FDA Sentinel Initiative: Status Update and Examples of Contributions to Regulatory Decisions

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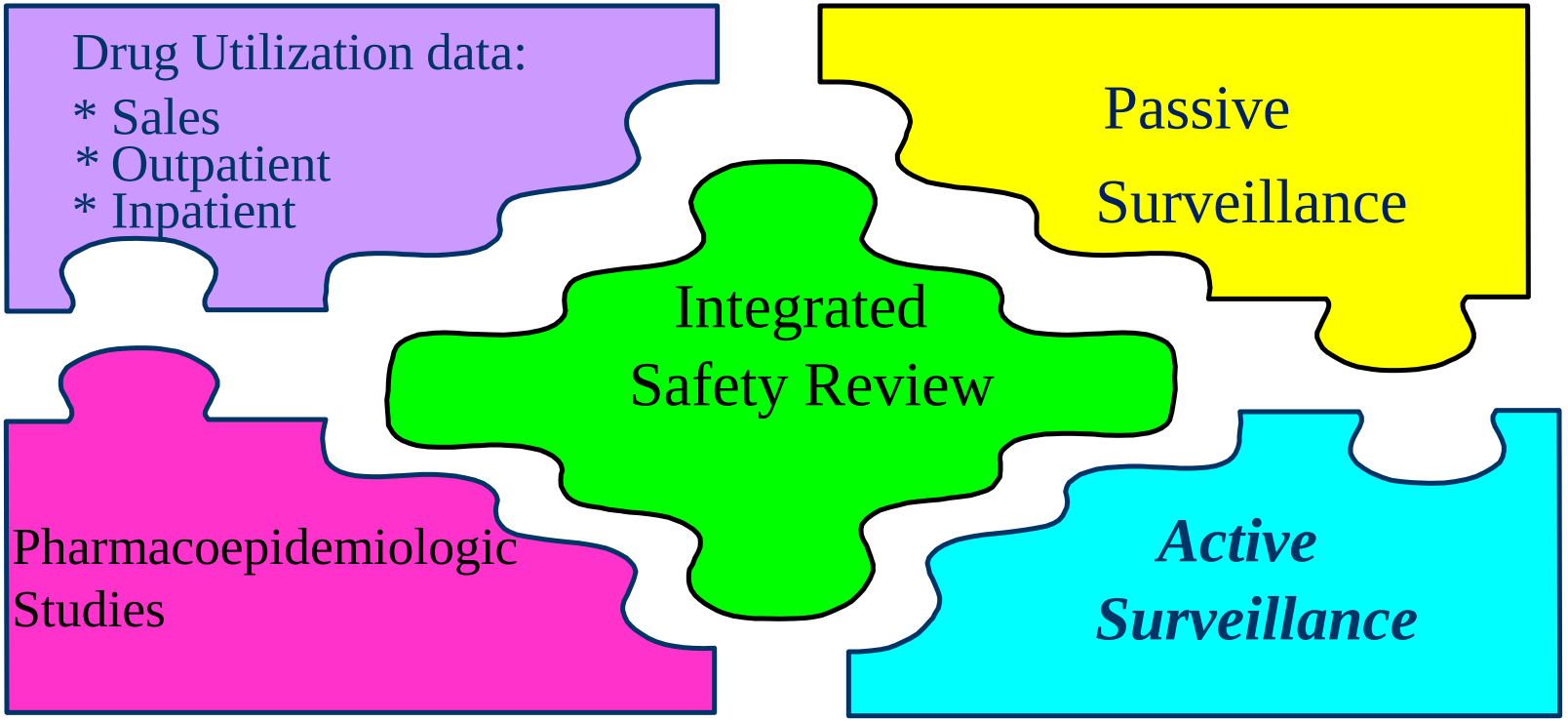
Agenda

- **Background**
  - Goals
  - Pilots: Mini-Sentinel (MS) & Federal Partners Collaboration
- **Data Infrastructure**
  - Database structure / Data elements
  - Querying the system
  - Enhancing data / Enhancing query tools
- **Capabilities / Challenges**
  - Exposures / Outcomes / Populations
- **Examples of Contributions to Safety Issues and Drug Safety Communications (DSCs)**
  - Dabigatran / Warfarin - Severe bleeds
  - Olmesartan / other Angiotensin II Receptor Blockers (ARBs) – severe GI symptoms

