Modular Program Report

The following report(s) provides findings from an FDA-initiated query using its Mini-Sentinel pilot. While Mini-Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Mini-Sentinel, and seeking to better understand the capabilities of the Mini-Sentinel pilot.

Data obtained through Mini-Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from the Mini-Sentinel pilot in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Mini-Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview	
Request Description	FDA requested use of MP #3 (version 2.1) to investigate gastrointestinal (GIH) and/or intracerebral hemorrhage (ICH) events following new use of warfarin among patients with a pre-existing condition of atrial fibrillation. The query was run with warfarin as the only exposure among patients with a pre-existing condition of atrial fibrillation and GIH/ICH events for the years 10/19/2008 to 11/30/2009 (query period). The package was distributed to Data Partners on June 5, 2012. Results provide counts of new users of warfarin, dispensings, total days supplied, treatment episodes, eligible members (denominator), and member days. Total days supplied are from the MSCDM outpatient pharmacy table for records identified using valid National Drug Codes (NDCs). Warfarin users were considered new if they had no use of warfarin in the prior 183 days. Counts of new gastrointestinal (GIH) or intracerebral hemorrhage (ICH) events and days at risk following exposure to warfarin are also presented. Events were considered new if the user had no event in the prior 183 days. Events found in the inpatient (IP) and emergent (ED) care settings were included.
Request ID	MSY3_MPR31 - Warfarin
Requester	FDA/CDER

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Notes:	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document.

Modular Program Specifications for Query ID MPR31 Part 3

FDA requested use MP #3 (version 2.3) to investigate gastrointestinal (GIH) and/or intracerebral hemorrhage (ICH) events following new use of warfarin among patients with a pre-existing condition of atrial fibrillation. The query was run against the Mini-Sentinel Distributed Database for the time period 10/19/2010 to 11/30/2009. For drug and exposure the episode gap was set to 10 days; the extention period was set to 10 days, and both minimum episode duration and minimum days supplied were set to 1 day. Age groups were split as follows: 0-40, 41-54, 55-64, 65-74, 75-84, and 85+ years. In total, 6 different scenarios were examined in this report with differing incidence type and event/outcome. See below for a description of each of these scenarios.

	Drug/Exposure						Pre-Existing Condition						Event/Outcome					
Scenario	Incident exposure	Incident w/ respect to:	Wash-out (days)	Incidence Type*	Min Episode Duration	Min Days Supplied	Pre-Existing Condition	Code Type	Lookback Period	Lookback Type	Care Setting	Principal Dx	Event/ Outcome	Washout (days)	Incidence Type**	Care Setting	Principal Dx	Blackout Period
1	Warfarin	Warfarin	183	Mult	1	1	Atrial fibrillation	DX	183	F	All	NO	GIH	183	Mult	ED, IP	NO	0
2	Warfarin	Warfarin	183	Mult	1	1	Atrial fibrillation	DX	183	F	All	NO	ICH	183	Mult	ED, IP	NO	0
3	Warfarin	Warfarin	183	Mult	1	1	Atrial fibrillation	DX	183	F	All	NO	GIH or ICH	183	Mult	ED, IP	NO	0
4	Warfarin	Warfarin	183	Single	1	1	Atrial fibrillation	DX	183	F	All	NO	GIH	183	Mult	ED, IP	NO	0
5	Warfarin	Warfarin	183	Single	1	1	Atrial fibrillation	DX	183	F	All	NO	ICH	183	Mult	ED, IP	NO	0
6	Warfarin	Warfarin	183	Single	1	1	Atrial fibrillation	DX	183	F	All	NO	GIH or ICH	183	Mult	ED, IP	NO	0

NDC codes checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

*Single Incidence Type for the exposure will only consider the first incident episode for each user during the query period that satisfies the Washout Period criteria (183 or 365 days). There can be at most one episode per user. A Multiple washout type for the exposure will consider all episodes for each member that meet the 183 washout period. There can be more than one incident episode per member.

**Multiple washout type for the event will only consider all valid incident events during the query period that satisfy the Washout Period criteria of 183 days. One individual can contribute more than one event.

Glossary of Terms in Modular Program 3*

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA).

Days at Risk - number of days supplied plus any episode gaps and exposure extension periods.

Eligible Members - Number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Member-Days - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout period.

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered

Minimum Episode Duration - specifies a minimum number of days in length of the epsiode for it to be considered

New Episodes - new treatment episodes; length of episode is determined by days supplied in one dispensing (or consecutive dispensings bridged by the episode gap.

New Users - number of members with incident exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Principal Diagnosis - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. YES will only consider diagnoses flagged as Principal

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Total Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Incidence Type (drug/exposure)- *Minimum incidence type* will consider the first treatment episode in the query period as long as it is the first treatment episode in the user's entire available history. *Single* and *Multiple incidence types* will use the washout period to establish incidence, however *Single* will only consider the first treatment episode whereas *Multiple* will consider all qualifying incident treatment episodes.

Incidence Type (event/outcome)- *Minimum incidence type* considers the first event in a valid episode as long as it is the first event in the user's entire available history. *Multiple incidence type* uses the washout period to establish incidence and considers all qualifying incident treatment episodes. The program will only consider one event per episode, but the *Multiple incidence type* will consider more than one event per user if a user has more than one incident episode.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1. Summary of Incident Warfarin Use and Outcomes in the MSDD between October 19, 2008 - November 30, 2009, by Outcome and Incidence Type among Members with a Pre-Existing Condition of Atrial Fibrillation

	New Users	Dispensings	Total Days Supplied	New Episodes	Days At Risk	New Events	Eligible Members	Member-Days	New Users/1k Eligible Members	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	New Events/ 100k Days at Risk
Multiple Incidence Type													
Outcome of GIH	49,501	128,857	4,935,496	49,788	5,285,760	161	363,059	55,789,641	136.3	2.6	99.7	38.3	3.0
Outcome of ICH	49,516	128,667	4,931,006	49,802	5,283,312	141	363,056	55,790,366	136.4	2.6	99.6	38.3	2.7
Outcome of GIH or ICH	49,282	128,061	4,909,711	49,567	5,252,933	298	363,042	55,787,343	135.7	2.6	99.6	38.3	5.7
Single Incidence Type													
Outcome of GIH	49,501	128,483	4,918,862	49,501	5,267,067	160	362,699	55,604,732	136.5	2.6	99.4	38.3	3.0
Outcome of ICH	49,516	128,294	4,914,327	49,516	5,264,594	141	361,650	55,403,242	136.9	2.6	99.2	38.3	2.7
Outcome of GIH or ICH	49,282	127,689	4,893,122	49,282	5,234,305	297	362,682	55,602,915	135.9	2.6	99.3	38.3	5.7

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Table 2. Summary of Incident Warfarin Use and Outcomes in the MSDD between October 19, 2008 - November 30, 2009, by Outcome, Incidence Type, and Age Group among Members with a Pre-Existing Condition of Atrial Fibrillation

Age Group	New Users	Dispensings	Total Days Supplied	New Episodes	Days At Risk	New Events	Member-Days	Member Days	Dispensings/ User	Dispensings /User	Days Supplied/ User	Days Supplied/ Dispensing	New Events/ 100k Days at Risk
Multiple Incidence Type													
Outcome of GIH													
0 to 40 years	610	1,443	48,330	614	52,957	0	15,307	1,654,309	39.9	2.4	79.2	33.5	0.0
41 to 54 years	4,051	10,327	349,874	4,070	380,938	7	38,658	4,959,827	104.8	2.5	86.4	33.9	1.8
55 to 64 years	9,770	25,255	923,462	9,825	994,206	20	64,308	8,610,535	151.9	2.6	94.5	36.6	2.0
65 to 74 years	14,407	37,554	1,498,624	14,490	1,598,860	55	86,411	12,711,828	166.7	2.6	104.0	39.9	3.4
75 to 84 years	15,203	39,475	1,579,148	15,280	1,687,067	60	103,727	16,494,659	146.6	2.6	103.9	40.0	3.6
85+ years	5,480	14,803	536,058	5,509	571,732	19	68,262	11,359,720	80.3	2.7	97.8	36.2	3.3
Outcome of ICH													
0 to 40 years	612	1,446	48,400	616	52,663	3	15,308	1,654,328	40.0	2.4	79.1	33.5	5.7
41 to 54 years	4,046	10,297	348,759	4,065	379,984	5	38,659	4,959,876	104.7	2.5	86.2	33.9	1.3
55 to 64 years	9,766	25,207	922,604	9,821	994,082	11	64,311	8,610,635	151.9	2.6	94.5	36.6	1.1
65 to 74 years	14,426	37,500	1,498,251	14,508	1,600,485	35	86,408	12,711,903	167.0	2.6	103.9	40.0	2.2
75 to 84 years	15,211	39,513	1,579,077	15,288	1,686,531	63	103,727	16,494,892	146.6	2.6	103.8	40.0	3.7
85+ years	5,476	14,704	533,915	5,504	569,567	24	68,259	11,359,976	80.2	2.7	97.5	36.3	4.2
Outcome of GIH or ICH													
0 to 40 years	610	1,443	48,330	614	52,572	3	15,307	1,654,278	39.9	2.4	79.2	33.5	5.7
41 to 54 years	4,035	10,276	347,979	4,054	378,775	11	38,656	4,959,734	104.4	2.5	86.2	33.9	2.9
55 to 64 years	9,730	25,125	920,026	9,785	989,893	31	64,308	8,610,265	151.3	2.6	94.6	36.6	3.1
65 to 74 years	14,356	37,338	1,492,113	14,438	1,591,006	89	86,407	12,711,257	166.1	2.6	103.9	40.0	5.6
75 to 84 years	15,128	39,249	1,570,046	15,205	1,674,675	121	103,720	16,493,827	145.9	2.6	103.8	40.0	7.2
85+ years	5,443	14,630	531,217	5,471	566,012	43	68,258	11,359,224	79.7	2.7	97.6	36.3	7.6
Single Incidence Type													
Outcome of GIH													
0 to 40 years	610	1,439	48,166	610	52,763	0	15,301	1,651,821	39.9	2.4	79.0	33.5	0.0
41 to 54 years	4,051	10,299	348,909	4,051	379,897	7	38,614	4,944,853	104.9	2.5	86.1	33.9	1.8
55 to 64 years	9,765	25,174	920,436	9,765	990,688	19	64,201	8,575,515	152.1	2.6	94.3	36.6	1.9
65 to 74 years	14,404	37,428	1,492,758	14,404	1,592,436	55	86,273	12,659,447	167.0	2.6	103.6	39.9	3.5
75 to 84 years	15,197	39,378	1,574,491	15,197	1,681,770	60	103,553	16,437,963	146.8	2.6	103.6	40.0	3.6
85+ years	5,474	14,765	534,102	5,474	569,513	19	68,172	11,336,371	80.3	2.7	97.6	36.2	3.3
Outcome of ICH													
0 to 40 years	612	1,442	48,236	612	52,469	3	15,278	1,649,083	40.1	2.4	78.8	33.5	5.7
41 to 54 years	4,046	10,269	347,794	4,046	378,943	5	38,545	4,935,357	105.0	2.5	86.0	33.9	1.3
55 to 64 years	9,761	25,126	919,578	9,761	990,564	11	64,047	8,552,014	152.4	2.6	94.2	36.6	1.1
65 to 74 years	14,423	37,375	1,492,400	14,423	1,594,086	35	86,031	12,615,987	167.6	2.6	103.5	39.9	2.2
75 to 84 years	15,204	39,415	1,574,330	15,204	1,681,144	63	103,188	16,365,742	147.3	2.6	103.5	39.9	3.7
85+ years	5,470	14,667	531,989	5,470	567,388	24	67,931	11,286,293	80.5	2.7	97.3	36.3	4.2

Table 2 cont. Summary of Incident Warfarin Use and Outcomes in the MSDD between October 19, 2008 - November 30, 2009, by Outcome, Incidence Type, and Age Group among Members with a Pre-Existing Condition of Atrial Fibrillation

Age Group	New Users	Dispensings	Total Days Supplied	New Episodes	Days At Risk	New Events	Eligible Members	Member Days	New Users/1k Eligible Members	Dispensings /User	Days Supplied/ User	Days Supplied/ Dispensing	New Events/ 100k Days at Risk
Single Incidence Type													
Outcome of GIH or ICH													
0 to 40 years	610	1,439	48,166	610	52,378	3	15,301	1,651,790	39.9	2.4	79.0	33.5	5.7
41 to 54 years	4,035	10,248	347,014	4,035	377,734	11	38,612	4,944,760	104.5	2.5	86.0	33.9	2.9
55 to 64 years	9,725	25,044	917,000	9,725	986,375	30	64,201	8,575,310	151.5	2.6	94.3	36.6	3.0
65 to 74 years	14,353	37,213	1,486,262	14,353	1,584,607	89	86,269	12,658,878	166.4	2.6	103.6	39.9	5.6
75 to 84 years	15,122	39,152	1,565,389	15,122	1,669,378	121	103,546	16,437,380	146.0	2.6	103.5	40.0	7.2
85+ years	5,437	14,593	529,291	5,437	563,833	43	68,168	11,336,040	79.8	2.7	97.3	36.3	7.6

Table 3. Summary of Incident Warfarin Use and Outcomes in the MSDD between October 19, 2008 - November 30, 2009, by Outcome, Incidence Type, and Sex among Members with a Pre-Existing Condition of Atrial Fibrillation

Sex	New Users	Dispensings	Total Days Supplied	New Episodes	Days At Risk	New Events	Eligible Members	Member Days	New Users/1k Eligible Members	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	New Events/ 100k Days at Risk
Multiple Incidence Type													
Outcome of GIH													
Male	20,181	54,486	2,056,396	20,282	2,197,355	66	165,134	25,923,816	122.2	2.7	101.9	37.7	3.0
Female	29,289	74,301	2,876,187	29,474	3,085,278	94	197,744	29,830,983	148.1	2.5	98.2	38.7	3.0
Unknown	31	70	2,913	32	3,127	1	181	34,842	171.3	2.3	94.0	41.6	32.0
Outcome of ICH													
Male	20,172	54,378	2,054,142	20,273	2,195,608	67	165,132	25,924,088	122.2	2.7	101.8	37.8	3.1
Female	29,313	74,219	2,873,951	29,497	3,084,575	74	197,743	29,831,436	148.2	2.5	98.0	38.7	2.4
Unknown	31	70	2,913	32	3,129	0	181	34,842	171.3	2.3	94.0	41.6	0.0
Outcome of GIH or ICH													
Male	20,076	54,083	2,043,778	20,177	2,181,586	132	165,127	25,922,736	121.6	2.7	101.8	37.8	6.1
Female	29,175	73,908	2,863,020	29,358	3,068,220	165	197,734	29,829,766	147.5	2.5	98.1	38.7	5.4
Unknown	31	70	2,913	32	3,127	1	181	34,841	171.3	2.3	94.0	41.6	32.0
Single Incidence Type													
Outcome of GIH													
Male	20,181	54,365	2,050,948	20,181	2,191,180	66	165,021	25,852,090	122.3	2.7	101.6	37.7	3.0
Female	29,289	74,050	2,865,061	29,289	3,072,825	93	197,499	29,718,035	148.3	2.5	97.8	38.7	3.0
Unknown	31	68	2,853	31	3,062	1	179	34,607	173.2	2.2	92.0	42.0	32.7
Outcome of ICH													
Male	20,172	54,257	2,048,694	20,172	2,189,433	67	164,513	25,751,270	122.6	2.7	101.6	37.8	3.1
Female	29,313	73,969	2,862,780	29,313	3,072,097	74	196,958	29,617,537	148.8	2.5	97.7	38.7	2.4
Unknown	31	68	2,853	31	3,064	0	179	34,435	173.2	2.2	92.0	42.0	0.0
Outcome of GIH or ICH													
Male	20,076	53,962	2,038,330	20,076	2,175,411	132	165,014	25,851,277	121.7	2.7	101.5	37.8	6.1
Female	29,175	73,659	2,851,939	29,175	3,055,832	164	197,489	29,717,032	147.7	2.5	97.8	38.7	5.4
Unknown	31	68	2,853	31	3,062	1	179	34,606	173.2	2.2	92.0	42.0	32.7

Table 4. Summary of Incident Warfarin Use and Outcomes in the MSDD between October 19, 2008 - November 30, 2009, by Outcome, Incidence Type, and Year among Members with a Pre-Existing Condition of Atrial Fibrillation

Year	New Users	Dispensings	Total Days Supplied	New Episodes	Days At Risk	New Events	Eligible Members	Member Days	New Users/1k Eligible Members	Dispensings /User	Days Supplied/ User	Days Supplied/ Dispensing	New Events/ 100k Days at Risk
Multiple Incidence Type													
Outcome of GIH													
2008	8,584	28,832	1,138,657	8,584	1,203,207	33	157,387	8,893,069	54.5	3.4	132.6	39.5	2.7
2009	41,099	100,025	3,796,839	41,204	4,082,553	128	328,490	46,896,572	125.1	2.4	92.4	38.0	3.1
Outcome of ICH													
2008	8,588	28,793	1,137,288	8,588	1,202,081	27	157,388	8,893,457	54.6	3.4	132.4	39.5	2.2
2009	41,109	99,874	3,793,718	41,214	4,081,231	114	328,485	46,896,909	125.1	2.4	92.3	38.0	2.8
Outcome of GIH or ICH													
2008	8,548	28,631	1,131,763	8,548	1,194,614	60	157,380	8,892,353	54.3	3.3	132.4	39.5	5.0
2009	40,914	99,430	3,777,948	41,019	4,058,319	238	328,476	46,894,990	124.6	2.4	92.3	38.0	5.9
Single Incidence Type													
Outcome of GIH													
2008	8,584	28,832	1,138,657	8,584	1,203,207	33	157,387	8,893,069	54.5	3.4	132.6	39.5	2.7
2009	40,917	99,651	3,780,205	40,917	4,063,860	127	326,809	46,711,663	125.2	2.4	92.4	37.9	3.1
Outcome of ICH													
2008	8,588	28,793	1,137,288	8,588	1,202,081	27	156,907	8,861,912	54.7	3.4	132.4	39.5	2.2
2009	40,928	99,501	3,777,039	40,928	4,062,513	114	325,847	46,541,330	125.6	2.4	92.3	38.0	2.8
Outcome of GIH or ICH													
2008	8,548	28,631	1,131,763	8,548	1,194,614	60	157,380	8,892,353	54.3	3.3	132.4	39.5	5.0
2009	40,734	99,058	3,761,359	40,734	4,039,691	237	326,801	46,710,562	124.6	2.4	92.3	38.0	5.9

Appendix. ICD-9-CM Diag for GIH and ICH

Event	Diagnosis Code	Description
GIH		
	531.0	Acute gastric ulcer with hemorrhage
	531.2	Acute gastric ulcer with hemorrhage and perforation
	531.4	Chronic or unspecified gastric ulcer with hemorrhage
	531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
	532.0	Acute duodenal ulcer with hemorrhage
	532.2	Acute duodenal ulcer with hemorrhage and perforation
	532.4	Chronic or unspecified duodenal ulcer with hemorrhage
	532.6	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
	533.0	Acute peptic ulcer of unspecified site with hemorrhage
	533.2	Acute peptic ulcer of unspecified site with hemorrhage and perforation
	533.4	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
	533.6	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
	534.0	Acute gastrojejunal ulcer with hemorrhage
	534.2	Acute gastrojejunal ulcer with hemorrhage and perforation
	534.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
	534.6	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation
	578.0	Hematemesis
ICH		
	431	Intracerebral hemorrhage