Sentinel Journey from Safety Question to Regulatory Action

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent the policies of the U.S. Food and Drug Administration

First, some background….

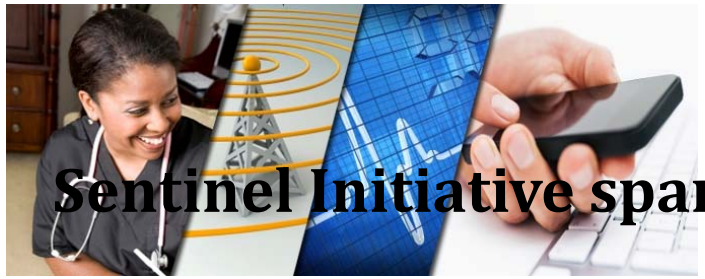
FDA regulates drugs and…

Food

Vaccines, Blood & Biologics

DRUGS

Safe and Effective



Medical Devices

Animal & Veterinary

Tobacco Products

Cosmetics

Radiation-Emitting Products

Sentinel Initiative spans multiple centers…

Source of images: fda website or fda flickr site

Center for Drug Evaluation and Research
Office of Biostatistics

Over 170 statisticians across 8 divisions,
Expertise in regulatory statistics in all phases of drug development across many drug therapeutic areas

Office of Biostatistics Regulatory Science Day, September 2014

Safety in (New) Drug Development

Drug Reasonably Safe for use in Humans

Marketing Application and Review of Benefits and Risks

Basic Research
Discovery
Preclinical

Randomized Clinical Trials

Post-Market Assessments

Div. of Biometrics 6

Div. of Biometrics 1-5

Div. of Biometrics 7

Safety Profile of The Drug

Safety Surveillance

Adapted from http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM207568.pdf

Why Post-Market Assessment? Example, Dabigatran

Approved on 10/2010 to reduce the risk of stroke in patients with atrial fibrillation

	PRADAXA 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% CI)
Patients randomized	6076	6022	
Stroke	123	187	0.64 (0.51, 0.81)
Ischemic stroke	104	134	0.76 (0.59, 0.98)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

How will the 2-3 million people in US with atrial fibrillation fare on this drug?

Randomized patients			
Patient-years			
Intracranial hemorrhag			
Life-threatening bleed	183 (1.5)	221 (1.9)	0.81 (0.67, 0.99)
Major bleed	409 (3.4)	426 (3.6)	0.94 (0.82, 1.08)
Any bleed	1997 (16.6)	2169 (18.4)	0.91 (0.85, 0.96)

*Patients contributed multiple events and events were counted in multiple categories.

Source: Pradaxa label, RE-LY Study

Post-Market Safety Assessment Data Include…

- Post-market randomized studies, observational studies and meta-analyses
- FDA adverse reporting system (FAERS)
- **FDA led observational studies***
  - **With Sentinel**
  - With SafeRx/federal data partners (CMS, DoD, VA)

*Section 905 of Food and Drug Administration Amendments Acts (09/2007)

Sentinel and Mini-Sentinel

Acknowledgments

My team in the Div. of Biometrics 7 is involved in *ongoing* projects investigating the safety of newly approved anticoagulants discussed today. However, most projects discussed today were initiated and/or completed prior to my involvement

- Special thanks to: Rongmei Zhang (DB7), Mark Levenson (DB7), Marsha Reichman (OSE), Mary-Ross Southworth (OND)

