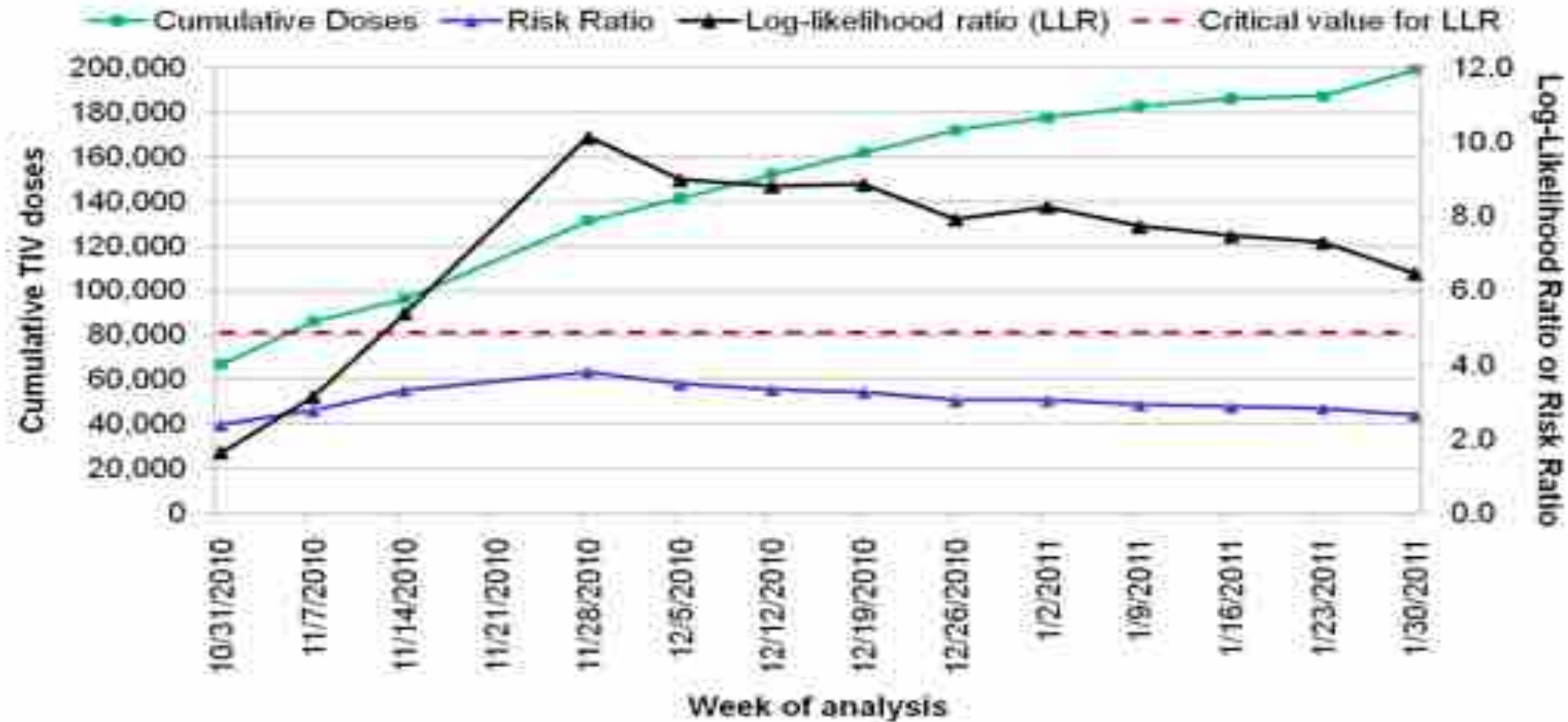
- Alternative approach: Current vaccinated vs. historical vaccinated