Components of a Comprehensive Post-marketing Surveillance Program at CDER



FDA Sentinel Initiative - Goals

- Develop a national electronic safety monitoring system
  - Leveraging multiple sources of currently available electronic data
  - By partnering with data holders
    - Healthcare systems, insurance companies, etc
- Enhance active post-market monitoring of medical product safety
  - More effectively look at common outcomes (e.g. MI, fractures)
  - Have denominators to easily calculate rates
  - Increase sample size with improved access to population subgroups
- Use validated design and statistical methods
- Near real-time monitoring by using a
  - Common data model & “Library” of tools/resources
- Integrate active surveillance with current post-market safety monitoring systems

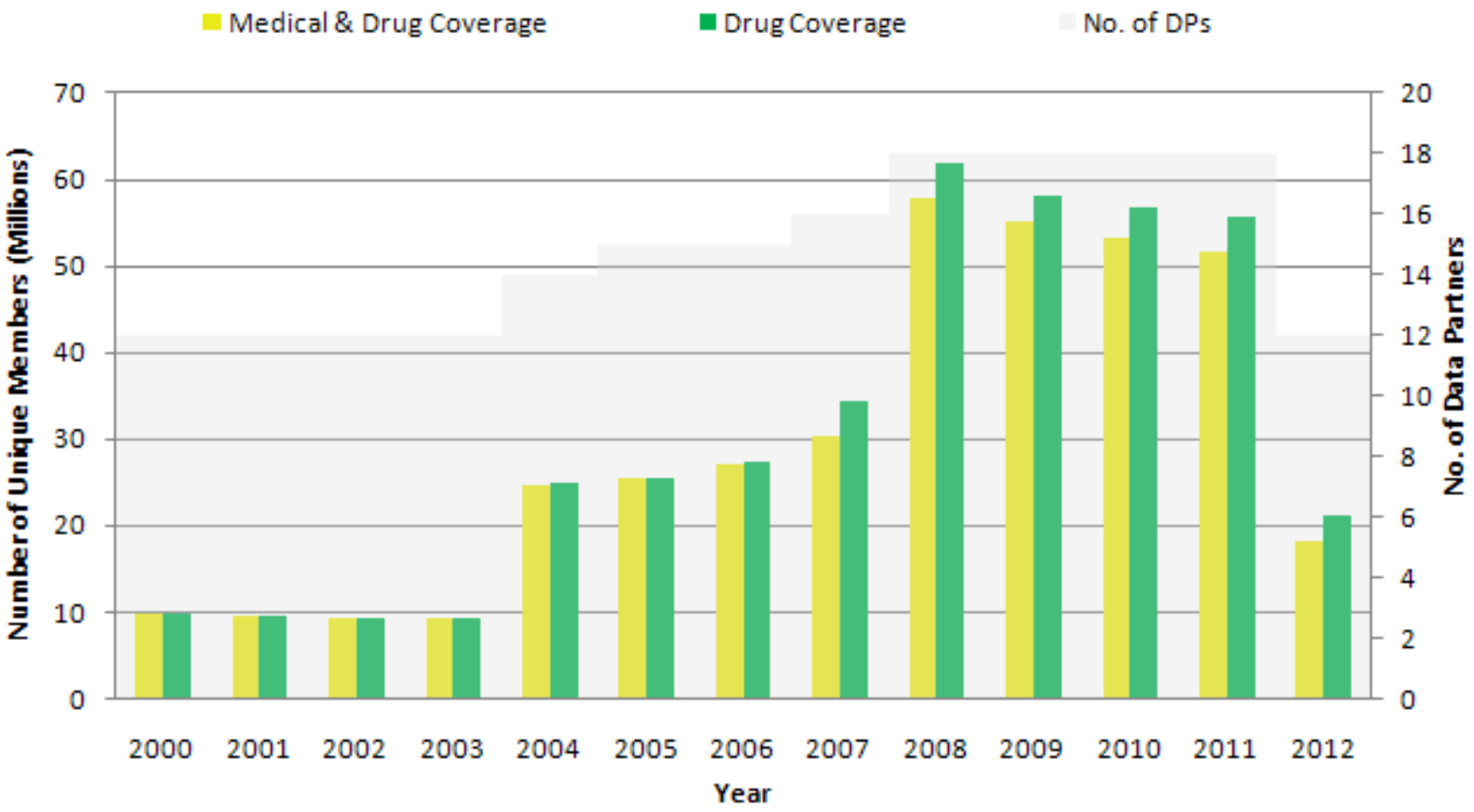
Sentinel Initiative Pilots: Data Structures