Take Home Messages

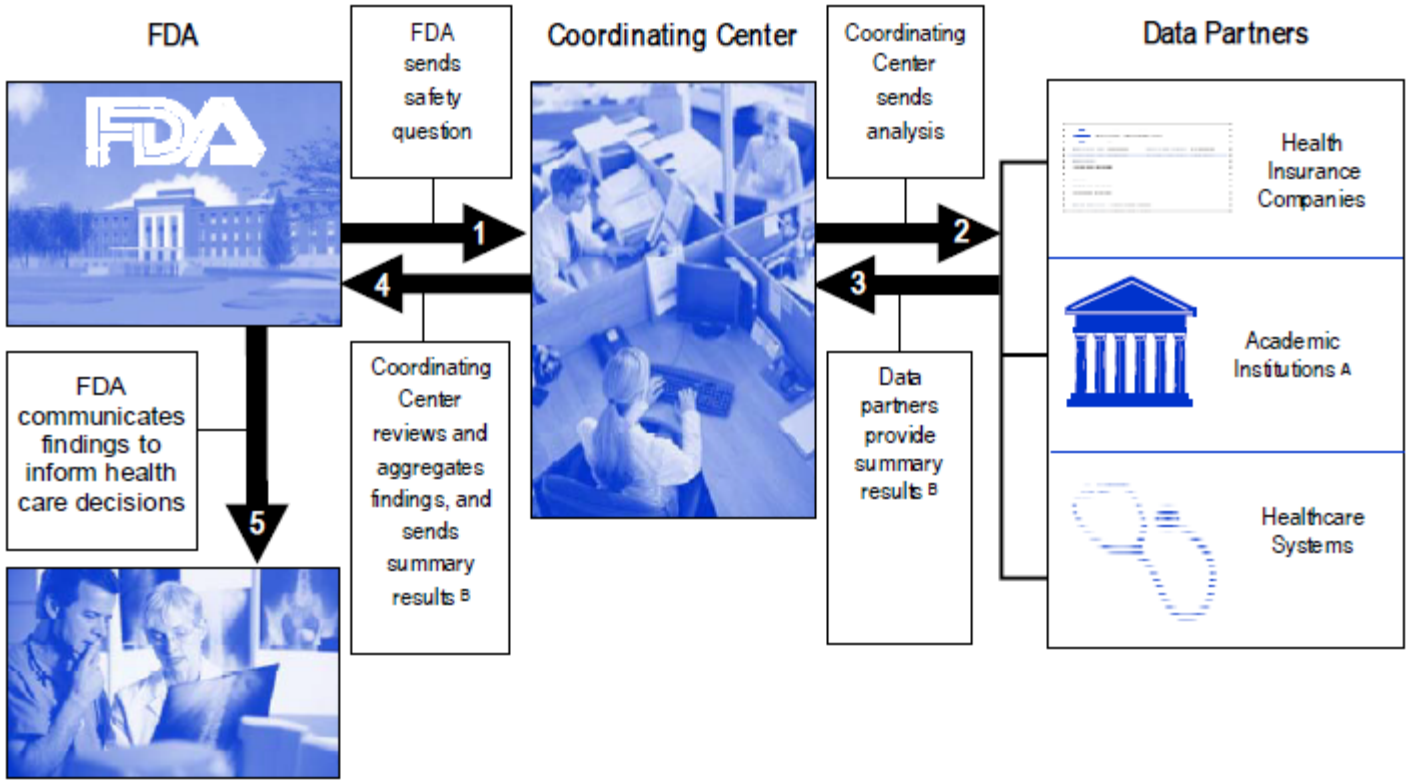
- Sentinel is an *active* surveillance system, one of many sources of safety data at FDA
- Mini-sentinel pilot implemented a structure to query sentinel and demonstrated its use
- Some methodological challenges lie ahead in post-market safety (Big data/rare outcomes, stratification, sequential analyses)

Sentinel Initiative Vision and Pilot Mini-Sentinel

- National safety *active* surveillance system of drugs and medical products *post-marketing*
- Results of safety *queries* are shared publically

- 48 million people currently accruing new data - 358 million person-years of observation time of drugs and vaccines
- Safety questions, protocols and results in mini-sentinel website

Sentinel System, Distributed Database



A. Only those academic institutions with electronic healthcare data will receive safety questions for evaluation.
B. Data partners will provide summary results from analyses conducted within their secure data environments. Those summary results will not include directly identifiable health information.

Safety Question:
Drug exposure(s) (test/comparator), outcome(s), and population of interest

Data: Electronic Healthcare Data

See FDA Guidance*

Statistical Inference Question: Estimation, detect or rule out risk

Feasibility of safety assessment?
Generalizability to population at risk?

