Integrating Sentinel into Routine Drug Review: A Snapshot of the First Year

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Disclosure

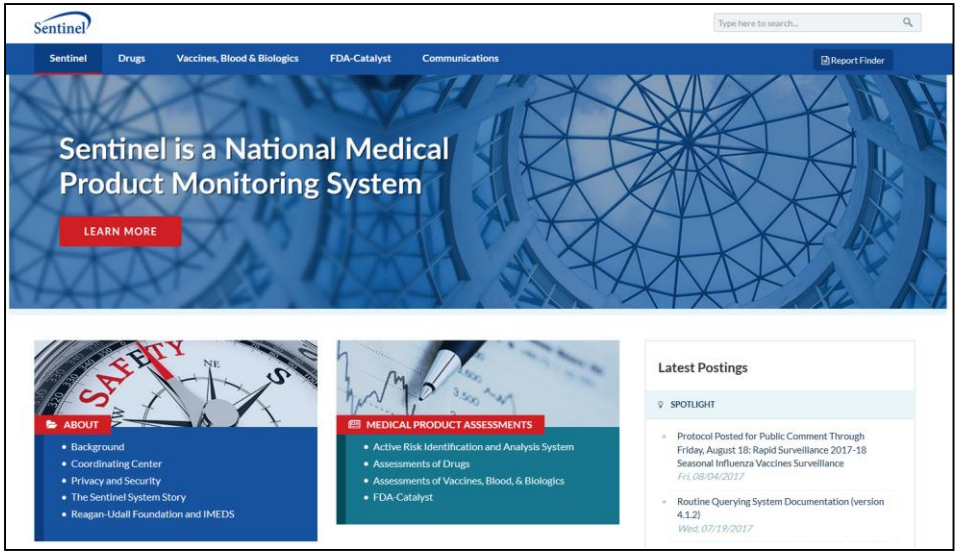
- Nothing to disclose

- This presentation reflects the views of the author only and should not be construed to represent FDA's official views or policies

FDA Sentinel System

- National medical product monitoring system
- 17 data partners with 178 million members with pharmacy and medical coverage
- Distributed system where data partners retain physical control of data to protect privacy and security

https://www.sentinelinitiative.org/



Data Partners

1. Aetna
2. Blue Cross Blue Shield of Massachusetts
3. HealthCore, Inc.
4. Harvard Pilgrim Health Care Institute
5. HealthPartners Institute
6. Humana Comprehensive Health Insights, Inc.
7. Marshfield Clinic Research Foundation
8. Meyers Primary Care Institute
9. Hospital Corporation of America
10. Kaiser Permanente Colorado
11. Kaiser Permanente Hawaii
12. Kaiser Permanente Mid-Atlantic
13. Kaiser Permanente Northern California
14. Kaiser Permanente Northwest
15. Kaiser Permanente Washington Health Research Institute
16. Optum: Optum Epidemiology
17. Vanderbilt University Medical Center

https://www.sentinelinitiative.org/data-partners

February 3, 2016

"Since our launch in 2008, we've been committed [to building the Sentinel Initiative]. We've had a successful Mini-Sentinel pilot and we have now transitioned – I can declare – Mini-Sentinel to a fully functioning Sentinel System, which was the vision and body that Congress directed us to do."

Janet Woodcock, MD
Director, Center for Drug Evaluation & Research
8th Annual Sentinel Initiative Public Workshop

https://healthpolicy.duke.edu/sentinel

Four L2 Analyses in this Symposium

Propensity Score Matching L2 tool

Venous thromboembolism after oral contraceptives
By David Moeny

Stroke after antipsychotics medications
By Lockwood Taylor

Self-controlled L2 tool

Seizures after ranolazine
By Efe Eworuke

Seizures after gadolinium based contrast agents
By Steve Bird

Requirement to Consider Sufficiency of ARIA before PMR

Section 905
Mandates creation of ARIA

Section 901
New FDAAA PMR authority

"The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the **active postmarket risk identification and analysis system** as available under subsection (k)(3) will not be **sufficient** to meet the purposes set forth in subparagraph (B)."

FDAAA = FDA Amendments Act 2007

Defining ARIA Sufficiency

- **Adequate data**
  - Drug of interest and comparator
  - Health outcome of interest
  - Confounders and covariates
- **Appropriate methods**
- **To answer the question of interest**
  - assess a known serious risk related to the use of the drug
  - assess signals of serious risk related to the use of the drug
  - identify an unexpected serious risk when available data indicate the potential for a serious risk
- **To lead to a satisfactory level of precision**