Mini Sentinel	Federal Partners Collaboration
No exchange of individual data	No exchange of individual data
Data maintained behind data owner's firewall	Data maintained behind data owner's firewall
Common Database Model (MSCDM)	Individual database models at each site
One protocol and one SAS program used at all sites distributed by MSOC	Protocol maintained as close as possible at each site, individual SAS programs at each site

FDA Sentinel Initiative: Mini-Sentinel Pilot

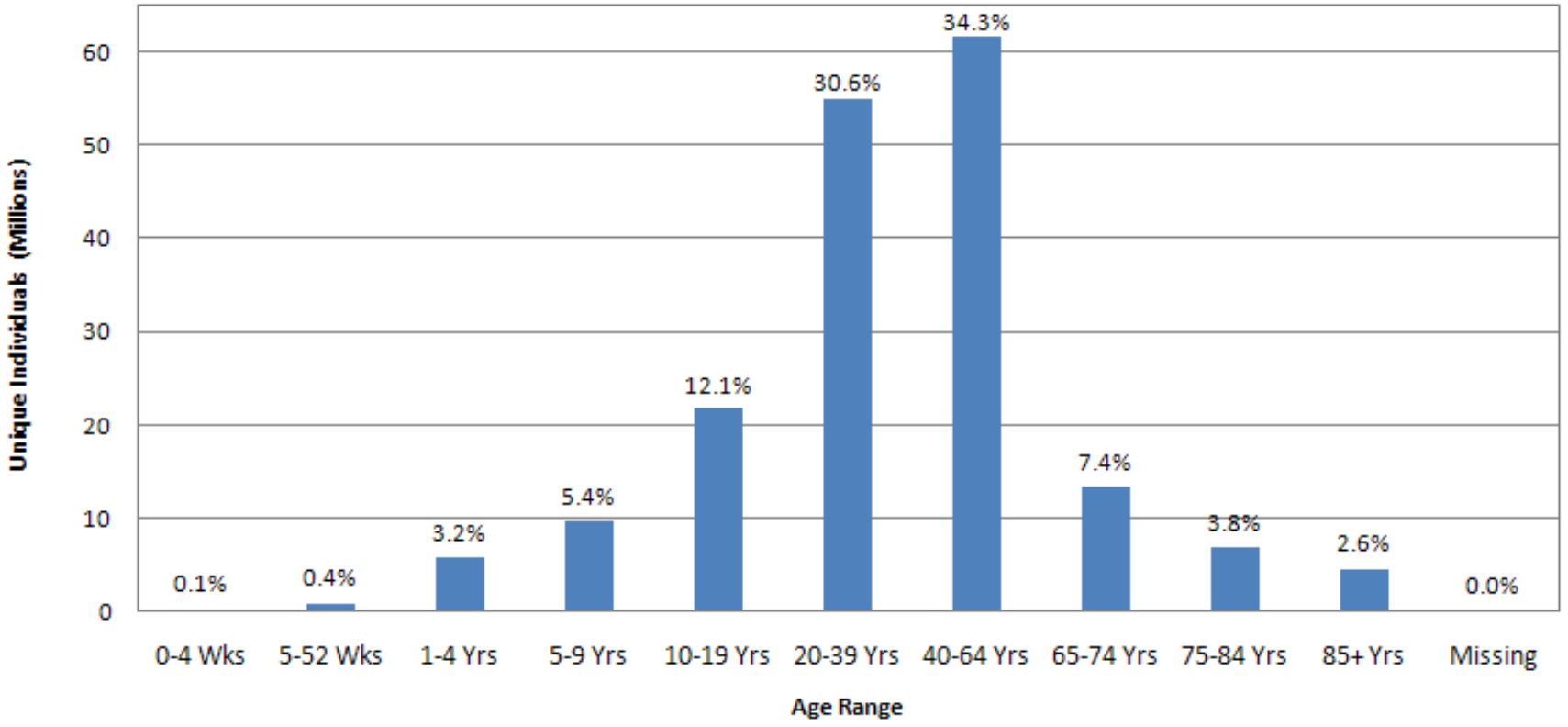
- Contract awarded: Sept 2009 to Harvard Pilgrim Health Care
- Data Partners: Humana, Healthcore, Aetna, Optum, HMO Research Network, Kaiser sites, Vanderbilt (Tennessee and Washington Medicaid)
- Approximately 140 million individuals, claims & administrative data, 2000 - present
  - Different sites have data for different time periods
  - Average length of enrollment (data availability) = 28 months
- 88 inpatient facilities - Kaiser, U Penn, Iowa, Cincinnati, U Illinois Chicago, Partners
- Device and disease registries - Outcome Sciences, Weill-Cornell, Duke, Kaiser
- 200+ investigators part of Mini-Sentinel team and may participate in various projects