Not Every Safety Question is Feasible in Sentinel

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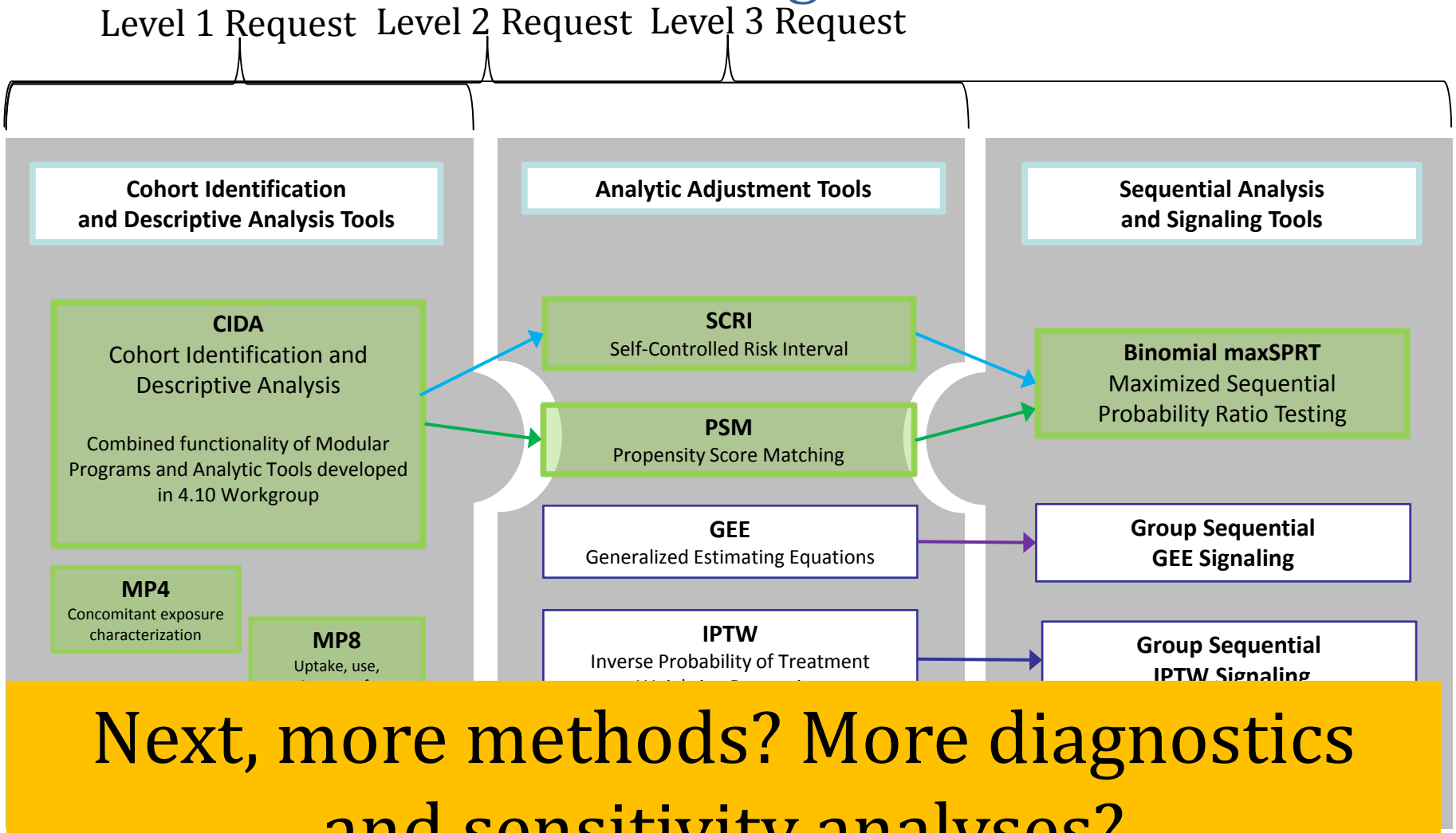
Mini-Sentinel Modular Program, Available Tools



Next, more methods? More diagnostics and sensitivity analyses?

Mini-sentinel, Distributed Database

- In each site
  - Control for confounding
  - Subgroup analyses
- Across sites
  - Stratified analyses of *pooled* results
- Data refresh quarterly

heterogeneity across sites? in time?