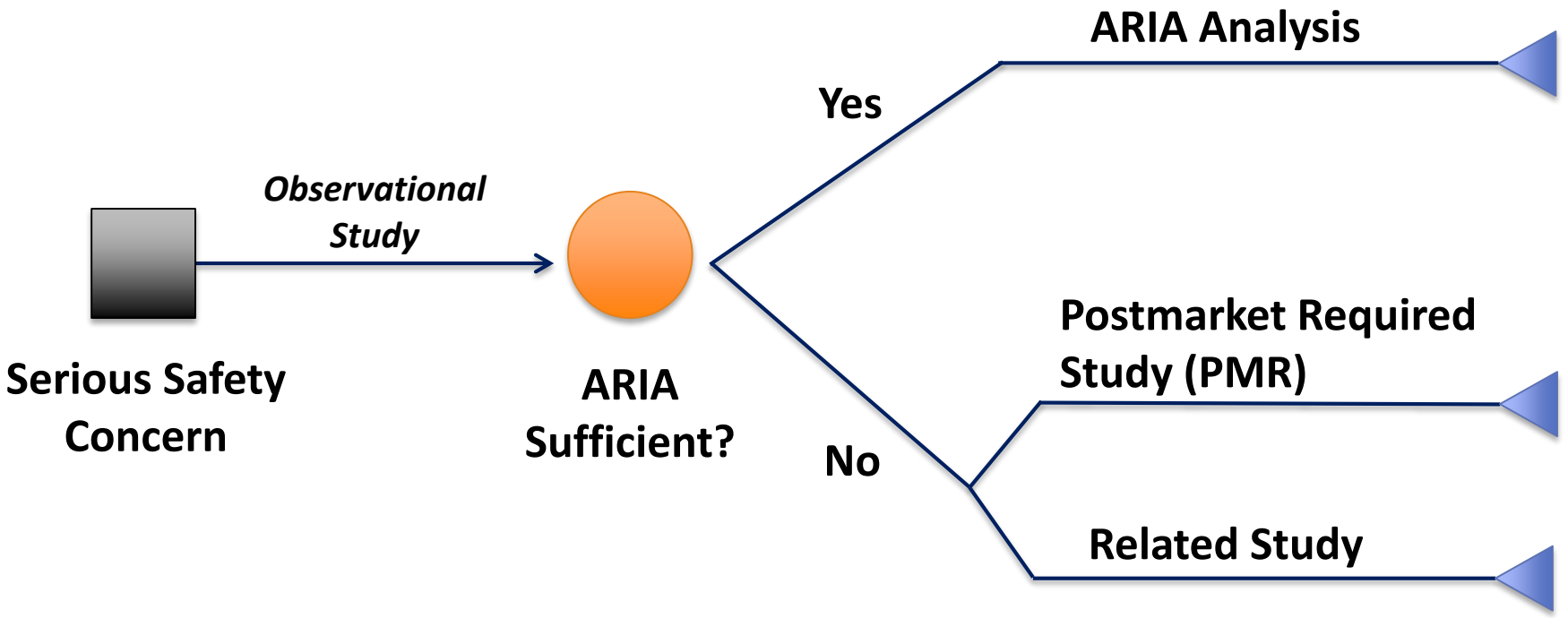
Defining ARIA

ARIA is a subset of Sentinel's full capabilities

* Pre-defined, parameterized, and re-usable tools that enable safety surveillance in Sentinel (in contrast to protocol based assessments with fully customized programming)

† Electronic claims data, without manual medical record review

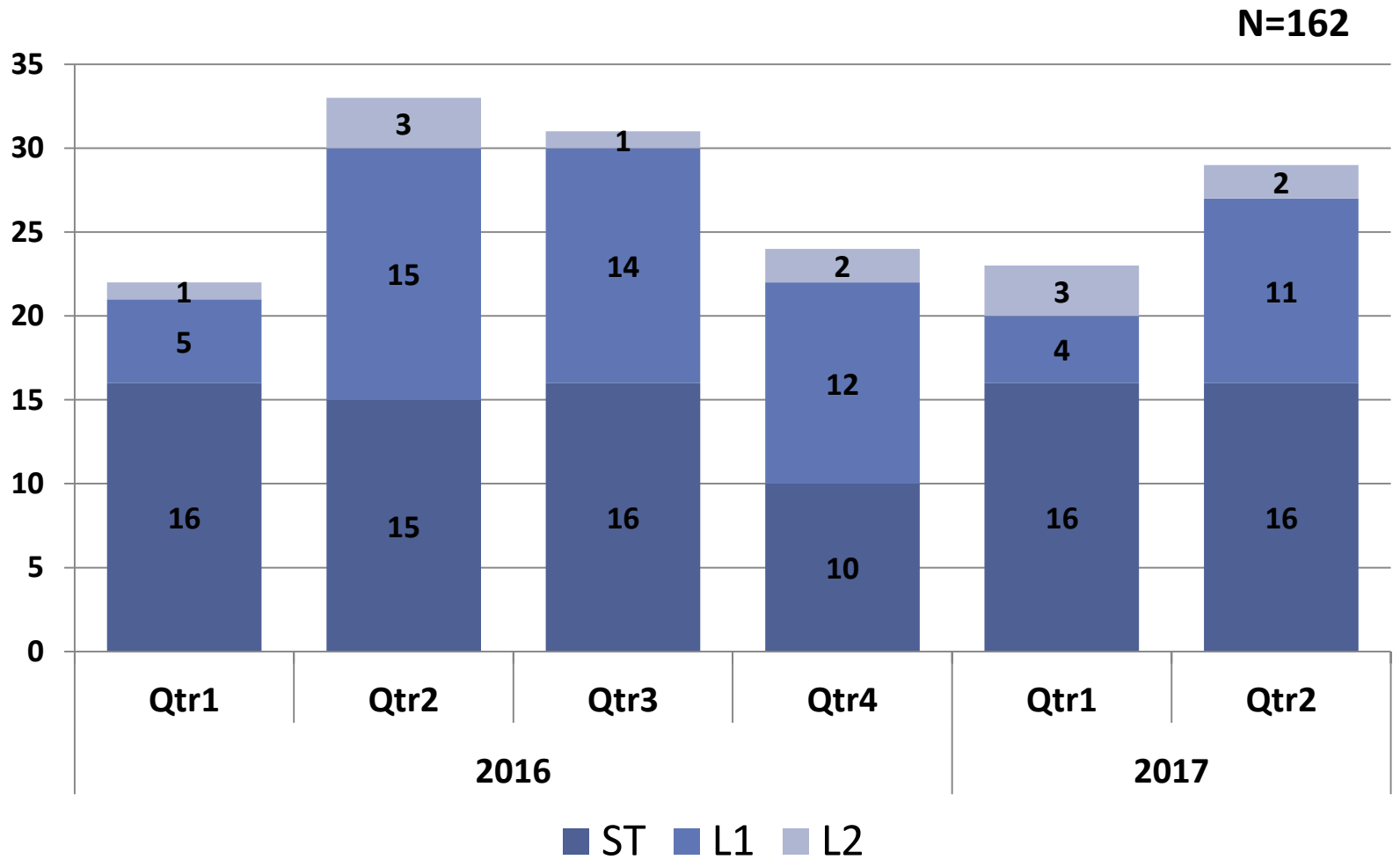
ARIA Must Be Considered Before a PMR Can be Issued



- ARIA is now integrated into the overall framework for drug safety in CDER
- ARIA sufficiency is assessed whenever further characterization of a safety issue is needed (i.e., for tracked safety issues)

Reaching the Goal with the Right Tools

ARIA Analyses by Quarter, FDA-wide



By date of distribution to data partners

Sentinel

Type here to search...