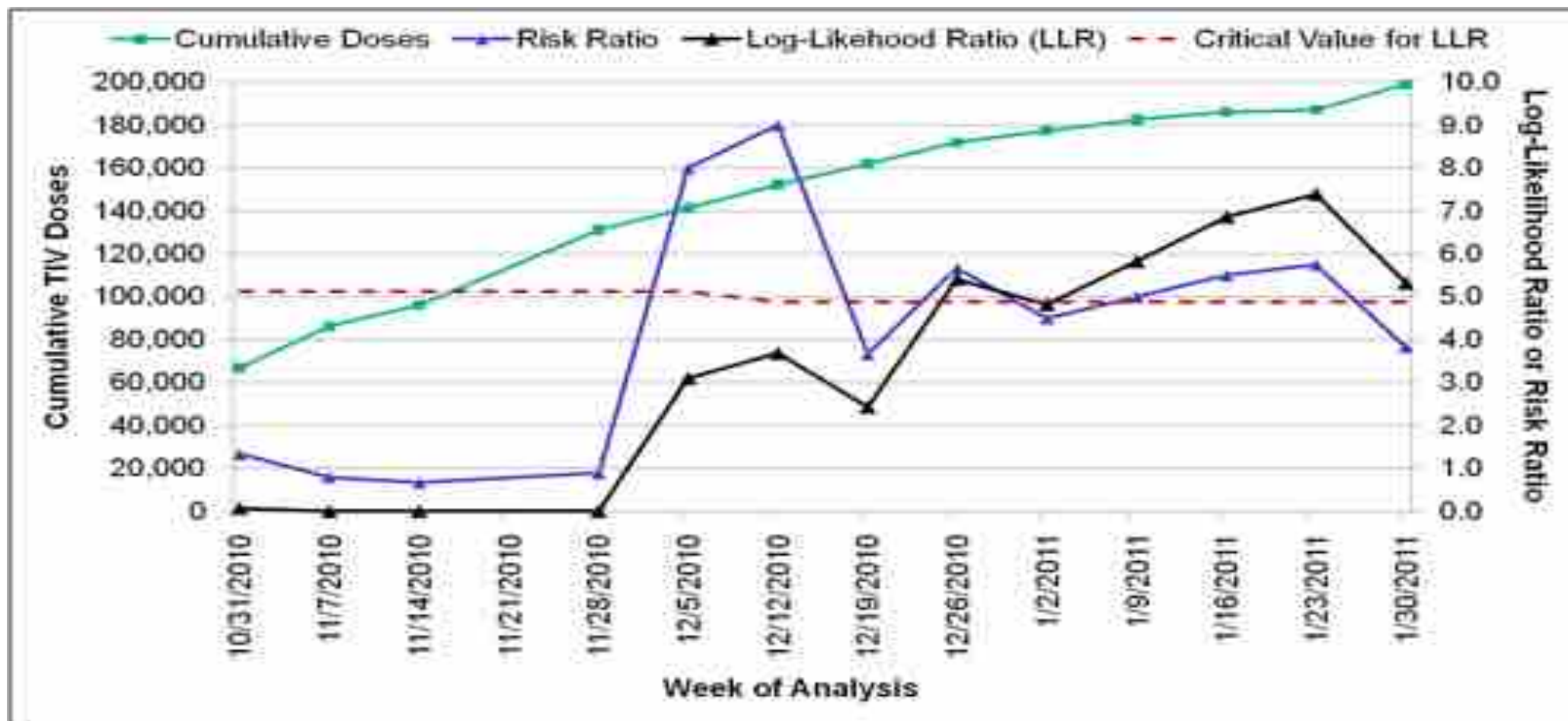
Sequential Analysis–Tools available

- Use sequential statistical methods to account for repeated testing done weekly
- Maximized sequential probability ratio test (maxSPRT) uses the log likelihood ratio (LLR)
 - Null hypothesis rejected if the LLR reaches a “critical value”
 - SCRI design → Binomial maxSPRT
 - Current vs. historical design → Poisson maxSPRT

Current vs. Historical, 6-59 mo



Self-Controlled Risk Interval, 6-59 mo



Signal Refinement & Evaluation

SCRI Design, Medical Record Review & Adjusted for Additional Confounders



Signal identification and evaluation for febrile seizures following trivalent inactivated influenza vaccine (TIV) during the 2010-2011 influenza season: Vaccine Safety Datalink Project, 2010-2011