Source of logos: Rich Platt's slide at mini-sentinel meeting in February 2015

The Role of the Division of Biometrics 7 in FDA led Projects

- Develop protocol and statistical analysis plans
- [Conduct Analyses]
- Review and interpret results
- Participate in methodology working groups, e.g.
  - Sentinel Survival
  - Sentinel Prospective Monitoring Tools (PROMPT) Enhancement

Sentinel Journey – Dabigatran Example

Reports Of bleeding (FAERS and literature)

Mini-sentinel (level 1) investigation (10/2012)

Approval of Dabigatran (10/2010)

Drug Safety Communication (12/2011) and change in labeling (01/2012)

Drug Safety Communication (11/2012) and NEJM publication

Approval of Rivaroxaban (11/2010)

Approval of Apixaban (12/2012)

Dabigatran Example (continued)

Safety Question

- Population of interest: subjects with atrial fibrillation (2-3 millions Americans)
- Exposure: Dabigatran versus Warfarin (anticoagulants)
- Outcomes:
  - Stroke
  - Serious bleeding

Electronic Claims Data

- Cohort: AF diagnosis and *new* filled prescription of dabigatran or warfarin, other inclusion/exclusion
- Outcomes identified with ICD-9 codes

positive predictive values > 80% for most outcomes

Dabigatran Example (continued) Modular Program Level 1 (10/2012)

Level 1: identifies cohorts of interest and, for some cohorts, can perform descriptive analyses

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

Source: N Engl J Med 2013; 368:1272-1274

Regulatory Actions

FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran)

The FDA has issued new information about this safety issue, see the FDA Drug Safety Communication issued 05-13-2014.

This update is a follow-up to the FDA Drug Safety Communication of 12/7/2011: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
References

Safety Announcement

[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of serious bleeding associated with use of the anticoagulants (blood thinners) dabigatran (Pradaxa) and warfarin (Coumadin, Jantoven, and generics). Following the approval of Pradaxa, FDA received a large number of post-marketing reports of bleeding among Pradaxa users. As a result, FDA investigated the actual rates of gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).[1] (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm

"...large numbers of reported cases of bleeding with dabigatran is an example of stimulated reporting. The Mini-Sentinel assessment suggests that bleeding rates with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY"
-April 2013

Sentinel Journey – Dabigatran Example (continued)

CMS/SafeRx Protocol based Investigation Final statistical Analysis plan (06/2013)

Mini-sentinel Rivaroxaban Protocol Based Assessment (level 3- *like*) (03/2014)

Mini-sentinel Protocol Based Assessment (level 2-*like*) (03/2014)

Drug Safety Communication based on CMS Study (05/2014)

Dabigatran Example
Protocol Based Assessment (level 2 *like* query)

Protocol

Mini-Sentinel

MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

A PROTOCOL FOR ASSESSMENT OF DABIGATRAN

Version 2

March 18, 2014

Prior versions:
Version 1: December 31, 2013

Prepared by: Alan S. Go, MD[1], Daniel Singer, MD[2], T. Craig Cheetham, PharmD MS[3], Darren Toh, ScD[4], Marsha Reichman, PhD[5], David Graham, MD MPH[5], Mary Ross Southworth, PharmD[6], Rongmei Zhang PhD[7], Monika Houstoun, PharmD[5], Yu-te Wu PhD[7], Katrina Mott MS[5], Joshua Gagne, PharmD ScD[8]

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http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Protocol-for-Assessment-of-Dabigatran.pdf

Adjusted Analysis

- New user cohort study
- Propensity score matching by site to control for confounding
- Primary analysis is time to event using cox regression **stratified by site**

Dabigatran Example
CMS – SafeRx Protocol Based Assessment

Circulation

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated with Dabigatran or Warfarin for Non-Valvular Atrial Fibrillation

Running title: *Graham et al.; Comparative safety of dabigatran and warfarin*

David J. Graham, MD, MPH[1]; Marsha E. Reichman, PhD[1]; Michael Wernecke, BA[2]; Rongmei Zhang, PhD[3]; Mary Ross Southworth, PharmD[4]; Mark Levenson, PhD[3]; Ting-Chang Sheu, MPH[2]; Katrina Mott, MHS[1]; Margie R. Goulding, PhD[1]; Monika Houstoun, PharmD, MPH[1]; Thomas E. MaCurdy, PhD[2,5]; Chris Worrall, BS[6]; Jeffrey A. Kelman, MD, MMSc[6]