Sentinel | Drugs | Vaccines, Blood & Biologics | FDA-Catalyst | Communications | Report Finder

Sentinel is a National Medical Product Monitoring System

LEARN MORE

ABOUT

- Background
- Coordinating Center
- Privacy and Security
- The Sentinel System Story
- Reagan-Udall Foundation and IMEDS

MEDICAL PRODUCT ASSESSMENTS

- Active Risk Identification and Analysis System
- Ongoing ARIA Assessments
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics
- FDA-Catalyst

DATA & SURVEILLANCE TOOLS

- Distributed Database and Common Data Model

COMMUNICATIONS

- FDA Safety Communications

Latest Postings

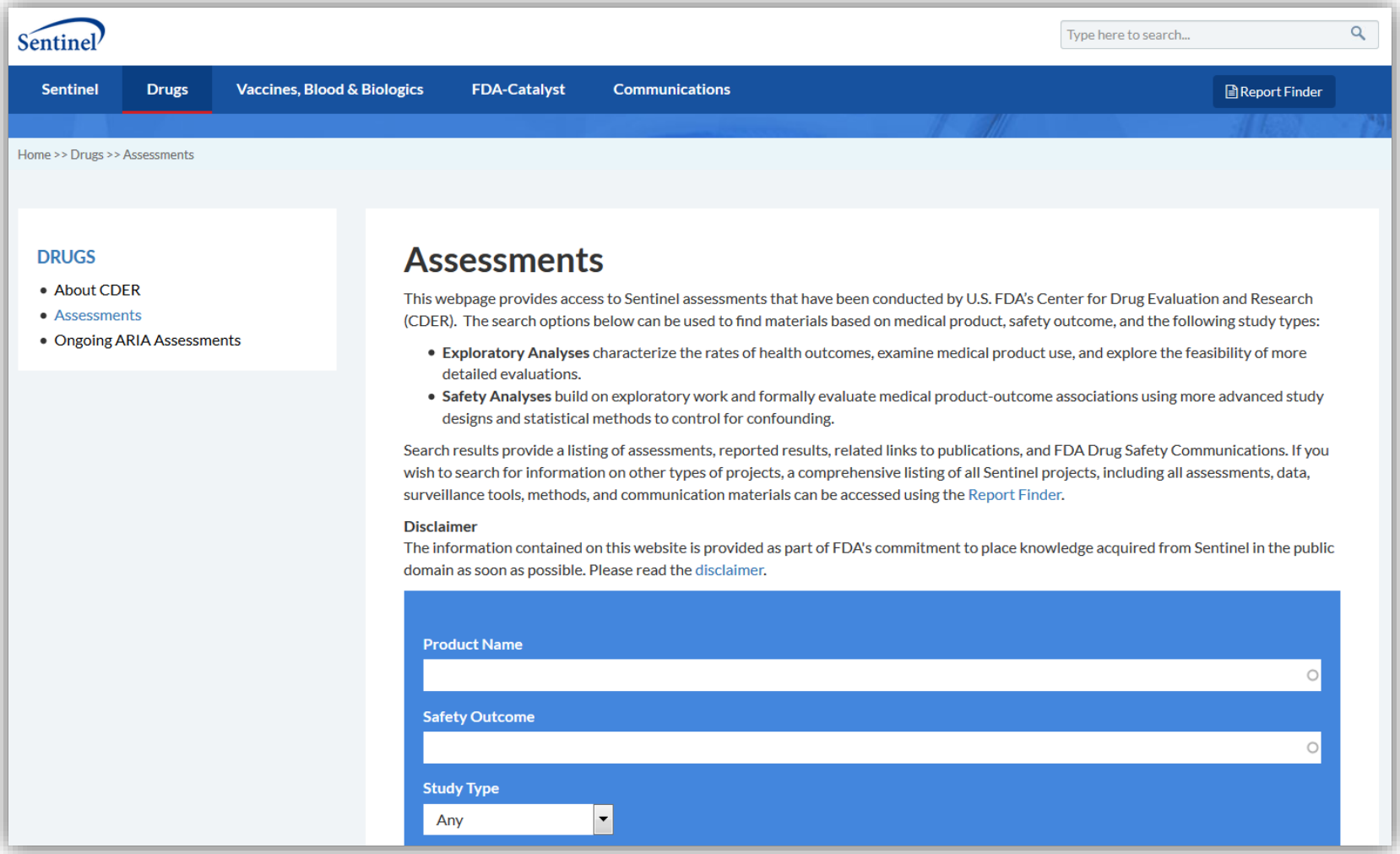
SPOTLIGHT

- Ongoing ARIA Assessments
  Wed, 08/23/2017
- Routine Querying System Documentation (version 4.1.2)
  Wed, 07/19/2017
- Sentinel Common Data Model v6.01
  Wed, 04/26/2017

ONGOING PROJECTS

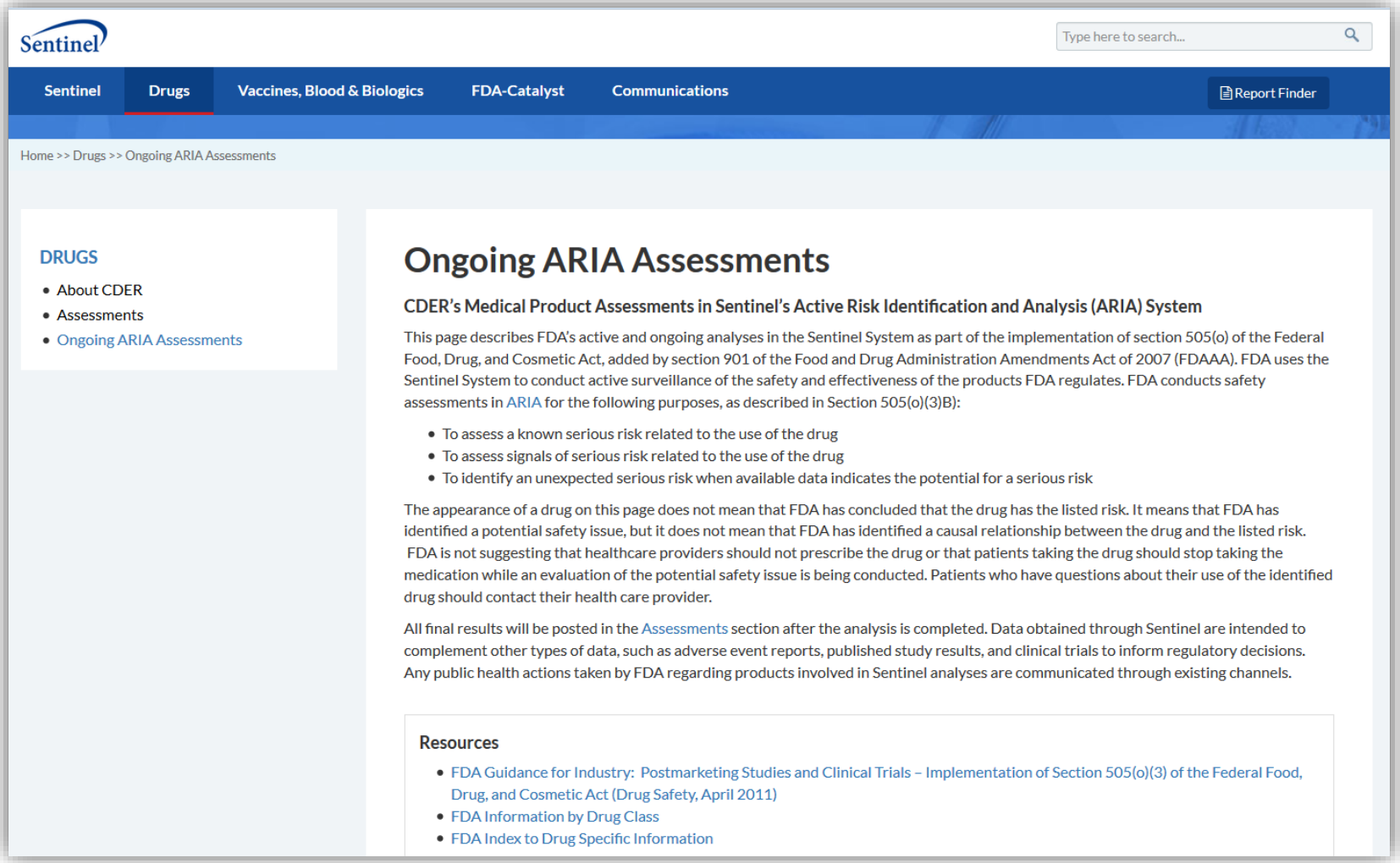
- Inverse Probability of Treatment Weighting Functional Specifications and Prototype Development
  Thu, 08/24/2017

