A NEW ANALYTIC TOOL DEVELOPED IN THE SENTINEL SYSTEM TO ASSESS ADHERENCE TO FDA'S SAFE USE RECOMMENDATIONS

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BACKGROUND

The US FDA utilizes approved product labeling, safety communications, and risk mitigation strategies (e.g., REMS) to mitigate serious risks of medical products and to provide recommendations on their safe use. Given the frequency of regulatory actions (45 REMS with elements to assure safe use, 14 that involve communications plans as of early 2018; 62 drug safety communications in 2015-2017) there is a need to facilitate rapid assessments of the impact of FDA's safe use recommendations on routine healthcare practices over time.

FDA's Sentinel System is an active surveillance system that uses routine querying tools and pre-existing electronic healthcare data from multiple sources to monitor the safety of regulated medical products.

OBJECTIVES

To develop a flexible, parameterized, reusable analytic tool in Sentinel to assess adherence to FDA's safe use recommendations over time, with two key capabilities:

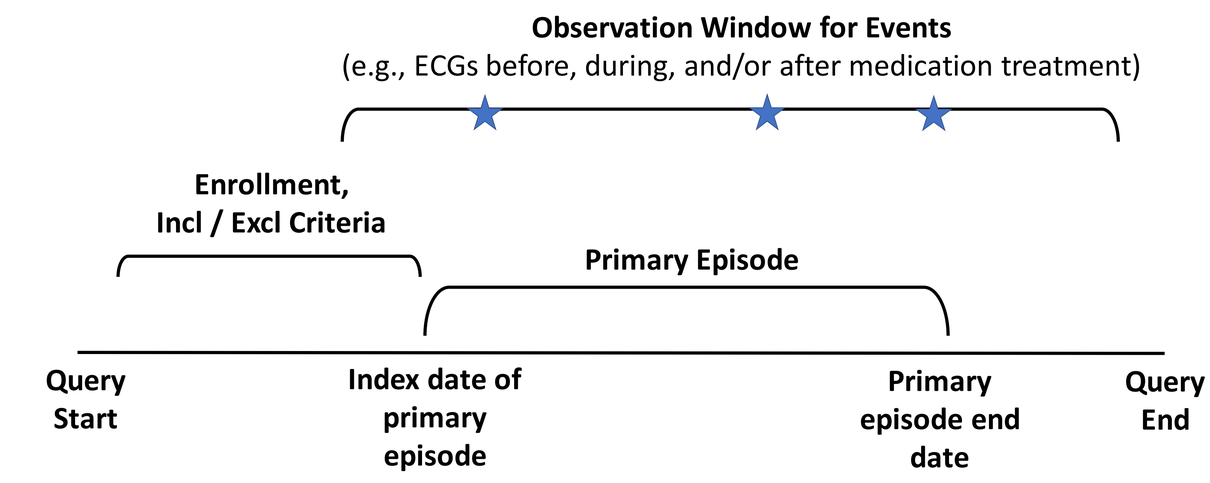
- Characterize adherence to patient monitoring recommendations for a drug, and
- Characterize concomitant medication use before, during, and/or after drug therapy.

METHODS

Developed, tested, applied the tool to data from 16 Sentinel Data Partners to assess whether the tool was sufficiently parameterized and produced the relevant indicators of adherence to prescribing behaviors. The two use cases were the following:

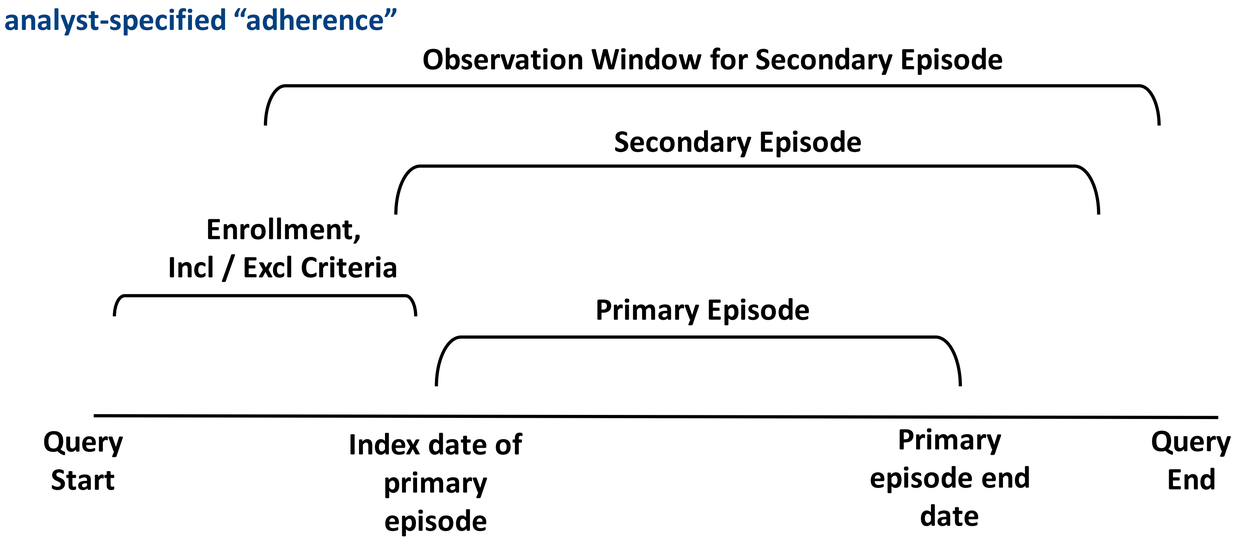
1. Frequency of cardiac monitoring related to dronedarone, an antiarrhythmic drug indicated for atrial fibrillation and atrial flutter patients
   - Label recommendation: monitor cardiac rhythm (i.e., electrocardiograms, ECG) "no less often than every 3 months" (per Dec. 2011 label change)
   - Cohort: new users of dronedarone (183 d washout) ≥18 years, July 2009 - Sept 2015, with 183 days of medical/pharmacy coverage; ≥90 days duration of dronedarone use
   - Tool output: characteristics of dronedarone users who received ECG per label guidelines; characteristics of treatment duration, time to first ECG, time between ECGs
2. Frequency of concomitant use of contraception among female users of mycophenolate
   - Label recommendation: 2 methods of contraception for the 4 weeks before initiation through 6 weeks after discontinuation of mycophenolate
   - Cohort: female new users of mycophenolate (183 d washout) 12-55 years, Jan 2006 - Sept 2015, with 183 days of medical/pharmacy coverage
   - Contraception episodes identified via NDCs for oral contraceptives, patches, vaginal rings; procedure codes for injectable, implantable, intrauterine device methods; diagnostic and procedure codes for surgical birth control procedures
   - Tool output: proportion of females dispensed mycophenolate who were also dispensed one prescription contraception method; assessed extent of overlap between episodes of contraceptive and mycophenolate