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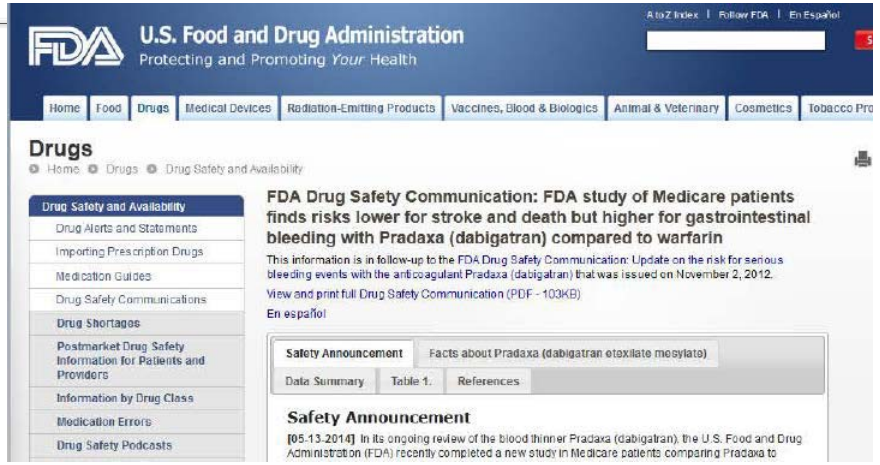
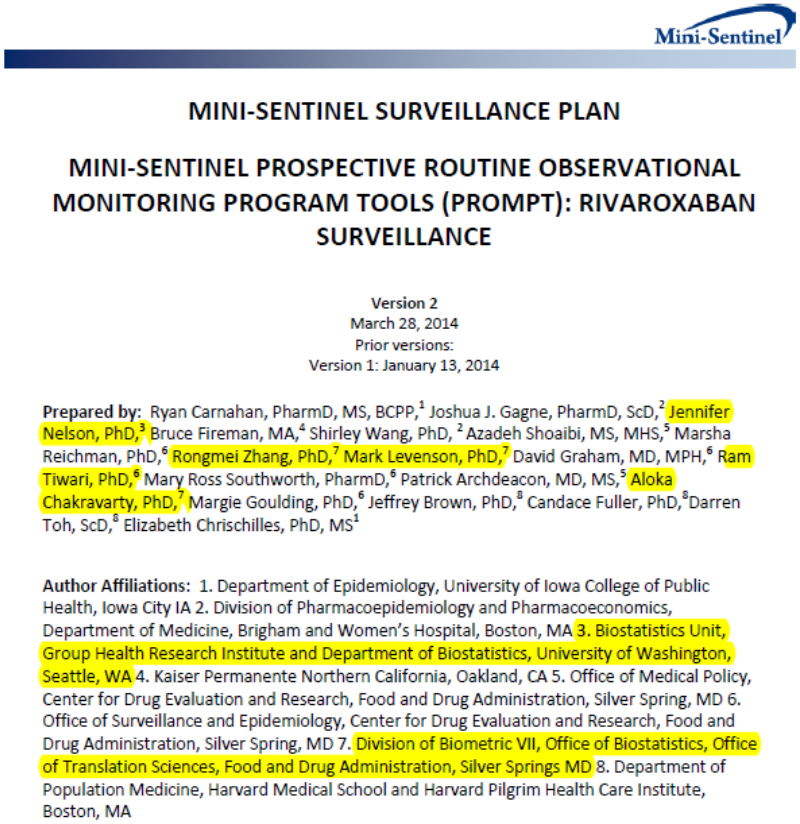


Published online October 2014

"In this study…Pradaxa was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin."
-May 2014

Rivaroxaban Example Protocol Based Assessment (level 3 *like* query)

Protocol



Mini-Sentinel

MINI-SENTINEL SURVEILLANCE PLAN

MINI-SENTINEL PROSPECTIVE ROUTINE OBSERVATIONAL MONITORING PROGRAM TOOLS (PROMPT): RIVAROXABAN SURVEILLANCE

Version 2
March 28, 2014
Prior versions:
Version 1: January 13, 2014

Prepared by: Ryan Carnahan, PharmD, MS, BCPP,[1] Joshua J. Gagne, PharmD, ScD,[2] Jennifer Nelson, PhD,[3] Bruce Fireman, MA,[4] Shirley Wang, PhD, [2] Azadeh Shoaibi, MS, MHS,[5] Marsha Reichman, PhD,[6] Rongmei Zhang, PhD,[7] Mark Levenson, PhD,[7] David Graham, MD, MPH,[6] Ram Tiwari, PhD,[6] Mary Ross Southworth, PharmD,[6] Patrick Archdeacon, MD, MS,[5] Aloka Chakravarty, PhD,[7] Margie Goulding, PhD,[6] Jeffrey Brown, PhD,[8] Candace Fuller, PhD,[8] Darren Toh, ScD,[8] Elizabeth Chrischilles, PhD, MS[1]