Where to Find Results



https://www.sentinelinitiative.org/drugs/assessments

Where to Find Ongoing Analyses



https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments

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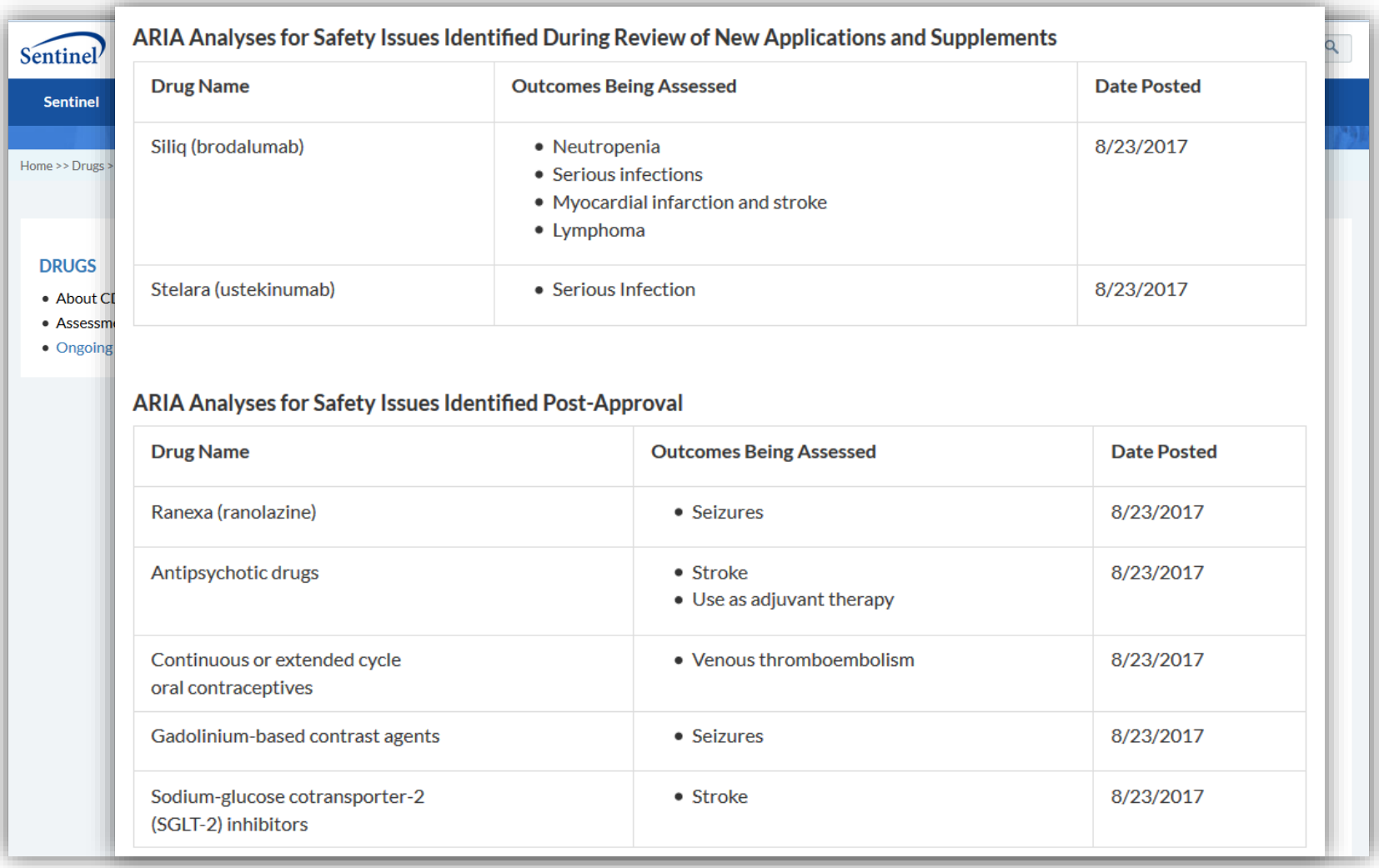


ARIA Analyses for Safety Issues Identified During Review of New Applications and Supplements