Alison T. ...
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- Concomitant influenza and PCV13 vaccines were associated with an increased risk of febrile seizures
- Risk of febrile seizures was higher in 2010-11
- Attributable risk varied by age, peaking at 45 per 100,000 doses at 16 months of age
- VIS and Label change

...where, an increased risk of febrile seizures was noted in young children... 24 h after receipt of trivalent inactivated influenza vaccine (TIV) manufactured by CSL... Although the CSL TIV vaccine was not recommended for use in young children in the US... during the 2010-2011 influenza season near real-time surveillance was conducted for febrile seizures in the 0-7 days following first dose TIV in a cohort of 206,174 vaccinated children ages 6 through 59 months in the Vaccine Safety Datalink Project. On a weekly basis, surveillance was conducted with the

Presented data to CDC, ACIP, AAP SOID and WHO (GACVS)

BEFORE

- Assumed decisions would depend on the quality of the data and our choice of study design and analytic approaches
- Focused on making sure these findings were robust (i.e. giving decision makers the best possible information available)

AFTER

- They believed our findings, but...
- Strong and varying opinions on what to recommend
 - Timing of communication regarding a “signal”?
 - Modifications to the immunization schedule to minimize risk of adverse events?

Influenza Vaccine

Inactivated

What You Need to Know

2012 - 2013

Many Vaccine Information Statements are available in Spanish and other languages.
See www.immunize.org/vis.

Hojas de Información Sobre Vacunas están disponibles en Español y en
muchos otros idiomas. Visite <http://www.immunize.org/vis>

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What are the risks from inactivated influenza vaccine?

Moderate problems:

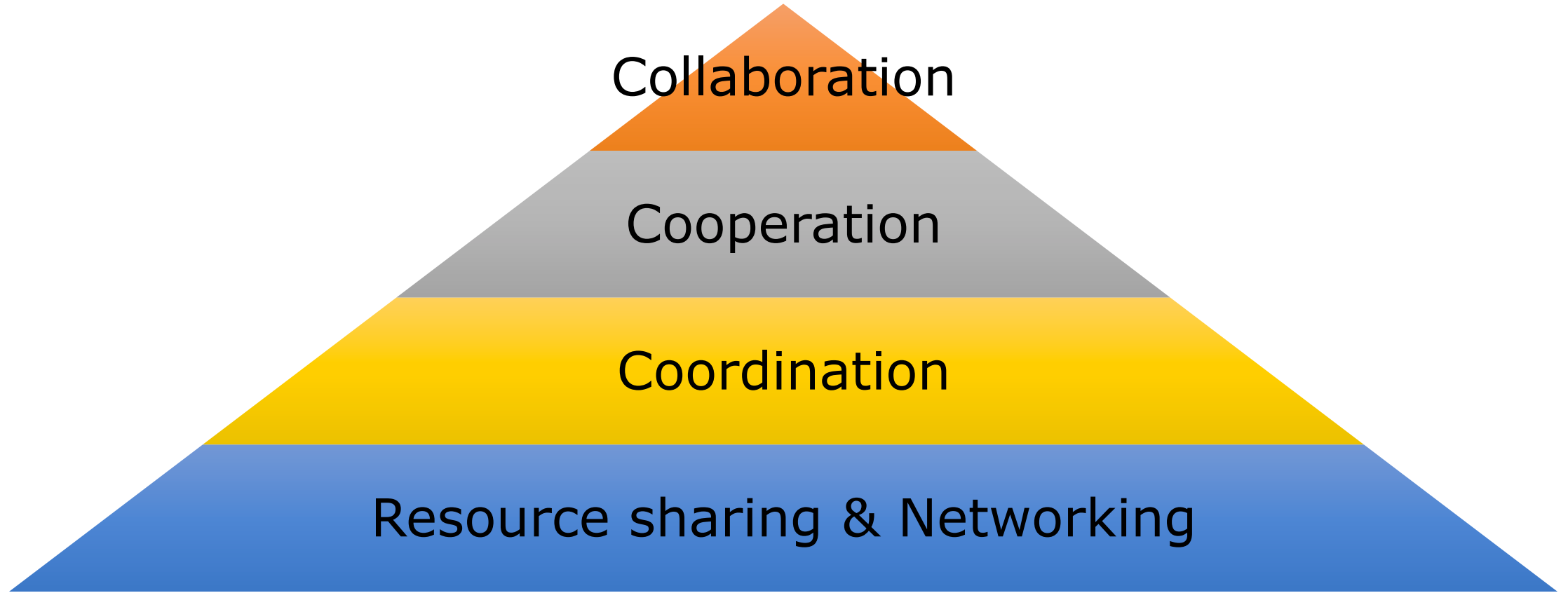
Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time appear to be at increased risk for seizures caused by fever. Ask your doctor for more information.

Tell your doctor if a child who is getting flu vaccine has ever had a seizure.

Decision-Making in Context

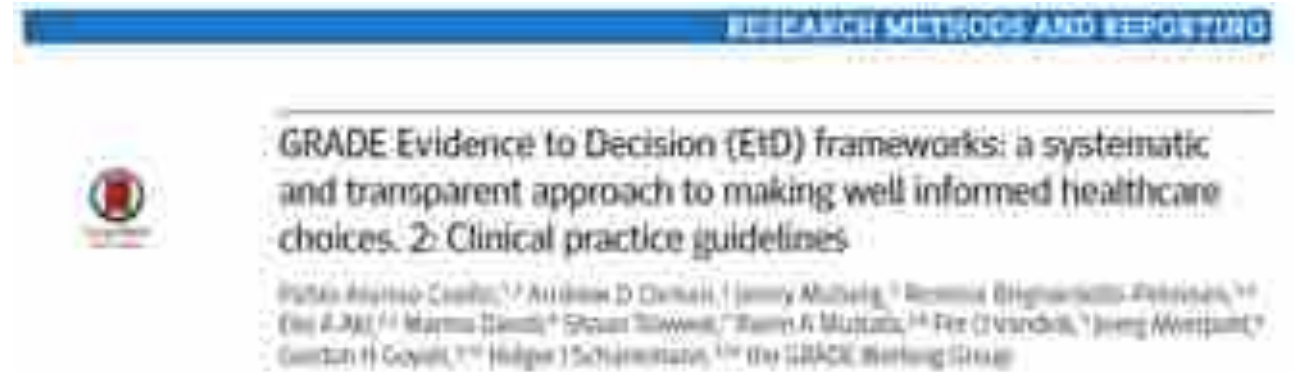
- If you give two smart, reasonable people (or organizations) the same information about benefits and risks, they can make different choices. Why?
 - Thresholds for decision-making may be different
 - Implicit values may be driving decisions
 - Uncertainty affects how each of us makes decisions
 - Mental models may drive our response to uncertainty
 - Need for transparency raises the stakes
- Reconsidering recommendations to incorporate new information demonstrates a robust and ongoing DM process, not a failure

Stages of Collaboration



Understanding Perspective*

- Mindset of clinicians and policy makers
 - Anticipate the impact of alternative findings
 - Address barriers to acceptance
- Drivers of decision making



- B-R assessment
- Outcome Importance
- Uncertainty
- Resource Use
- Health Equity
- Acceptability
- Feasibility

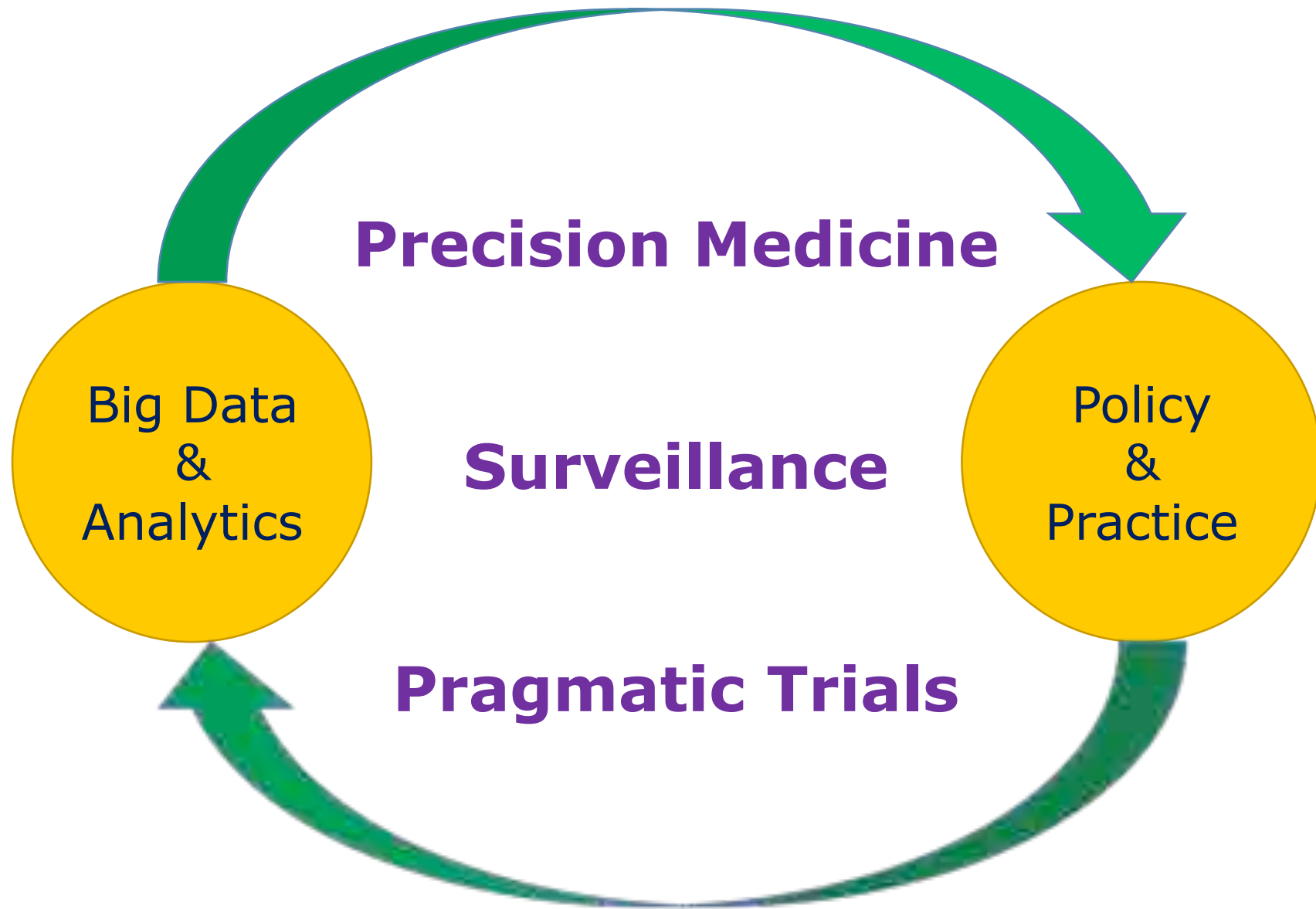
Improvement Mindset



Build Culture into the System

Culture is important for sustainability:

- Develop a shared vision
 - Patients, public health, population health
- Establish values, standards and norms
 - Language is important
 - “When you speak to local authority representatives... it’s like talking to an alien.” (Public Health Academic)
- Create opportunities for connection & communication



VSD RCA Collaborators - Partial List (>125 VSD staff)

Centers For Disease Control, VSD team

- Frank DeStefano, MD
- Mike McNeil, MD
- Claudia Vellozzi, MD MPH
- Eric Weintraub, MPH
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- Julianne Gee, MPH
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Harvard Pilgrim Health Care

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Marshfield Clinic Research Foundation.

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PRISM Collaborators



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 - Sandra Feibelman
 - David Cole
 - Lauren Zichetella
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 - Megan Reidy
 - Ashleigh Goff
 - Tricia Kennedy
- FDA/CBER
 - Steve Anderson
 - Azadeh Shoaibi
 - Michael Nguyen
 - David Martin
 - Robert Ball
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 - Rich Platt
 - Jeff Brown
 - Darren Toh
 - Nicolas Beaulieu
 - Roberta Constantine
 - Susan Forrow
 - Kim Lane
 - Jim Marshall
 - Lisa Trebino
 - Melisa Rett
- And many, many other MS Collaborators