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http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_PROMPT_Rivaroxaban-Surveillance-Plan.pdf

Adjusted, Sequential Analyses

- New user cohort study
- Variable ratio propensity score matching by site to control for confounding
- Sequential looks (5) with Pocock stopping boundary
- Primary analysis is time to event using cox regression stratified by site

Sentinel – Some Regulatory Science Challenges

- Regulatory response to a safety signal, considerations of
  - Statistical significance
  - Clinical relevance
  - Benefit-Risk
  - Speed of sharing results with public
  - confidence in results

Take Home Messages

- Sentinel is an *active* surveillance system, one of many sources of safety data at FDA
- Mini-sentinel pilot implemented a structure to query sentinel and demonstrated its use
- Some methodological challenges lie ahead in post-market safety (Big data/rare outcomes, stratification, sequential analyses)

WANT TO GET INVOLVED?

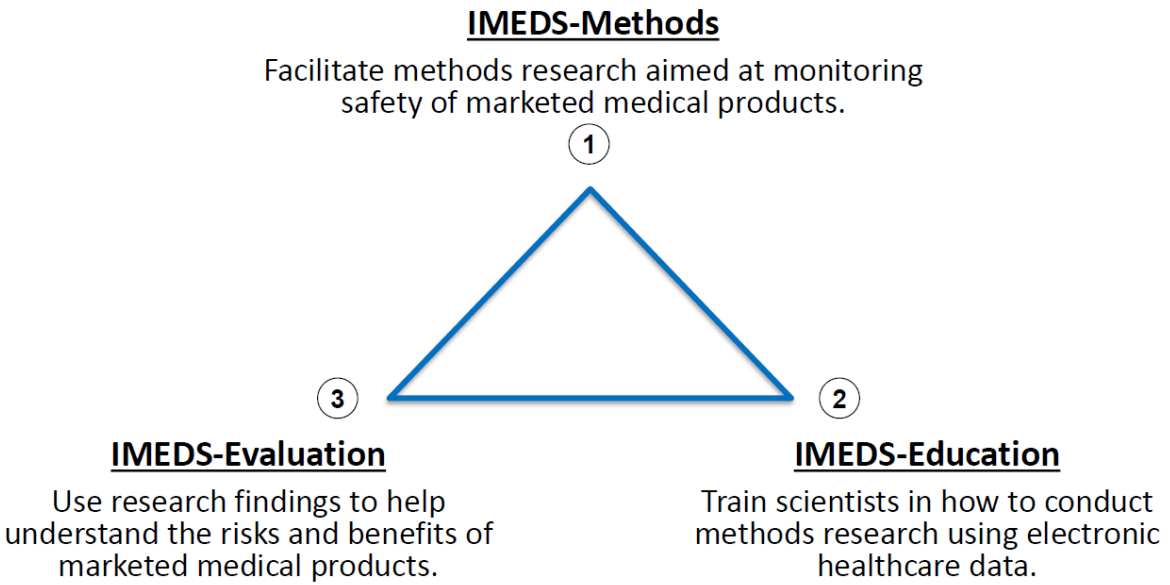
IMEDS Methods

REAGAN - UDALL FOUNDATION FOR THE Food and Drug Administration

IMEDS Program

Key Areas

IMEDS will help the FDA, regulated industry, and clinicians improve patient care and the safety of medical products by focusing on three areas.