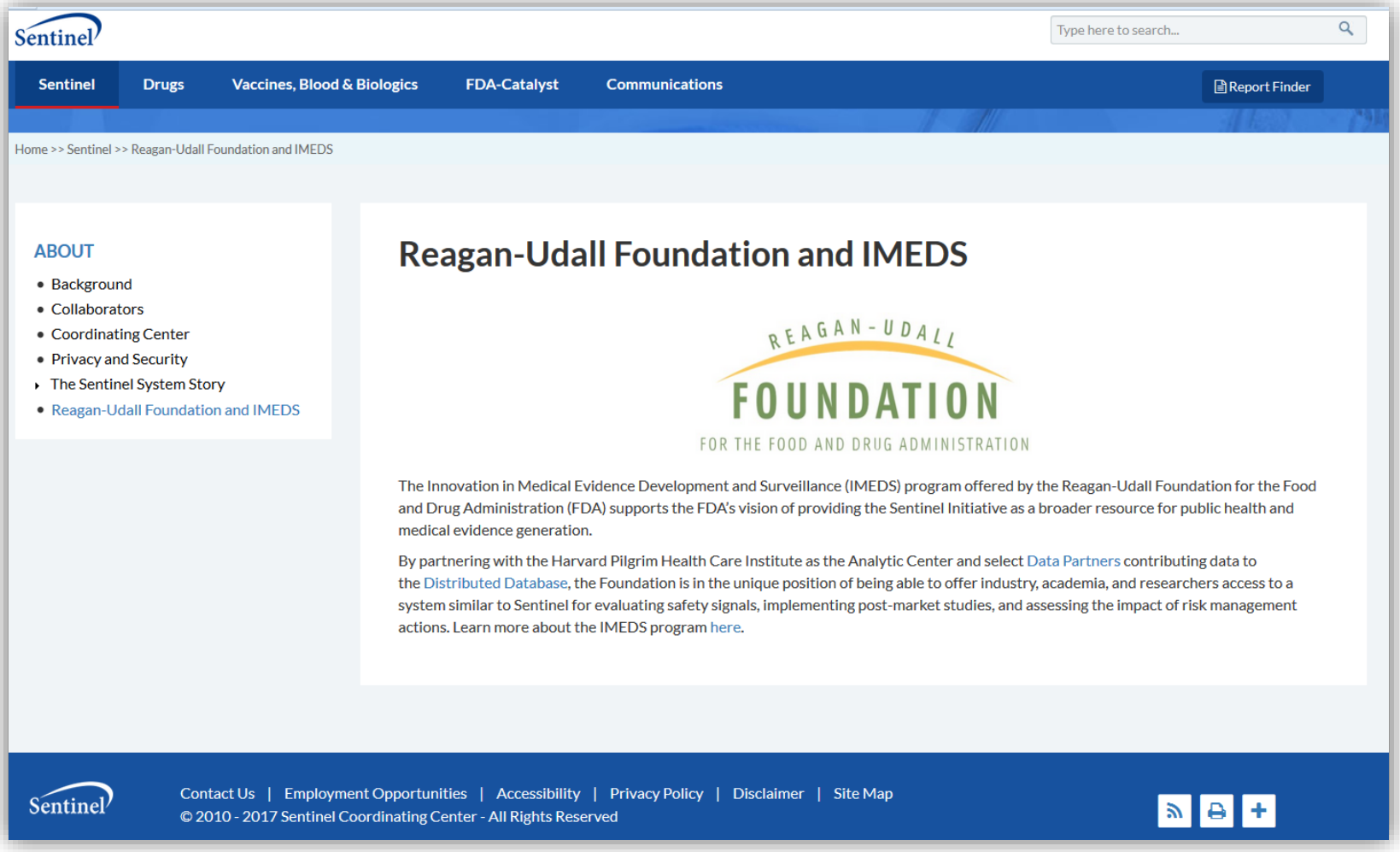
Drug Name	Outcomes Being Assessed	Date Posted
Siliq (brodalumab)	• Neutropenia • Serious infections • Myocardial infarction and stroke • Lymphoma	8/23/2017
Stelara (ustekinumab)	• Serious Infection	8/23/2017

ARIA Analyses for Safety Issues Identified Post-Approval

Drug Name	Outcomes Being Assessed	Date Posted
Ranexa (ranolazine)	• Seizures	8/23/2017
Antipsychotic drugs	• Stroke • Use as adjuvant therapy	8/23/2017
Continuous or extended cycle oral contraceptives	• Venous thromboembolism	8/23/2017
Gadolinium-based contrast agents	• Seizures	8/23/2017
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	• Stroke	8/23/2017

https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments

Making Sentinel Available to Others

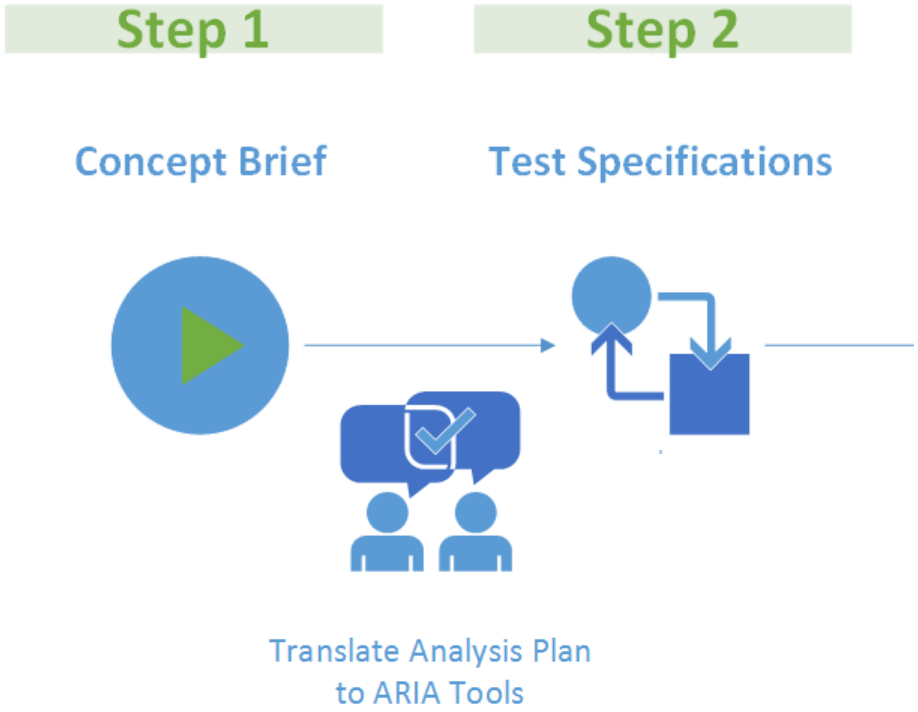


https://www.sentinelinitiative.org/sentinel/reagan-udall-foundation-and-imeds

IMEDS and Sentinel

http://reaganudall.org/innovation-medical-evidence-development-and-surveillance

Query Development Process



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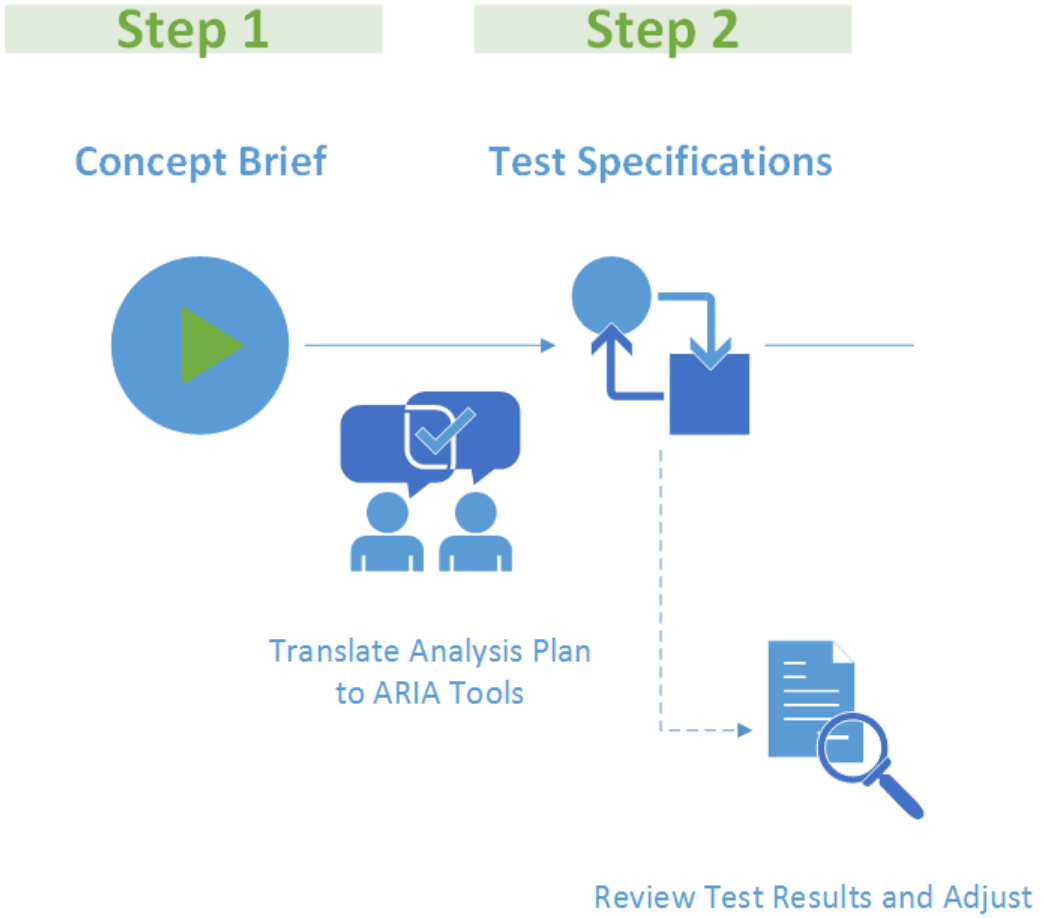

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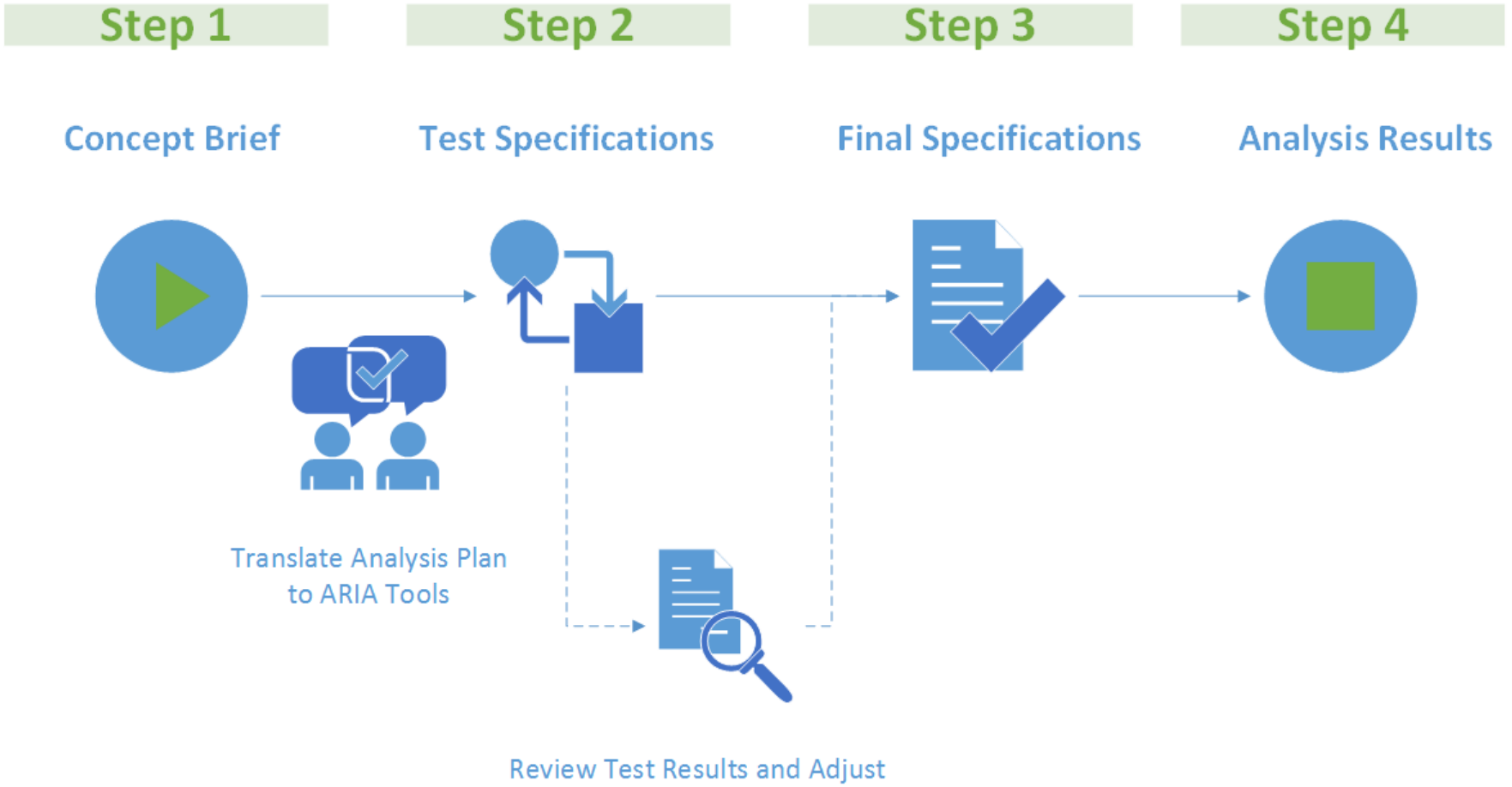
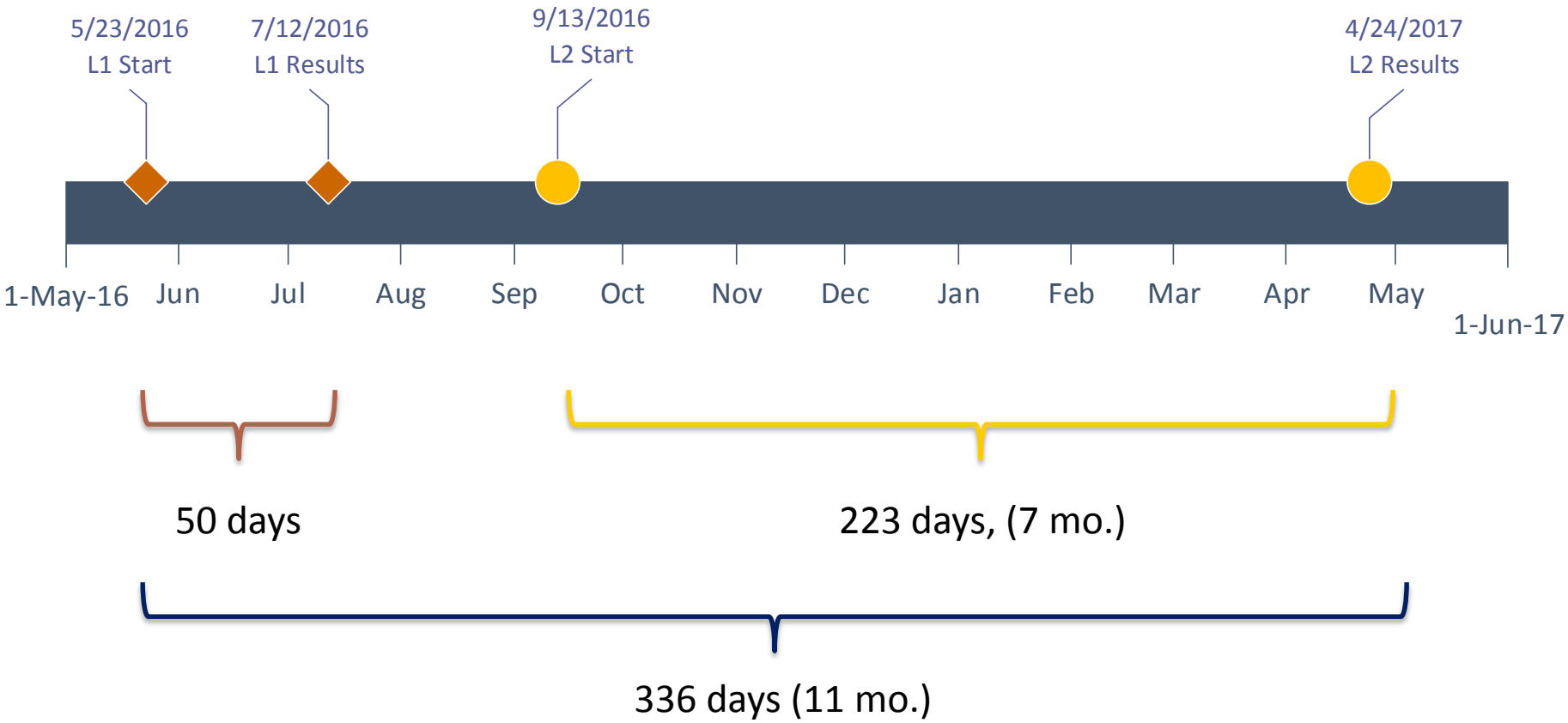
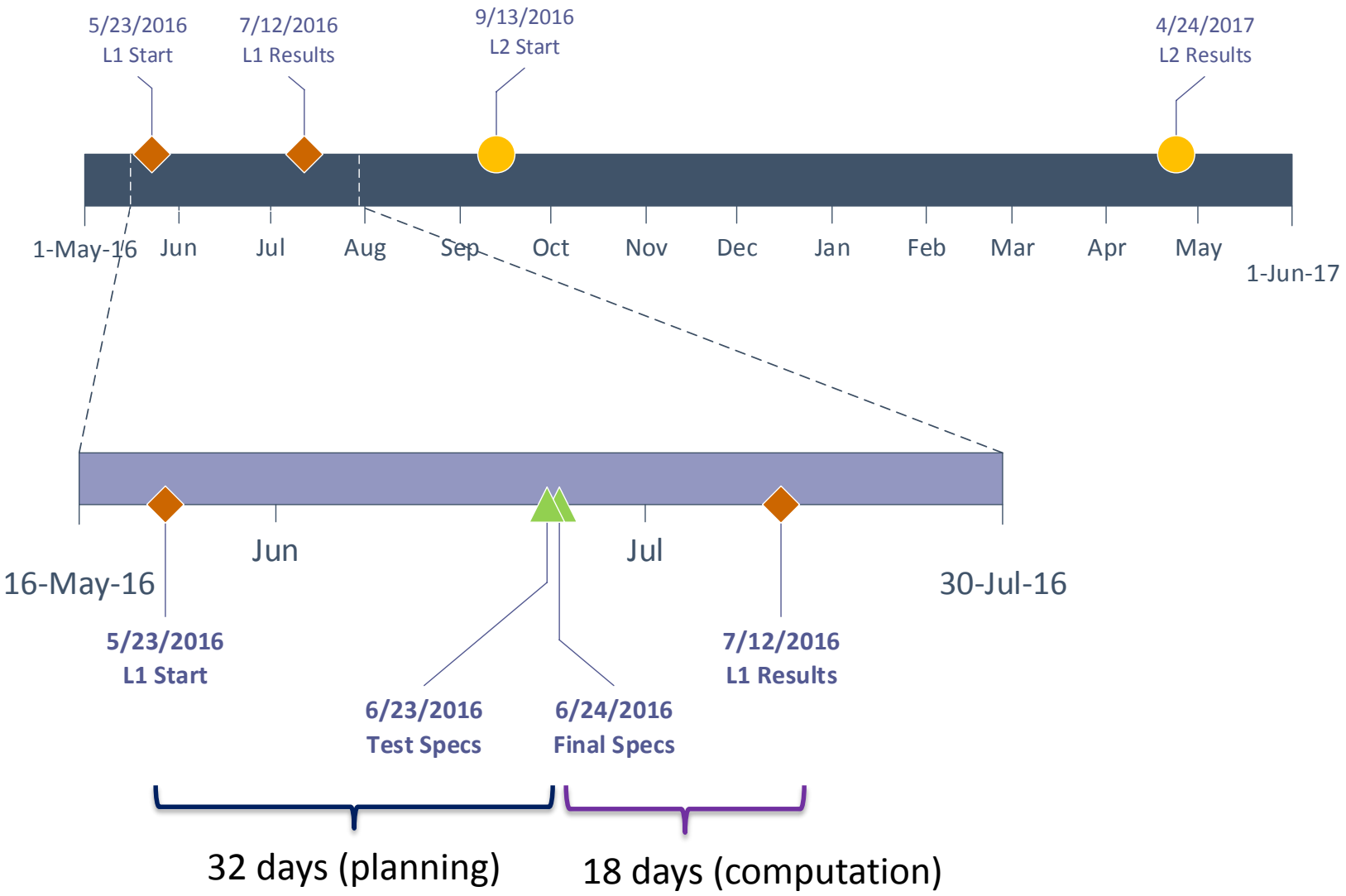


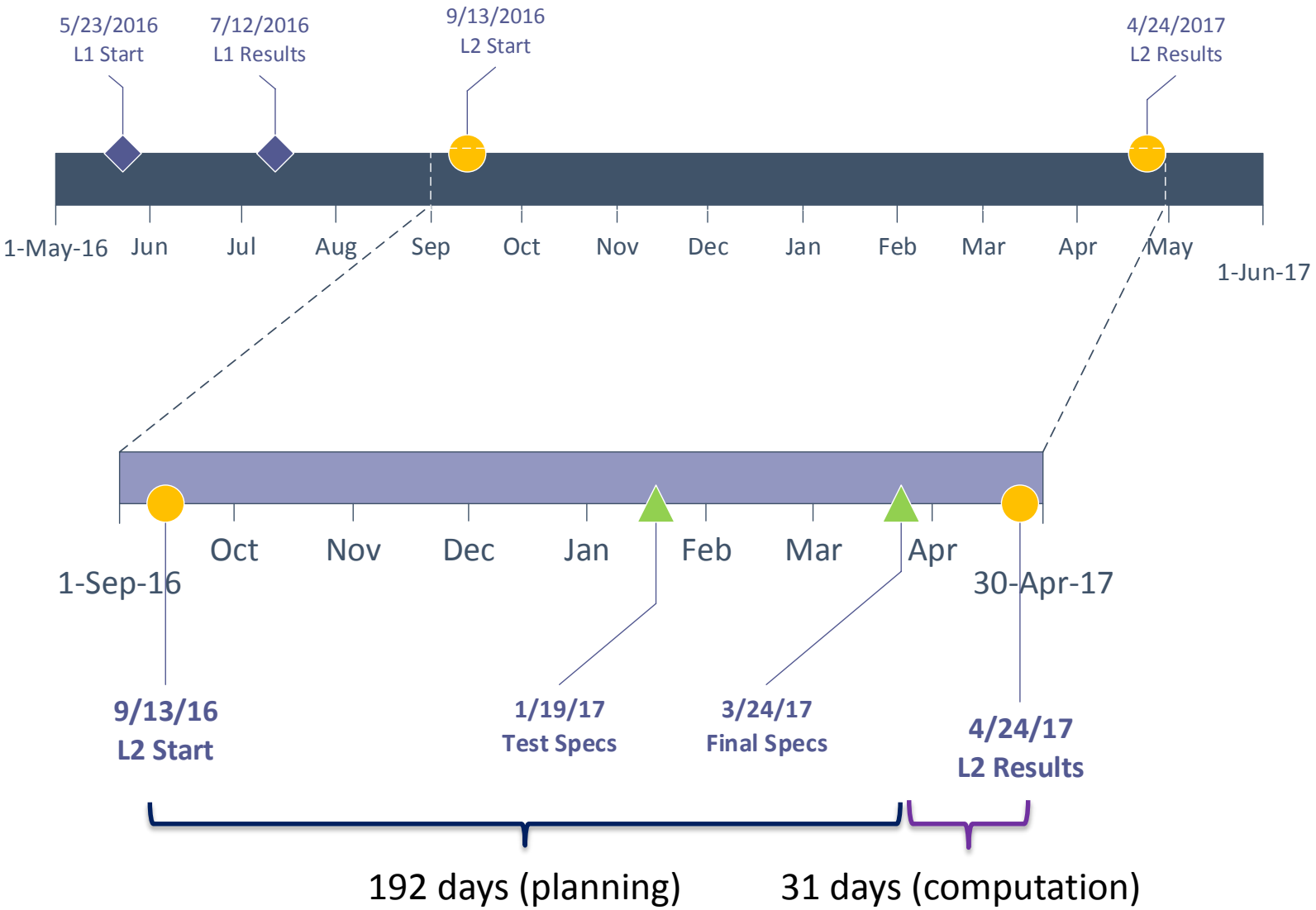
Example Timeline: Oral Contraceptives



Detailed Timeline: L1



Detailed Timeline L2



Total Time to Assess Safety Issue

Safety Issue	Type and No. Analyses	Total Time, days
Ranexa (ranolazine)	ST, L1, L2	302 (10 mo.)
Gadolinium contrast agents	L1, L2	741 (24 mo.)
Antipsychotics	L1, L2	277 (9 mo.)
Oral contraceptives	L1, L2	336 (11 mo.)

- ST = Summary table, simple counts
- L1 = Level 1, complex descriptive analysis
- L2 = Level 2, inferential analysis

ARIA: A Snapshot of the 1st Year

- Since activation in 2016, ARIA has been used robustly in CDER to evaluate the safety of FDA approved drugs
- Evaluating ARIA sufficiency informs strategic development of Sentinel System
- Each safety analysis relies upon the full complement of ARIA tools and can be completed in <12 months
- ARIA tools accelerate computation time, but do not abbreviate study design or planning process
- ARIA tools are a flexible, efficient analytic platform to meet FDA's mission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