Number of Unique Members (in Millions) by Enrollment Coverage Type



Source: Enr_l3_enrmd_y dataset from last approved data refresh for each Data Partner as of December 31, 2012

Demographic Table: Distribution of Age Group



Source: Dem_l3_ageyrsdist2 dataset from last approved data refresh for each Data Partner as of December 31, 2012

Available Data

Individual Level Data Held by Data Partners

- Characteristics of People/Enrollees
  - Enrollment
    - Enrollment period start and end
    - Type of coverage – drug coverage, medical coverage
  - Demographic
    - Birth date, Sex,
    - (Race, Hispanic Origin – 70% Unknown)
- Drug Dispensing
  - Outpatient
    - Date, NDC, Days supplied, Amount
  - Inpatient – not available

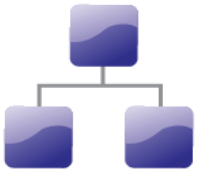
Available Data

Individual Level Data Held by Data Partners

- Medical Care Utilization
  - Encounter
    - Admission/Start date, Discharge/End date, Provider, Care Setting (IP, ED, AV, etc.), Facility, etc.
  - Diagnoses
    - Date, Provider, Care Setting, Diagnosis code(s), etc.
  - Procedures
    - Date, Provider, Care Setting, Procedure code(s), etc.
- Laboratory and Vital Sign Data - being added to database where available; currently initial laboratory data is being examined for quality assurance

Common Data Model: Administrative and Claims Data

Enrollment



Demographics

Outpatient Pharmacy Dispensing

Utilization (Encounters, Diagnosis, Procedures

Mortality (Death, Cause of Death)

CDM Tables & Data Elements

Enrollment
PatID
Enc_Start
Enc_End
Med_Cov
Drug_Cov

Demographic
PatID
Birth_Date
Sex
Hispanic
Race

Dispensing
PatID
RxDate
NDC
RxSup
RxAmt

Encounter
PatID
EncounterID
Adate
Ddate
Provider
Facility_Location
EncType
Facility_Code
Discharge_Disposition
Discharge_Status
DRG
DRG_Type
Admitting_Source

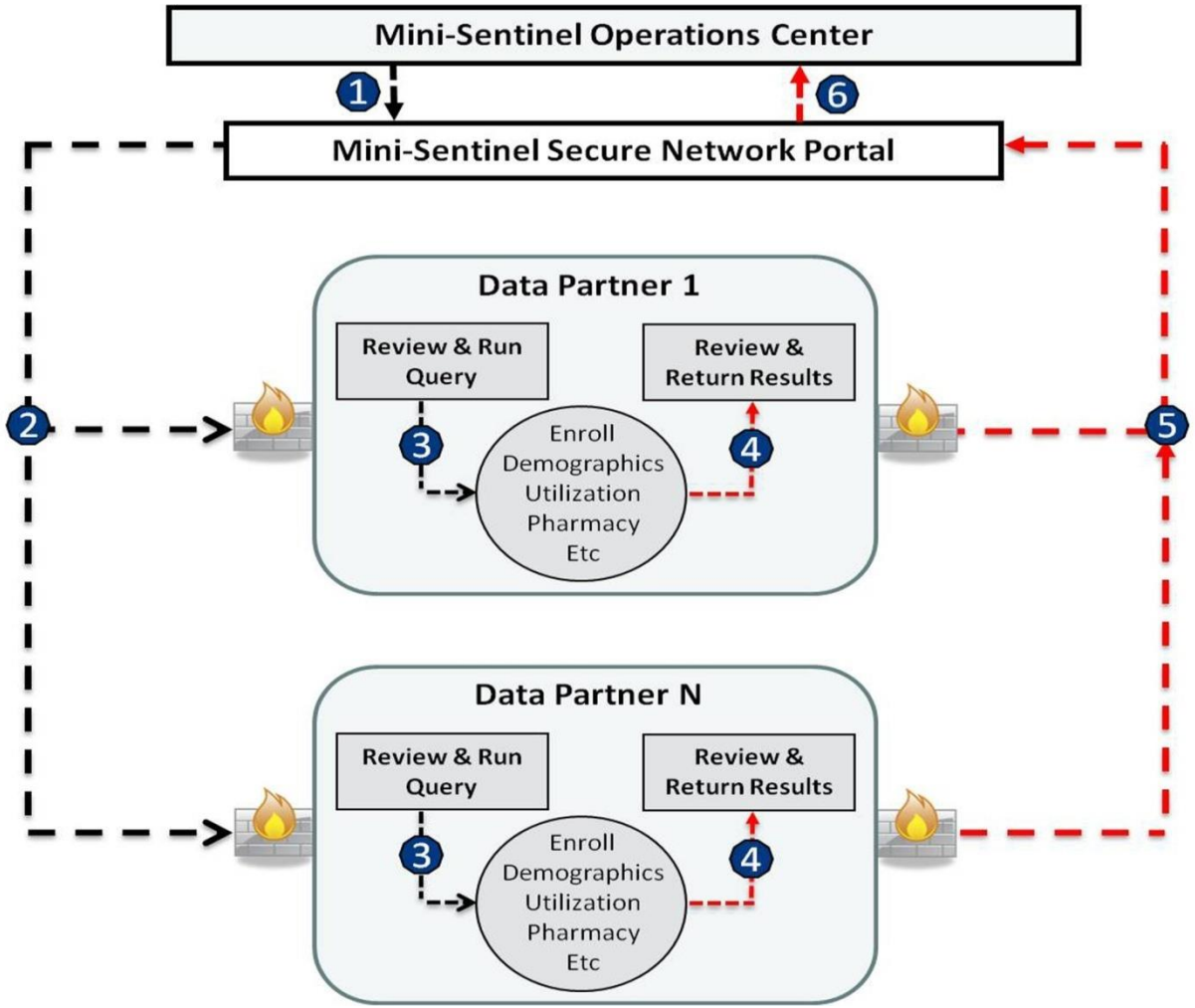
Diagnosis
PatID
EncounterID
Adate
Provider
EncType
Dx
Dx_Codetype
OrigDX
PDX

Procedure
PatID
EncounterID
Adate
Provider
EncType
PX
PX_Codetype
OrigPX

Death
PatID
DeathDt
DtImpute
Source
Confidence

Cause of Death
patID
COD
CodeType
CauseType
Source
Confidence

Mini-Sentinel Distributed Analysis



1- User creates and submits query to MSOC.

MSOC creates a computer program for data partners

2- Data partners retrieve program

3- Data partners review and run program against their local data

4- Data partners review results

5- Data partners return results via secure network to MSOC

6 MSOC aggregates results into a report for CDER/FDA

Data Capabilities and Challenges

- Drugs/Dispensings
  - Outpatient – complete
  - Inpatient – not available
  - IV, Infusion – currently being examined; depends on care setting
- Diagnoses/Outcomes
  - Many validated in published observational studies; some MS validation
  - Difficult Outcomes – suicide, severe pancreatitis, seizures, rhabdomyolysis (need lab value), etc.
- Numbers of Data Partners change over time
  - Denominators must be specific for individual query
  - Rates are needed for trends

MS Query Tools

Multiple ways to query data:

1) Summary tables – precalculated tables; updated quarterly
2) Modular SAS programs – reusable, similar to SAS Procs, some adjustment for confounding
3) Enhanced modular programs - de novo programming increasing capabilities of modular programs
4) Protocol based assessments - custom SAS programs for in-depth assessments
5) PROMPT - Prospective Routine Observational Monitoring Program Tools; semi-automated, increased adjustment for confounding

Gastrointestinal and Intracranial Hemorrhage in New Users of Dabigatran and Warfarin: Mini-Sentinel Distributed Database

Dabigatran / Warfarin

- Approved October 19, 2010 indication of non-valvular atrial fibrillation
- Unexpected level of reports to FAERS on severe bleeding, primarily GI
- Modular Programs to examine drug use and exposure / outcomes in Mini-Sentinel; also protocol based assessments planned in MS and CMS Medicare data

- New users of dabigatran and warfarin
- 183 day period prior to index dispensing w no dispensing of study drugs, no outcome diagnoses, and with a diagnosis of atrial fibrillation in any care setting
- GI bleeding and ICH diagnosed in an in-patient setting

New User Definition: Dabigatran vs Dabigatran & Warfarin

Dabigatran

- Drug and Medical Coverage: 51.07% of new users of dabigatran have also *not* used warfarin in the preceding 183 days

Warfarin

- Drug and Medical Coverage: 99.22% of new users of warfarin have also *not* used dabigatran in the preceding 183 days

Conclusion

- Examine events among new users defined by previous use of drug of interest only and defined by use of either drug of interest.

Table 1. New GIH Events/100k Days at Risk

***Data from report 41 Tables 3,4,9 and 10**

Drug Washout Period for Same Drug Only				
Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
22,356	2.0	A.Fib – 183 days	44,415	3.4
24,916	2.0	No requirement -183 days	120,896	3.1
Drug Washout Period for Both Dabigatran and Warfarin				
Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,599	1.6	A.Fib – 183 days	43,541	3.5
12,195	1.6	No requirement -183 days	119,940	3.1

Conclusions / Limitations

- No evidence for increased GI bleeding w dabigatran compared to warfarin
- DSC in November 2012

- No adjustment for confounding
- No diagnosis exclusions (e.g. joint replacement, etc)
- Don’t have data on deaths in absence of medical billing
- No examination of population characteristics
- Algorithms not validated in this observational data

Olmesartan, Other ARBs and Sprue-Like Enteropathy

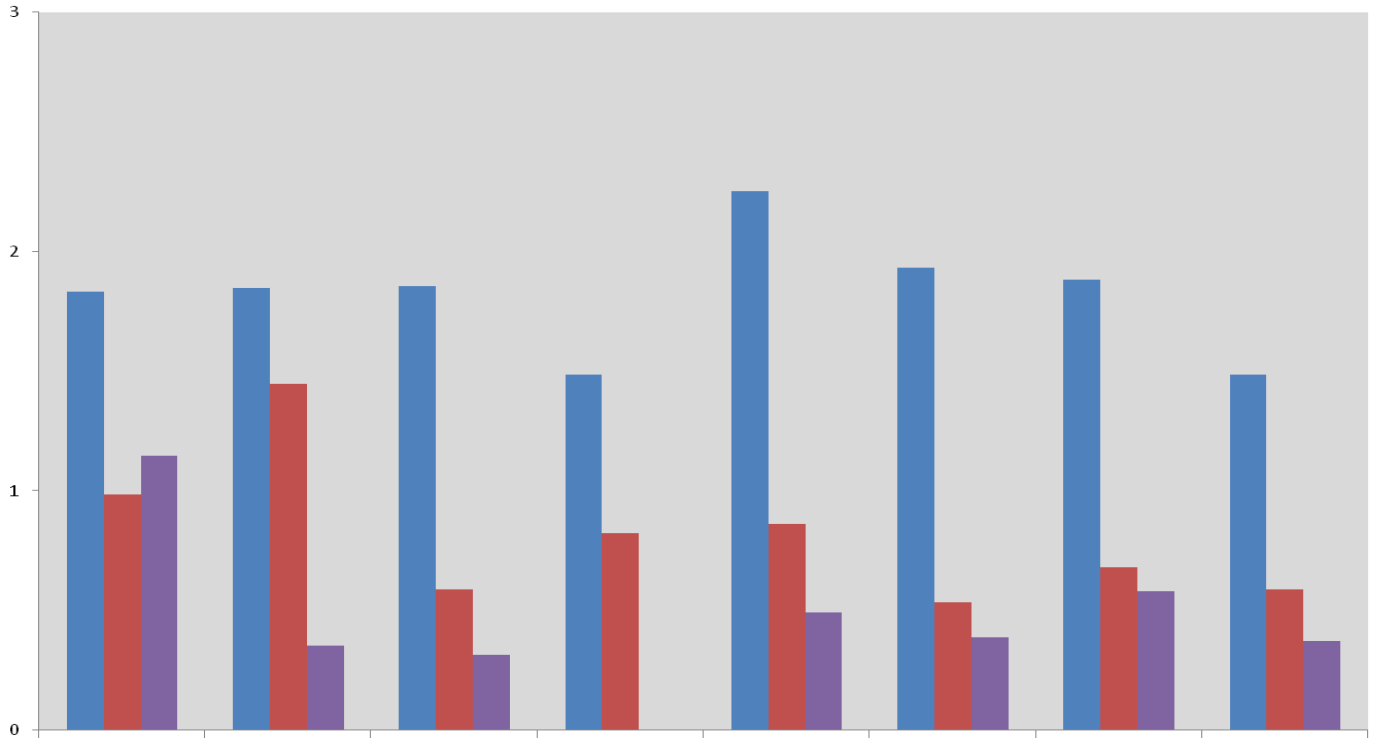
Regulatory History

- Olmesartan approved in April 2002 for the treatment of HTN, alone or in combination with other agents
- Labeling: Adverse Reactions - Diarrhea
- Severe GI symptoms: severe, long-term diarrhea, substantial weight loss, villous atrophy
- FAERS reports, case series, positive dechallenge and rechallenge
- Late onset, median of 2 ½ yrs of exposure
- Celiac disease ruled out in most cases

Mini-Sentinel Data Assessment

- Secondary use of observational data collected largely for reimbursement and cost accounting purposes
- Define outcomes strictly in terms of codes: NDC, ICD-9, and procedure codes.
- Use Celiac Disease as marker for severe GI symptoms
- Examine outcomes after various times of drug exposure
  - 0 days
  - 365 days
  - 730 days
- Individual ARBS
- Negative Controls (hydrochlorothiazide, atenolol, and amlodipine

Mini-Sentinel
New Events/1 Million Days at Risk by Product and Minimum Drug Episode Duration
(1st treatment episode only, ARBS with min of 20,000 new users with 0 minimum exposure)



	Olmesartan	Irbesartan	Losartan	Telmisartan	Valsartan	Hydrochlorothiazide	Atenolol	Amlodipine
0 MinEpiDur	1.8	1.8	1.9	1.5	2.3	1.9	1.9	1.5
365 MinEpiDur	1.0	1.4	0.6	0.8	0.9	0.5	0.7	0.6
730 MinEpiDur	1.1	0.4	0.3	0.0	0.5	0.4	0.6	0.4

MS Assessment: Conclusions/Limitations

- Incidence rate of Celiac Disease diagnoses for olmesartan is similar to other ARBs and negative controls when no minimum exposure is required.
- When 365 days exposure required only olmesartan and irbesartan have incidence rates >1.
- When 730 days exposure required only olmesartan has an incidence rate >1.

- No adjustment for confounding.
- Outcome does not include all severe GI symptoms.
- Most exposure in MS is limited to less than one year.

Thank You,

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www.minisentinel.org