Source: Susan Gruber slide at sentinel meeting in February 2015

To find out more…

- Mini-sentinel website

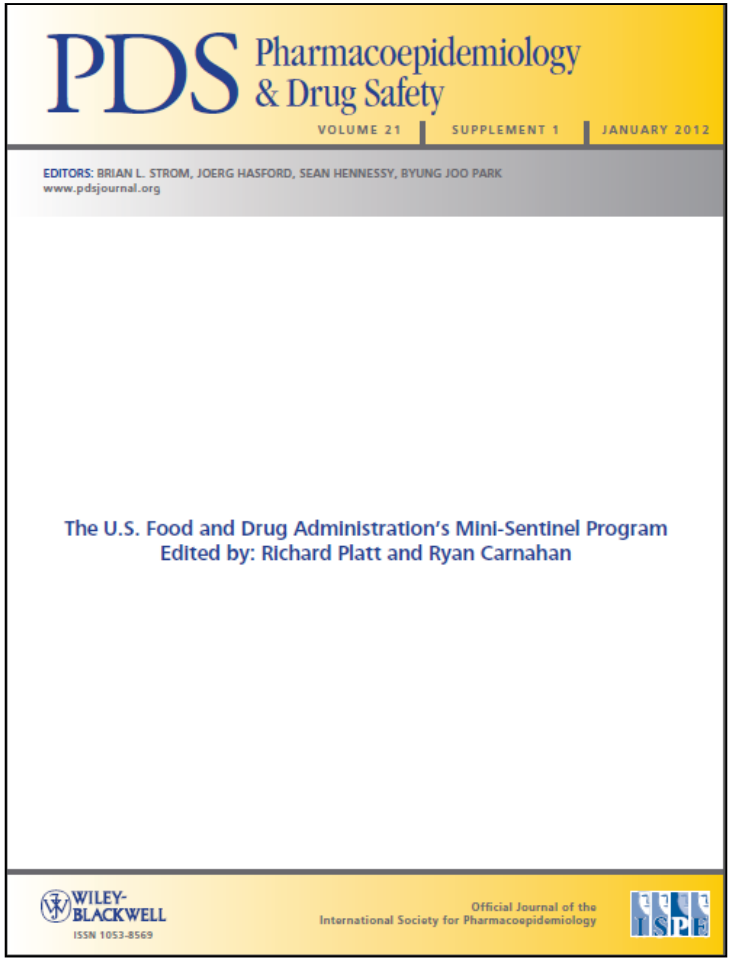
http://www.mini-sentinel.org/

- Sentinel Initiative Public Workshop

http://www.brookings.edu/events/2015/02/05-fda-sentinel-initiative-workshop

- FDA/Sentinel initiative website

http://www.fda.gov/Safety/FDASentinelInitiative/ucm149341.htm



http://onlinelibrary.wiley.com/doi/10.1002/pds.v21.S1/issuetoc

THANK YOU

Back up

Sentinel – Some Data Limitations

- Include claims data, will include more electronic medical records and lab data
- Ascertainment of exposure, drug dispensed and gaps in exposure
- Ascertainment of outcomes
- Ascertainment of confounders
- Safety outcomes are usually r

Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Not Every Safety Question is Feasible in Sentinel

Sentinel – Some Design and Analyses Challenges

- Modeling rare outcomes

- Controlling and/or assessing
  - Unmeasured confounding bias
  - Confounding by indication, channeling biases
  - Selection bias
- Assessing time varying treatments and adhere

Diagnostics and sensitivity analyses are important

Sentinel – Some Design and Analyses Challenges (continued)