Figure 1. Capability 1 - Assess occurrence of events during an observation window relative to a primary episode of interest and determine analyst-specified "adherence"



Key components:
- Analyst specified "observation window" during which events are assessed
- Descriptive data generated include time to first event, time between events, episode duration
- "Adherence" can be defined by four parameters: episode duration, minimum number of events, time to first event, and event gap*

Figure 2. Capability 2 - Assess concomitant occurrence of 2 episodes of interest and determine analyst-specified "adherence"



Key components:
- Analyst specified "observation window" when secondary episode concomitancy is assessed
- Analyst specified cutoffs of proportion of primary episode overlapped by secondary episode
- Descriptive data include primary episode duration and overlap (mean, median, etc.)
- "Adherence" defined by min. proportion of primary episode overlapped by secondary episode*

*Because of limitations in the Sentinel data this definition might not accurately reflect the degree to which providers and patients correctly follow the labeled recommendations.

RESULTS

Table 1. Dronedarone and ECGs by dronedarone duration and age, 7/2009 – 9/2015

N=61,334,874 eligible members	No. dronedarone episodes	Percent of dronedarone episodes with ≥1 ECG	Percent of dronedarone episodes meeting adherence*
All episodes	21,457	85.9%	21.6%
Episode duration (days)			
90-180	8,881	78.8%	45.0%
181-270	3,774	86.5%	13.6%
271-360	2,206	89.1%	4.0%
≥361	6,596	94.2%	0.6%
Age (years)			
18-34	101	77.2%	17.8%
35-44	435	87.4%	26.9%
45-64	8,370	86.3%	21.4%
65-74	6,674	86.2%	22.3%
≥75	5,877	85.2%	20.8%

*Adherence definitions for this analysis:

Dronedarone duration (days)	90-180	181-270	271-360	≥361
Min. number of ECGs	1	2	3	4
Required time to first ECG	≤90 days (1-90 days)			
Required gap between ECGs	≤90 days (0-90 days)			

Table 2. Concomitant use of contraception 4 weeks before through 6 weeks after mycophenolate use, by age, Jan 2006 - Sept 2015

	Mycophenolate						
	No. users	No. episodes	Mean duration (days)	Percent of all episodes	Percent of episodes with ≥1day contraception overlap	Percent of episodes meeting adherence*	Mean duration (days): mycophenolate; contraception (episodes with ≥1day overlap)
Total	19,071	21,942	151	100%	15.5%	11.8%	
12-24 yrs	2,659	3,129	147	14.3%	24.0%	16.7%	201; 578
25-44 yrs	8,641	9,876	141	45.0%	22.3%	17.1%	176; 822
45-55 yrs	8,060	8,937	164	40.7%	5.1%	4.2%	195; 1096

There were 38,961,366 eligible members.

*Adherence defined as at least 50% of the mycophenolate episode observation window (i.e., 4 weeks before through 6 weeks after) being overlapped by concomitant contraception use. Members could contribute >1 qualifying mycophenolate episode so summing across age groups is greater than the total.

CONCLUSIONS

- We found most dronedarone episodes ≥90 days in duration have ≥1 ECG, and identified a trend towards decreased adherence to routine ECG monitoring with increasing episode duration.
- We found a low proportion of mycophenolate users with concomitant contraception use, likely due to limitations in assessing contraception need and use in claims data (see Limitations).
- The tool performed as expected and can be used to address a variety of questions about safe use of medications.
- The tool also creates a privacy preserving aggregated dataset for longitudinal evaluations, such as interrupted time series studies to assess impacts of FDA regulatory actions.
- This publicly available tool substantially expands FDA's – and others' – ability to rapidly assess adherence to safe use recommendations as well as changes in trends in relation to safety communications or other regulatory actions.

LIMITATIONS

Any patient characteristic, treatment, or care not captured in claims data are unknown. Specific to the mycophenolate and contraception use case:

- Claims data do not allow us to assess whether a woman was sexually active and thus in need of contraception while on mycophenolate.
- We likely underestimated contraception use as only contraception for which a claim was generated was captured. Long-term forms of contraception will not be captured if procedures were performed prior to a member's entry into the database.

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