

MINI-SENTINEL METHODS

DEVELOPMENT OF THE MINI-SENTINEL TAXONOMY PROMPT SELECTION TOOL: YEAR THREE REPORT OF THE MINI-SENTINEL TAXONOMY PROJECT WORKGROUP

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September 30, 2013

Mini-Sentinel is a pilot project sponsored by the [U.S. Food and Drug Administration \(FDA\)](#) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the [Sentinel Initiative](#), a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Methods
Development of the Mini-Sentinel Taxonomy PROMPT Selection Tool:
Year Three Report of the Mini-Sentinel Taxonomy Project Workgroup

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I. OVERVIEW OF TAXONOMY

A key function of the Mini-Sentinel pilot program is to develop the capacity to perform semi-automated prospective routine observational monitoring of newly approved medical products. Toward that end, Mini-Sentinel investigators have developed four programs, called Prospective Routine Observational Monitoring Program Tools (PROMPTs), that implement epidemiological and statistical methods to perform sequential analyses of data as they accrue in the Mini-Sentinel Distributed Database to assess the association between medical products and health outcomes of interest.

One PROMPT uses a within-person (i.e., self-controlled) design whereas the other three use between-person (i.e., cohort designs). Briefly, *PROMPT: Group Sequential Analysis with Self-Control Design* makes within-person comparisons while *PROMPT: Cohort Matching*, *PROMPT: Group Sequential GEE (GS GEE) Cohort Regression* and *PROMPT: Group Sequential Inverse Probability of Treatment Weighting (GS IPTW) Regression* compare independent exposure groups. The key design and estimation distinctions among the three cohort-based approaches is that *PROMPT: Cohort Matching* uses propensity score matching to address confounding and estimates hazard ratios and rate ratios, *PROMPT: GS GEE Cohort Regression* uses outcome regression modeling to address confounding and estimates risk ratios, and *PROMPT: GS IPTW Regression* uses inverse probability of treatment weighting to address confounding and estimates risk differences. More details about each PROMPT are available in the PROMPT Users' Manual, and in technical users' guides that accompany each PROMPT.

These PROMPTs are designed to take in a small number of input parameters (including the medical product of interest, the outcome of interest, the relative timing of exposure and outcome, and covariates of interest) and permit rapid, semi-automated, sequential analysis of the association between the medical product and outcome of interest across the Mini-Sentinel Distributed Database. In addition to selecting the input parameters, a key consideration in the implementation of a routine monitoring activity is deciding on the most appropriate PROMPT. An approach to expediting the decision-making process is essential to ensure expeditious implementation of each routine monitoring activity.

A. SUMMARY OF YEARS 1 AND 2 WORK

The overarching goals of the Mini-Sentinel Taxonomy Workgroup were to: (1) categorize potential medical product safety scenarios that could be monitored within a Sentinel System according to select key characteristics; (2) map these categories to appropriate design and analytic methods suitable for active safety monitoring using electronic healthcare data; and (3) provide clarity and practical advice for choosing the most appropriate signal refinement methodology for the Mini-Sentinel program in order to support efficiency and transparency in decision-making.

The Taxonomy Workgroup was established during Year 1 of the Mini-Sentinel program and focused on identifying typical scenarios that may be subject to monitoring within the Sentinel System. Initially, key characteristics of exposures, health outcomes of interest (HOI), and the relations between them were identified.¹ The Workgroup then distilled the list down to scenarios defined by combinations of characteristics that influence monitoring design choice. Workgroup members then sought to identify the methodological design options for studying these scenarios and mapped a preferred design (or designs) to each scenario type. The key considerations for the design decisions were: (1) strength of within- and between-person confounding; (2) circumstances that may predispose to misclassification of exposure or misclassification of the timing of the HOI; and (3) whether the exposure of interest is transient or sustained.^{1,2}

The Year 2 Taxonomy Workgroup expanded the decision table beyond design choices to include analytic approaches that are most suitable for each scenario. Specifically, the Workgroup (1) identified current analytic methods most readily applicable to signal refinement activities in a distributed network of electronic healthcare databases; (2) mapped monitoring scenarios (as defined by combinations of characteristics) to analytic options; (3) addressed additional specific methodological considerations likely to arise in routine active monitoring activities; (4) identified methodological gaps; and (5) developed a glossary of terms to help harmonize the language of active monitoring.³

B. OBJECTIVES OF TAXONOMY 3

The overall objective of the Year 3 Taxonomy Workgroup was to operationalize the previously developed Taxonomy Framework into a user-friendly tool to assist in efficient and transparent selection

of the most appropriate PROMPT for a given routine monitoring activity. In particular, the Year 3 Taxonomy Workgroup sought to: (1) develop an interactive Excel-based tool to facilitate the use of the Taxonomy Framework; (2) identify a sample of exposure/outcome pairs that could be monitored within Mini-Sentinel and evaluate them in the Taxonomy framework; and (3) provide support to the PROMPT Steering Committee by applying the framework to routine monitoring activities as needed.

II. TAXONOMY PROMPT SELECTION TOOL

A. DESIGN AND ELEMENTS

We operationalized the Mini-Sentinel Taxonomy Framework into an interactive decision-support tool that uses Microsoft Excel. The tool includes 11 items, classified into four groups of characteristics. Each item is represented as a column in the tool. Users specify the scenario by typing in the name of the medical product of interest and the HOI as a row in the table. The interactive tool then allows users to select a single option for each of the 11 items. A screenshot of the tool is included as Appendix A of this report.

To select an option, users click on a light gray cell corresponding to the row (i.e., scenario) and column (i.e., the particular item) of interest. An arrow appears (though the appearance may vary depending on the version of Excel being used), which the user can click on to select from among up to four options for each item. Alternatively, the user can click on a cell of interest and begin typing the desired option. The option will automatically appear, which the user can click on to select. If the user types the option into the cell, the spelling formatting and punctuation must appear exactly as it does in the list of options below the table in order for the tool to function properly. For this reason, we suggest selecting options using the drop down menu, which will guarantee proper functioning. The four categories, 11 items, and options for each item are listed below:

1. Characteristics determined by stakeholder/investigator
 - a. Effect measure of interest
 - i. Difference measure
 - ii. Ratio measure
 - b. Number of comparison groups

- i. One
 - ii. Multiple
 - c. Comparison exposure
 - i. Active comparator
 - ii. Unexposed (could be exposed to other products as part of standard care – e.g., as add-on)
- 2. Exposure
 - a. Exposure use pattern
 - i. Transient (1-7 days)
 - ii. Intermediate (8-30 days)
 - iii. Not transient (>30 days)
- 3. Potential exposure/HOI link
 - a. Relative frequency of exposure vs. outcome
 - i. More exposed individuals
 - ii. Similar numbers of exposed individuals and individuals with outcomes
 - iii. More individuals with outcomes
 - iv. Uncertain
 - b. Onset of exposure risk window
 - i. Acute (0-14 days)
 - ii. Intermediate (15-42 days)
 - iii. Delayed (>42 days)
 - iv. Uncertain
 - c. Duration of exposure risk window
 - i. Short (1-7 days)
 - ii. Intermediate (8-30 days)
 - iii. Long (>30 days)
 - iv. Uncertain
 - d. Strength of between person confounding
 - i. Negligible or addressable
 - ii. Likely unaddressable

- iii. Uncertain
 - e. Strength of within person confounding
 - i. Negligible or addressable
 - ii. Likely unaddressable
 - iii. Uncertain
- 4. HOI
 - a. HOI trend in population during observation
 - i. Uniform
 - ii. Changing (increasing, decreasing, cyclical)
 - iii. Uncertain
 - b. Expected degree of onset misclassification
 - i. Minimal (0-3 days)
 - ii. Moderate (4-10 days)
 - iii. Substantial (>10 days)
 - iv. Uncertain

Once the user has selected an option for each of the 11 items for a given exposure-HOI pair, the tool will automatically generate a design and adjustment strategy (corresponding to the four PROMPTs) along with warning messages, if applicable.

Options for each item are listed below the set of rows. A brief explanation of each item is also provided in the tool. Options can be changed at any time. As long as an option is selected for each item, changing the option selection for an item will potentially result in a real-time change in the recommended design and adjustment strategies.

B. SCORING

The tool uses a scoring system to implement the guidance developed as part of the Taxonomy Framework. Each scenario receives a numeric value for each of the eight items that have bearing on the choice between a within- versus between-person design (i.e., number of comparison groups, comparison exposure, exposure use pattern, onset of exposure risk window, duration of exposure risk

window, strength of between person confounding, strength of within person confounding, and expected degree of onset misclassification), depending on the option selected. Positive values indicate that the option selected favors a within-person comparison and negative values indicate that the option favors a between-person comparison. The sizes of the values reflect the relative degree to which the given option favors the particular design approach. The values are summed across each of the eight items. A score of zero indicates that a self-controlled or cohort appropriate would be equally appropriate, given the characteristics of the scenario. A score of -1 would indicate a slight preference for a between-person comparison whereas a score of 1 would indicate a slight preference for a within-person comparison. Values smaller than -1 reflect a stronger preference for a between-person comparison and values larger than 1 reflect a stronger preference for a within-person comparison. The resulting recommendation is indicated in the blue “Design” column corresponding to the given scenario row. The weights assigned to each option are indicated in **Table 1**. Weights were determined by consensus among Workgroup members.

Table 1: Weights assigned to options for items that affect the design choice

Item	Options	Weight
Number of comparison groups	One	0
	Multiple	-1
Comparison exposure	Active comparator	-9
	Unexposed (could be exposed to other products as part of standard care -- e.g., as add-on)	1
Exposure use pattern	Transient (1-7 days)	1
	Intermediate (8-30 days)	-1
	Not transient (>30 days)	-2
Onset of exposure risk window	Acute (0-14 days)	1
	Intermediate (15-42 days)	0
	Delayed (> 42 days)	-1
	Uncertain	-1
Duration of exposure risk window	Short (1-7 days)	1
	Intermediate (8-30 days)	0
	Long (>30 days)	-1
	Uncertain	-1
Strength of between person confounding	Negligible or addressable	0
	Likely unaddressable	4
	Uncertain	3
Strength of within person confounding	Negligible or addressable	0
	Likely unaddressable	-2

Item	Options	Weight
	Uncertain	-1
Expected degree of onset misclassification	Minimal (0-3 days)	1
	Moderate (4-10 days)	0
	Substantial (>10 days)	-1
	Uncertain	-1

One item (HOI trend in population during observation) has bearing on whether adjustment is needed in a self-controlled design. If the design recommendation is a within-person approach and the user specifies that the HOI trend is either changing or uncertain, then the tool will indicate that adjustment is needed. Three items influence the adjustment strategy if a between-person design is recommended: effect measure of interest, number of comparison groups, and relative frequency of exposure versus outcome. These are weighted separately from the design scores. Both the *PROMPT: Cohort Matching* and the *PROMPT: GS IPTW Regression* can provide estimates based on difference measures, whereas *PROMPT: GS GEE Cohort Regression* provides only a relative effect estimate. Thus, if the “difference measure” option is selected, the propensity score- and IPTW-based approaches receive a value of 10 and the outcome regression approach receives a value of zero, which deterministically excludes the outcome regression approach from further consideration.

Three items influence selection of the adjustment strategy: “number of comparison groups”, “effect measure of interest”, and “relative frequency of exposure vs. outcome”. The *PROMPT: Cohort Matching* and the *PROMPT: GS GEE Cohort Regression* can provide estimates based on ratio measures, whereas *PROMPT: GS IPTW Regression* cannot. Thus, if the “ratio measure” option is selected, the propensity score- and outcome regression-based approaches receive a value of 10, which deterministically excludes the IPTW approach from further consideration. Of the three cohort-based approaches, only the *PROMPT: GS GEE Cohort Regression* can easily accommodate multiple comparison groups. Thus, if the “multiple” option is selected for the “number of comparison groups” the *PROMPT: GS GEE Cohort Regression* receives a score of 1 and the other two approaches receive zeros. This option is not deterministic as the other two programs can be run multiple times to accommodate multiple exposure groups. The approaches receive no points if the “one” option is selected since all three approaches can similarly handle a single exposure group.

If the “more exposed individuals” option is selected for the “relative frequency of exposure vs. outcome” item, then the PS and IPTW approaches receive a score of 1 and the outcome regression approach receives a score of zero because modeling the exposure would likely be more robust than modeling the outcome. If the “similar numbers of exposed individuals and individuals with outcomes” or the “uncertain” option is selected, then there is no preference for modeling either exposure or outcome, so no approach receives points. If there are “more individuals with outcomes” then there is an advantage to modeling the outcome, so the outcome regression-based approach receives a point. Points are then summed across the three items that influence selection of the adjustment strategy in cohort approaches and the strategy or strategies with the highest total populate the blue “Adjustment” column in the “Recommendation” section of the tool.

C. INSTRUCTIONS FOR USE

Below we provide step-by-step instructions for using the tool. These instructions are also provided in the Mini-Sentinel Taxonomy PROMPT Selection Tool implementation guide, which is included as an Appendix B to this report.

Step 1: Open the Taxonomy Module Selection Tool from the Mini-Sentinel webpage. An example scenario comes preloaded.

Step 2: Type the name of the medical product into the “Medical product” column (column B). The tool can accommodate up to 35 scenarios. See below for instructions on how to expand to more than 35 scenarios.

Step 3: Type the name of the health outcome of interest in the “Health outcome of interest (HOI)” column (column C).

Step 4: Select the appropriate option for each of the 11 characteristics in columns D through N. Brief explanations and options available for each characteristic are provided immediately below the table. To select an option for a given characteristic, click on the cell in which the column for that characteristic intersects with the row for the particular scenario (e.g., cell D6 for “Effect measure of interest” for

scenario 1). Either click on the arrow to make a selection or type in one of the available options. Typing will cause the option to appear. To select it, simply click on the name of the option. The tool requires that the options in each cell exactly match one of the options below the table; else an error will occur. Options can be changed at any time. A selection for each of 11 characteristics is required in order to have the recommended design and analysis appear.

Step 5: Once an option has been selected for each of the 11 characteristics, the tool will provide a recommended design and analysis approach. The tool will also provide important warnings, where appropriate, about potential limitations and how they may affect the interpretation of the analytic findings.

Step 6: Save the file if you would like to return to the specified inputs. Be sure to save the file with a new name to prevent overwriting files. An original blank version can be downloaded from [[link to Mini-Sentinel webpage](#)].

The tool accommodates up to 35 scenarios at a time. If a user wishes to include more than 35 scenarios, multiple files can be used. Users may want to estimate both a difference measure (e.g., risk difference) and a ratio measure (e.g., rate ratio) of association for a particular scenario. To accomplish this, the medical product and HOI pair should be inserted on two separate rows, with *difference measure* selected as the “Effect measure of interest” in one row and *ratio measure* selected in the other row. Cells outside of those used to select the scenario characteristics (i.e., non-gray cells) are locked to prevent accidental changes to the formulas in the tool. Instructions and the password to unlock the spreadsheet are available from Joshua Gagne (info@mini-sentinel.org).

III. TEST SAMPLE

To evaluate the Mini-Sentinel Taxonomy PROMPT Selection Tool, we developed a list of 35 scenarios, including drug, vaccine, and blood product exposures (**Table 2**). These exposure-outcome pairs represent a diverse set of scenarios with respect to exposure and outcome characteristics. The Workgroup then used the tool to select the most appropriate options for each characteristic item for each scenario. Selections were discussed until consensus was reached on each. We then evaluated the design and adjustment strategy recommendations to ensure that they made clinical and methodological

sense for each scenario. This process was helpful to ensure that the logic behind the scoring and weighting system was appropriate and to identify bugs in the code to automatically generate recommendation. In addition, this process led to many improvements in the wording of items, their options, and their explanations.

Table 2: List of 35 scenarios used to evaluate Taxonomy PROMPT Selection Tool

Exposure	Health outcome of interest
ticagrelor (Brilinta)	Anaphylaxis
ticagrelor (Brilinta)	Agranulocytosis
ticagrelor (Brilinta)	severe acute liver injury
ticagrelor (Brilinta)	gastrointestinal bleeding
ticagrelor (Brilinta)	hemorrhagic stroke
belimumab (Benlysta)	Anaphylaxis
belimumab (Benlysta)	Agranulocytosis
belimumab (Benlysta)	severe acute liver injury
belimumab (Benlysta)	Depression
belimumab (Benlysta)	Pneumonia
telaprevir (Incivek)	Anaphylaxis
telaprevir (Incivek)	Agranulocytosis
telaprevir (Incivek)	severe acute liver injury
telaprevir (Incivek)	skin reactions (EMM, SJS)
telaprevir (Incivek)	acute renal failure
ezogabine (Potiga)	Anaphylaxis
ezogabine (Potiga)	Agranulocytosis
ezogabine (Potiga)	severe acute liver injury
ezogabine (Potiga)	Torsades
ezogabine (Potiga)	Suicidality
indacaterol (Arcapta)	Anaphylaxis
indacaterol (Arcapta)	Agranulocytosis
indacaterol (Arcapta)	severe acute liver injury
indacaterol (Arcapta)	myocardial infarction
indacaterol (Arcapta)	gastrointestinal bleeding
dabigatran (Pradaxa)	Anaphylaxis
dabigatran (Pradaxa)	Agranulocytosis
dabigatran (Pradaxa)	severe acute liver injury
dabigatran (Pradaxa)	gastrointestinal bleeding
dabigatran (Pradaxa)	myocardial infarction
influenza virus vaccine (fluzone)	Anaphylaxis
influenza virus vaccine (fluzone)	Myocarditis
pneumococcal vaccine (Prevnar 13)	kawasaki disease
immune globulin (Carimmune)	acute renal failure
immune globulin (Gammagard liquid)	arterial thromboembolism (MI/stroke)

The set of test cases demonstrated a role for all four PROMPTs in active monitoring. This process also revealed that multiple PROMPTs may be suitable for a given scenario, based on the characteristics included in the Taxonomy PROMPT Selection Tool. When multiple PROMPTs are appropriate, it may be useful to run each recommended PROMPT as similar results from multiple methods that rely on different assumptions can bolster confidence in those results. However, there might also be theoretical or practical considerations for choosing one PROMPT over another that cannot be codified in or are outside of the scope of the Taxonomy Framework, such as computational time and ancillary aspects of the ways in which the methods are implemented and subsequent results are presented.

IV. RECOMMENDATIONS

The Mini-Sentinel Taxonomy PROMPT Selection Tool can facilitate the selection of PROMPTs in routine monitoring activities in which rapid implementation is critical. The PROMPT Users' Manual includes the use of this tool as an integral part of the development of the surveillance plan. The recommendations provided by the tool should be viewed as a methodological guide, but the ultimate decision about which PROMPT(s) to use should consider other factors, as described above. As new PROMPTs and enhancements to existing programs become available, the Taxonomy PROMPT Selection Tool will necessarily require updating, both with respect to available recommendations it provides and with respect to the characteristics that factor into those recommendations.

During the development and testing of the tool, the Workgroup identified the lack of a case-indexed self-controlled design (e.g., case-crossover and its variants) and the lack of use of historical data as particularly important gaps in the suite of methods available among the PROMPTs. Case-indexed approaches can be useful for scenarios in which a self-controlled design is preferred, but exposure-indexed methods may be biased, such as when the occurrence of an outcome influences the probability of exposure within an individual or censors follow-up.^{4,5} Physicians can and do change prescribing based on the occurrence of an event. For example, having a bleeding outcome will likely reduce the probability of later exposure to warfarin or, in a more extreme setting, death would preclude exposure and lead to spuriously strong effect sizes.

Data from historical cohorts can be useful for obtaining expected event frequencies against which to compare observed event frequencies when a new medical product enters the market. Historical comparators can be especially useful for assessing the safety of new vaccines, since events are often

very rare and new products have such complete uptake in the population that there are few concurrent patients that are unexposed or exposed to appropriate comparators. Historical data can also be used to derive disease risk scores that can then be applied to adjust for confounding in an assessment using a concurrent comparator.⁶

The Taxonomy Workgroup recommends the development of a case-indexed module and the ability to leverage data on historical cohorts within the Mini-Sentinel Distributed Database to round out the methods available to FDA for routine monitoring.

V. ACKNOWLEDGEMENTS

We thank Michael Nyguen and Patrick Archdeacon from FDA for their helpful input on the selection and characterization of the sample of test scenarios.

VI. REFERENCES

1. Gagne JJ, Fireman B, Ryan PB, et al. Design considerations in an active medical product safety monitoring system. *Pharmacoepidemiol Drug Saf* 2012;21 Suppl 1:32-40.
2. Taxonomy for monitoring methods within a medical product safety surveillance system: Report of the Mini-Sentinel Taxonomy Project Work Group., 2010. (Accessed at http://www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_FinalTaxonomyReport.pdf.)
3. Taxonomy For Monitoring Methods Within A Medical Product Safety Surveillance System: Year Two Report Of The Mini-Sentinel Taxonomy Project Workgroup. 2012. (Accessed at http://www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Taxonomy-Year-2-Report.pdf.)
4. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. *Biostatistics* 2009;10:3-16.
5. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;25:1768-97.
6. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. *Pharmacoepidemiol Drug Saf* 2012;21 Suppl 2:138-47.

VIII. APPENDIX B: MINI-SENTINEL TAXONOMY PROMPT SELECTION TOOL IMPLEMENTATION GUIDE

PURPOSE

The Mini-Sentinel Taxonomy Module Selection Tool is intended to facilitate the decision-making process when selecting a Mini-Sentinel Prospective Routine Observational Monitoring Program Tool (PROMPT) for a routine active surveillance activity.

DESCRIPTION

Mini-Sentinel has developed four PROMPTs to conduct routine active surveillance: (1) self-control; (2) propensity score; (3) regression; (4) inverse probability weighting. Details about the programs can be found elsewhere [[link to PROMPT documentation on Mini-Sentinel webpage](#)].

The Taxonomy Module Selection Tool is a Microsoft Excel-based program that guides users through the Mini-Sentinel Taxonomy Framework and provides recommendations for design and analytic strategies for active monitoring scenarios based on user-specified parameters. The tool requires users to specify 11 scenario characteristics, which are categorized as those determined by the stakeholder or investigator, those pertaining to exposure, those pertaining to the health outcome of interest (HOI) and those pertaining to the (potential) link between the exposure and the HOI. For each characteristic, users select from among up to four options.

INSTRUCTIONS FOR USE

Step 1: Open the Taxonomy Module Selection Tool from [[insert link to Mini-Sentinel webpage](#)]. An example scenario comes preloaded.

Step 2: Type the name of the medical product into the “Medical product” column (column B). The tool can accommodate up to 35 scenarios. See below for instructions on how to expand to more than 35 scenarios.

Step 3: Type the name of the health outcome of interest in the “Health outcome of interest (HOI)” column (column C).

Step 4: Select the appropriate option for each of the 11 characteristics in columns D through N. Brief explanations and options available for each characteristic are provided immediately below the table. To select an option for a given characteristic, click on the cell in which the column for that characteristic intersects with the row for the particular scenario (e.g., cell D6 for “Effect measure of interest” for scenario 1). Either click on the arrow to make a selection or type in one of the available options. Typing will cause the option to appear. To select it, simply click on the name of the option. The tool requires that the options in each cell exactly match one of the options below the table; else an error will occur. Options can be changed at any time. A selection for each of 11 characteristics is required in order to have the recommended design and analysis appear.

Step 5: Once an option has been selected for each of the 11 characteristics, the tool will provide a recommended design and analysis approach. The tool will also provide important warnings where appropriate.

Step 6: Save the file if you would like to return to the specified inputs. Be sure to save the file with a new name to prevent overwriting files. An original blank version can be downloaded from [*insert link to Mini-Sentinel webpage*].

ADDITIONAL INFORMATION

- The tool accommodates up to 35 scenarios at a time. If a user wishes to include more than 35 scenarios, multiple files can be used.
- Users may want to estimate both a difference measure (e.g., risk difference) and a ratio measure (e.g., rate ratio) of association for a particular scenario. To accomplish this, the medical product and HOI pair should be inserted on two separate rows, with *difference measure* selected as the “Effect measure of interest” in one row and *ratio measure* selected in the other row.
- Cells outside of those used to select the scenario characteristics (i.e., non-gray cells) are locked to prevent accidental changes to the formulas in the tool. Instructions and password to unlock the spreadsheet are available from Joshua Gagne (info@mini-sentinel.org).