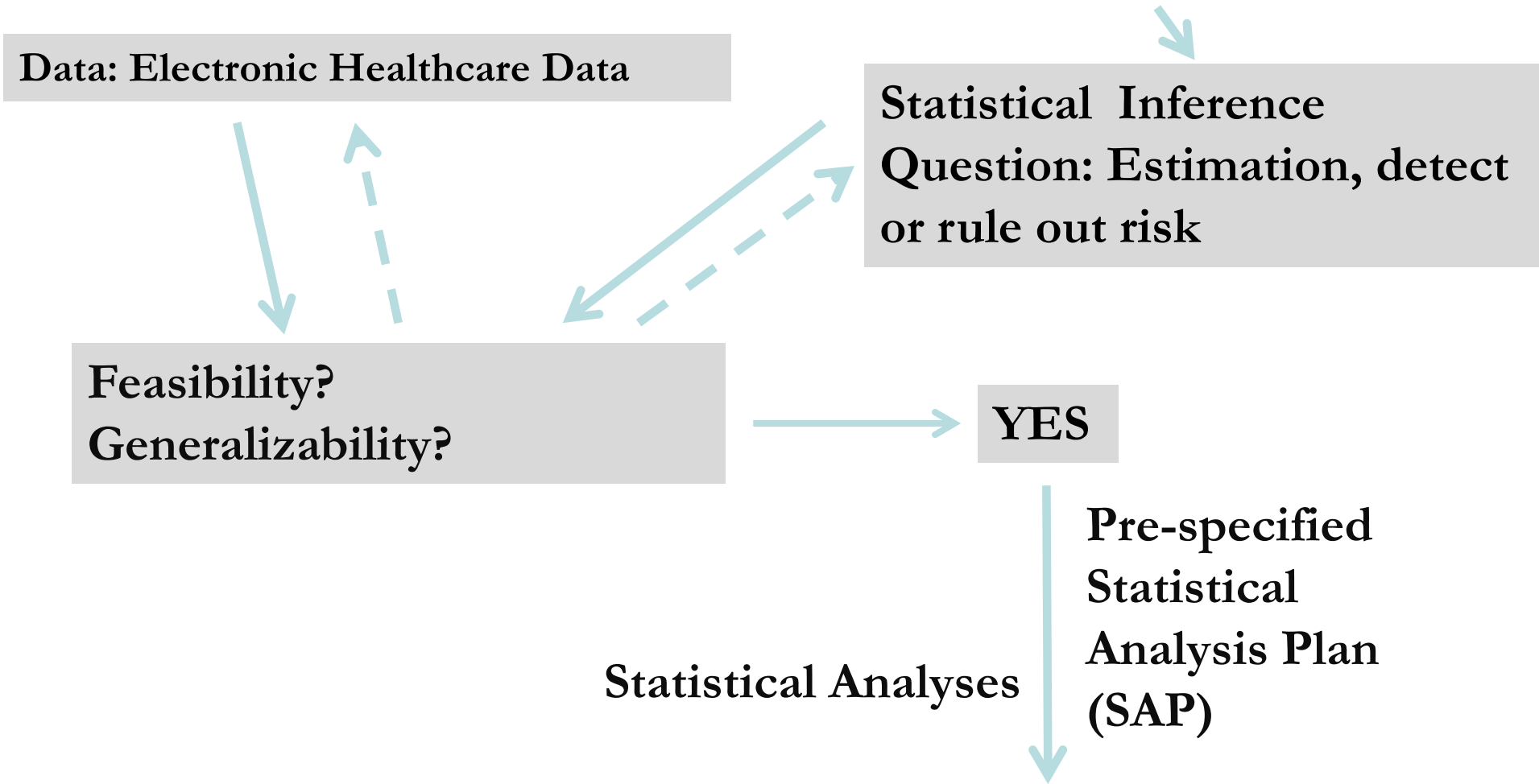
- Working around limit on pooling data across sites
  - Control for confounders in each site
  - Subgroup analyses in each site
  - Simple stratified analyses across sites
- Sequential testing

Assessing heterogeneity across sites and in time is important

Sentinel – Some Regulatory Science Challenges

- Regulatory response to a safety signal, considerations of
  - Statistical significance
  - Clinical relevance
  - Benefit-Risk
  - Confidence in results
  - Speed of sharing results

Safety Question:
Drug exposure(s) (test/comparator), outcome(s), and population of interest



Dabigratran, FAERS reports of Bleeding

Table 1. Leading suspect drugs ranked by number of direct reports to FDA 2011

Rank	Drug Name	Brand Name	Year Approved	Direct Reports
1	DABIGATRAN	PRADAXA	2010	817
2	WARFARIN	COUMADIN	1954	490
3	LEVOFLOXACIN	LEVAQUIN	1996	393
4	CARBOPLATIN	N/A	1989	376
5	LISINOPRIL	ZESTRIL	1988	351
	All other drugs			18,575
	Total (all cases)			**21,002**

Source: Institute of Safe Medication Practice Reporting on FAERS data

Why Safety Question Post-Marketing?

- Biological plausibility of adverse event
- Pre-clinical signal
- Imbalance in clinical studies
- Safety signal in published studies
- Many adverse event reports

Safety concern due to higher risk than expected and/or rare but serious risk

Sentinel – Some Data Limitations

- Includes mostly claims data
- Ascertainment of exposure, drug dispensed and gaps in exposure
- Ascertainment of outcomes and covariates
- Control for confounding
- Sa
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Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

Not Every Safety Question is Feasible in Sentinel

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf