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# Taxonomy for monitoring methods within a medical product safety surveillance system: Report of the Mini-Sentinel Taxonomy Project Work Group

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## Executive Summary

The mission of Sentinel System requires an approach to active medical product monitoring that is collaborative, standardized, transparent, intelligible, consensus-designed, timely, and cost-efficient. The goal of the Mini-Sentinel Taxonomy Work Group was to characterize analytic methods suitable for signal refinement and to provide clarity and practical advice for choosing the most appropriate signal refinement methodology for the Mini-Sentinel System in order to support expediency and transparency in decision-making. The principles and recommendations contained herein can also be extended to signal generation and signal evaluation.

This project involved convening a large group of Mini-Sentinel collaborators, Observational Medical Outcomes Partnership staff, and FDA staff, to focus on identifying all possible types of scenarios that may be subject to monitoring within the Sentinel System. Initially, all characteristics of exposures, health outcomes of interest (HOI), and the relations between them were identified. The Work Group then distilled the list down to 64 scenarios defined by combinations of characteristics that influence monitoring design choice. Work group 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, which leads to misclassification of exposure; and (3) whether the exposure of interest is transient or sustained.

A key recommendation is that when the basic assumptions of self-controlled designs are fulfilled (i.e. transient exposure, lack of within-person, time-varying confounding, and abrupt HOI), self-controlled designs are to be preferred because of their inherent ability to avoid confounding by time-invariant confounding without having to measure those confounding factors. As scenarios diverged from those in which these assumptions were tenable, cohort-type approaches are generally preferred. When either self-controlled or cohort approaches are recommended (or when one is preferred but the other is listed as a possibility), several additional considerations are

recommended, including whether absolute measures of risk (e.g. risk difference) can be estimated, and the availability of a reasonable active comparator.

It is intended that the preemptive mapping of question categories to signal refinement approaches will expedite the implementation of appropriate methods for the questions as they are brought to Sentinel and will help FDA and Sentinel stakeholders understand the capabilities and limitations of Sentinel. A supplement to this report also summarizes gaps in existing methodology for active medical product safety monitoring and recommended next steps with regard to methodological development.

## Introduction

This report summarizes the work of the FDA's Mini-Sentinel Taxonomy Work Group, which was intended to provide clarity and practical advice for choosing the most appropriate safety monitoring methodology for the Mini-Sentinel System (Sentinel). The mission of the Sentinel System requires an approach to medical product monitoring that is collaborative, standardized, transparent, intelligible, consensus-designed, timely, and cost-efficient. This report focuses on methods for signal refinement, which may include (1) activities undertaken to monitor a safety issue identified during a medical product's development program or to monitor a potential safety issue that may not have been seen during development but may be thought plausible due to class effects or pharmacological properties of the medical product; and (2) activities undertaken to evaluate a safety issue that is identified by various sources at some point after marketing. However, the methodological principles discussed and general recommendations made in this report can also be extended to signal generation and signal evaluation activities. In a supplement to this report, we propose new areas of methods development to pursue in year 2 and beyond, based, in part, on the work of the Taxonomy Work Group.

Potential associations between medical products and health outcomes of interest (HOI) that arise from monitoring within Sentinel (whether in generation, refinement, or evaluation activities) will be due to three possible explanations – bias, chance, and true causal relations. Bias – including, confounding, selection, and information biases – can be reduced by making appropriate fundamental "*design choices*" and "*analytic choices*," thereby facilitating subsequent assessment of causal relations by "*signaling methods*." We define design choices as constraints on observation time intended to yield the most valid comparisons. For example, constraints may be used to restrict signal refinement to a particular patient population defined by a certain age range or by presence of a specific underlying medical condition. Constraints could also be used to define a period of observation time to serve as a basis for comparison, such as the identification of a comparator group (through matching or restriction, for example) or ascertainment of an alternate observation period in a patient's history. Analytic choices pertain to statistical methods, applied within the context of design choices, to promote valid estimation of associations. Signaling methods imply analytic approaches used to determine when sufficient

evidence – beyond chance – exists, indicating a product-HOI association requiring further attention (e.g. a test statistic or a decision rule).

It is critical to understand which types of product-HOI pairs (i.e. *"monitoring scenarios"*) can be reliably investigated by Sentinel, which methods are preferred for the different types of product-HOI pairs regarding their statistical and practical properties, and which analytic data structures will best support the preferred methods. We define an analytic data structure as the way in which source data (from a common data model, for example) are organized to conform to the design choice, to support the analytic method, and to enable the application of signaling methods. In addition to selection of the best signal refinement methods for particular scenarios, valid estimation of apparent risk, and the bounds of the risk, is central to active medical product monitoring in order to facilitate risk communication and public health decision-making.

## Goals

The purpose of the Taxonomy Work Group was to categorize potential medical product safety scenarios that will be subject to monitoring within Sentinel, according to select key characteristics, to map these categories to appropriate design, analytic, and signaling methods for active safety monitoring using electronic healthcare data, and to identify the analytic data structure needed to facilitate the implementation of these approaches.

This report is limited to major design choices and does not yet include analytic choices or signaling methodologies. It is intended that the preemptive mapping of question categories to signal refinement approaches will expedite and increase the transparency of the implementation of appropriate methods for the scenarios as they are brought to Sentinel and will help FDA and Sentinel stakeholders understand the capabilities and limitations of the system. In this report, we summarize recommended next steps and gaps in existing methodology for active medical product safety monitoring.

## Processes

The Taxonomy Work Group held an in-person kick-off meeting on April 11, 2010 in conjunction with the International Society for Pharmacoepidemiology's (ISPE's) annual Mid-Year meeting, which was held in Raleigh, North Carolina. At this meeting, participants brainstormed potential characteristics of monitoring scenarios that could drive signal refinement methods decisions. Leaders of the Observational Medical Outcomes Partnership (OMOP) also provided an overview of related work, which catalyzed the discussion. The main outcome of this meeting was the initial development of a table classifying monitoring scenarios according to the identified dimensions.

Following the kick-off meeting, a summary of the discussion at the meeting was drafted which served as the basis of this working document. This document was further revised through monthly teleconferences among Work Group participants. Between teleconferences, the Core Writing Group met periodically to address and incorporate into the working document critical comments raised during the calls. Three drafts of the working document were circulated among Work Group participants and additional comments were elicited.

On June 22, 2010, members of the Core Writing Group provided an overview of the project and a status update to members of the FDA's internal Sentinel Methods Working Group via teleconference. FDA Sentinel Methods Working Group members were invited to review and comment on the then-current iteration of the working document, which resulted in further important revisions. The July Work Group teleconference focused on working through an example of a hypothetical monitoring scenario (lisinopril and angioedema) to pilot-test the maturing decision table. This discussion was followed by another in-person meeting of Work Group members on August 20, 2010 at the ISPE annual meeting in Brighton, England. Based on revisions to the document and structured decision table from the pilot-test example, four additional monitoring scenarios were mapped into the table. The discussions surrounding these five examples, described below, informed the more general mapping of monitoring scenarios to appropriate design choices. Potential revisions were discussed with FDA staff on October 21, 2010 and are incorporated in this report.

## Approach

The appropriate methods for particular monitoring scenarios depend largely on the characteristics of the medical product to be monitored, characteristics of the monitoring HOI, and characteristics of the relation between them. This report focuses on signal refinement activities within Sentinel, including sequential identification of medical product users and outcomes prospectively, or single epidemiologic inquiries performed retrospectively if a safety issue emerges late in a product's post-marketing experience.

All relevant characteristics of exposures, HOIs, and the relations between them were identified. While we focused on characteristics that are likely to influence decisions regarding best design, analytic, and signaling methods for signal refinement, this framework can also apply to signal generation and signal evaluation.

### *1.1 Exposure characteristics*[*]

Signal refinement questions brought to Sentinel may involve various types of regulated medical products with differing exposure patterns that may influence the choice of signal refinement methods. For example, use of some medical products is measured as fixed exposures at single points in time, such as vaccines and single-use devices (e.g. embolic protection device). Other products, such as intrauterine devices, are also measured once but are left in the body to confer continuous exposure. Other medical products are used more than once but for short periods, such as on an intermittent, as needed, or episodic basis, including drugs such as antibiotics, triptans for migraine, and analgesics. Other exposures are intended for sustained continuous use, such as statins and other medications for chronic conditions, though actual use may vary because

[*]*Note: not all medical products of interest are captured in usual electronic healthcare data. For example, some devices, such as contact lenses and dermal fillers, may require special data sources, if they are at all amenable to active safety monitoring within Sentinel. Furthermore, the Taxonomy project is intended to guide decisions regarding the best methodology for given monitoring scenarios, but it may be possible that the best choices are impracticable because of data limitations (e.g. poor data quality, missing covariate information, etc.) or because implementation of the best methods across a distributed data network is intractable. When the best methods cannot be implemented, decisions will need to be made about whether to proceed with an inferior approach or address the underlying limitations in other ways.*

of non-adherence. Such exposures will typically be identifiable in electronic healthcare data as repeated prescription refills.

Each aspect of the types of exposures investigated by Sentinel was discussed and was boiled down to a single important distinction that will drive design choice – exposure persistence; that is, whether the exposure is transient or sustained. The purpose of this dichotomy is that validity of results of certain signal refinement designs depends strongly on the transience of the exposure [the reference to this statement is the preliminary, working report of the Mini-Sentinel Work Group on Case-Based Approaches].

It is important to note that some transient exposures (e.g. exposure to an implanted device) have both transient aspects (e.g. the surgery and initial exposure to the device) and a sustained change in structure (e.g. the ongoing presence of the implant). Analogously, some sustained exposures can have both transient and sustained aspects. Drug initiation can be conceptualized as a transient event followed by sustained presence of the drug with repeated use. Also note that certain medical products can be classified as both transient and sustained exposures because some patients use them briefly while others use them repeatedly over a long period. For signal refinement questions involving medical products that can be classified as either transient or sustained, the choice of which to use should be guided by the particular question. For example, in attempting to determine whether a newly marketed antibiotic causes anaphylaxis, the transient initiation of the drug is more relevant than sustained exposure to it. On the other hand, if the question regards cancer in relation to exposure to the antibiotic, initiation may be less relevant than sustained exposure. It is important to note that, within electronic healthcare data, measurements of exposure persistence may not correspond with biological exposure persistence, which is the actual quantity of interest. For example, a vaccination may be recorded once and regarded as a transient exposure whereas implantation of a device may also be recorded once but be regarded as a sustained exposure.

Whether the medical product of interest is commonly used is another exposure attribute that may influence the choice or implementation of a signal refinement method. For example, exposures

may be common, such as anti-inflammatory drugs, or uncommon, such as chemotherapeutic agents. It was determined that the frequency of exposure in a population does not have an important influence on fundamental design choice (though it may limit the use of certain data sources), but that this could impact on the analytic choice (e.g. whether propensity score techniques or disease risk score methods are employed). Special types of exposure may also warrant different considerations, such as non-prescription drug products (aka "over the counter" drugs), drug-drug interactions, dose escalations or reductions, and combination products (e.g. drug-eluting stents). These are areas requiring additional investigation.

### *1.2 Health outcome of interest (HOI) characteristics*

HOIs can be classified according to several characteristics that may influence the choice of signal refinement methods. HOIs may have an abrupt onset (e.g. stroke, acute myocardial infarction [AMI]) or they may be insidious in nature (e.g. diabetes, heart failure). The accurate ascertainment of the timing of HOI onset is critical to traditional epidemiologic designs based on incidence and risk. In cohort-type analyses, delayed identification of onset of an insidious HOI can result in misclassification of the HOI. In self-control-type analyses, incorrect identification of onset time can result in misattribution of exposures to case- and control-times. Because self-controlled designs are very sensitive to changes in risk with time, the deleterious effects of misclassification of outcome onset time may be more severe in self-controlled designs than in cohort-type approaches.[1,2] Although non-differential misclassification of exposures and HOIs is generally considered conservative in epidemiologic research, since it typically biases estimates towards the null, there is no reason to expect non-differentiality in healthcare database. Even if it could be assumed, such bias cannot be considered conservative in adverse event monitoring since it can result in false negative signals.

HOIs can also be classified across a gradient of background frequencies. For example, while AMI occurs infrequently in the general population, incidence of Stevens-Johnson syndrome is exceedingly rare. The *frequency of the monitoring* HOI has implications for the analytic choice (e.g. disease risk scores may be difficult to estimate in a monitoring population in which the HOI is rare, particularly early in the signal refinement timeframe, unless historical or external data are

considered) and for the precision of estimates (or statistical power), which may affect the decision between test-based signaling methods (e.g. maximum sequential probability ratio test [maxSPRT])[3] and estimate-based approaches (e.g. disproportionality measures). However, even though power considerations may also be important in deciding upon the underlying design (e.g. cohort-type vs. self-controlled),[4] it was decided that this consideration is secondary to making appropriate design choices for validity reasons, but may be an important element for analytic choices and decisions regarding signaling methods.

The periodicity, or opportunity for recurrence, of HOIs was also considered. For example, some HOIs occur repeatedly (or episodically; e.g. seizure) and others do not (e.g. mortality). For practical purposes, however, we felt that this characteristic does not affect fundamental design choices since, often, signal refinement will focus on only the first occurrence of repeatable HOIs. For example, while thromboembolism can occur repeatedly, it is unlikely that monitoring HOIs will focus on multiple thromboembolic occurrences.

### *1.3 Characteristics of the (potential) causal link between exposure and health outcome of interest (HOI)*

Some attributes are characteristic of both the exposure and the HOI. For example, timing of the event, relative to the exposure, may have implications for signal refinement methods decisions. The question is whether the risk window is short or long, and tied closely in time to initiation of exposure. In general, the later-appearing effects have a wider interval over which they may appear. The interval over which the exposure confers risk (i.e. the exposure-risk window) is a function of both the use pattern and also the biological mechanism that links the exposure with the HOI. For some pairs, a single dose of a medication may be considered a transient exposure with an *onset of exposure-risk window* immediately following the drug use. Regardless of the timing of the onset of the exposure-risk window, the interval over which an immunomodulating agent, for example, may confer risk depends on the HOI. For example, if the HOI is risk of infection, we may concern ourselves only with risk in the short-term. However, we might instead be interested in a longer-term HOI, such as lymphoma. Thus, with either immediate or delayed onset, the *duration of the exposure-risk window* may be short or long. Similarly, for

implantable devices with sustained exposure (e.g. total hip implant) we may be interested in either short-term outcomes (e.g. infection), long-term outcomes (e.g. revisions), or both. These scenarios depend both on timing of HOI onset (e.g. abrupt vs. insidious) and exposure use patterns (e.g. the medical product may confer risk only through continuous, or cumulative, exposure), as well as on the relative timing (e.g. immediately after exposure or delayed) of the HOI to the exposure.

Another attribute of the causal link is the measured strength of an association. HOIs that occur in short time windows have very high relative risks, but those for which there is an extended period may have a low relative risk. While it is unlikely that expected strength of an association would drive signal refinement methods and subsequent data structure decisions, it may have implications for the signaling method. Another, related domain, is the probable *nature of confounding* in a particular monitoring scenario, which may have bearing on the decision for appropriate signal refinement method. Confounding by indication can be strong or not strong depending on the way in which treatment decisions are made. Confounding by indication is likely to be strongest in situations in which the HOI (or correlates of the HOI) is anticipated or in which risk factors for the HOI drive treatment decisions.

Variation in confounding, whether strong or not, can present on two axes – between-person confounding and within-person confounding. Some approaches are more suitable for dealing with certain confounding scenarios than others.[5,6] Answering the following question can help understand the strength of within-person confounding for a particular scenario: Does the treatment indication (i.e. the onset or worsening of the condition for which the medical product is used) cause the HOI such that the use of the medical product is a marker for the indication? For example, initiation of an antidiabetic medication is a marker for diabetes, which is a risk factor cardiovascular events. To understand the strength of between-person confounding, we can ask a different, but related question: Does an active comparator (or some other comparison group) exist such that the effect of the medical product indication on the HOI in those patients is similar to the effect in those patients exposed to the medical product of interest? In monitoring the risk of cardiovascular events associated with a particular antidiabetic medication, focusing on new

users of another antidiabetic drug as a comparison group will likely reduce the magnitude of confounding by indication as the reasons for prescribing the two antidiabetic medications are similar.

The availability of an appropriate active comparator is an important characteristic of the monitoring scenarios. When substantial unmeasured confounding between users and non-users of a particular medical product is expected, the use of an active comparator can help mitigate unmeasured confounding.[7] However, the appropriateness of an active comparator depends on both the exposure of interest and the outcome of interest. An active comparator is a type of negative control requiring two key assumptions to substantially mitigate confounding by indication and yield valid results: (1) that the reasons for initiation (i.e. the indications) of the active comparator are similar to those for the medical product of interest; and (2) that the active comparator does not cause the HOI (or, if it does, that this is recognized and that it is understood that the signal refinement question becomes one of comparative safety).

The structured decision table lists all combinations of exposure, HOI, and exposure-HOI link, characteristics that may be used to inform decisions about the most appropriate signal refinement design choice. The table also includes two monitoring scenario characteristics that are important for analytic choices and for choosing optimal signaling methods. Current and future Mini-Sentinel Work Groups are evaluating methods to better inform these decisions, which will be incorporated into this living document at a future time.

## Considerations for design families

Design choices include selection of an appropriate comparison group, restriction through inclusion and exclusion criteria, restriction through matching and other constraints applied to observation time.[8] Design choices are made to optimize validity of comparisons for generating signal refinement results. When focusing on pre-specified HOIs, medical product signal refinement resembles ordinary epidemiologic analyses.[9]

All signal refinement designs can be conceptualized as different approaches to sampling person-time from an underlying population of interest. A fundamental distinction in design choice is whether variation in exposure occurs within individuals over time or between individuals.[5] A limited set of exposure and HOI characteristics and their measurement, as well as the nature and magnitude of confounding are critical in deciding between the two fundamental approaches.

### *1.4 Within-person comparisons (i.e. self-controlled designs)*

Observational designs that involve within-person comparisons, or so-called "self-control" designs, include the self-controlled case series (SCCS),[10] the case-crossover design,[6] and the case-time-control design.[11] For a given monitoring scenario, only individuals who experience a HOI and have variation in the exposure of interest contribute to the analysis of self-control designs.[5,6] Self-control designs are most valid when the exposure is transient, the HOI is abrupt, and risk factors for the HOI are fixed within individuals over the (often short) observation period.[5,6] As in case-control studies,[12] further assumptions about the baseline risk in the study population are required to estimate absolute effect measures.

Additional considerations about how best to implement a self-control design may also be specific to the given monitoring scenario. For example, whether control-periods (or referent-periods) are allowed to occur after the HOI will depend on assumptions about whether the HOI may influence future exposure decisions. Self-controlled designs may also be more sensitive to misclassifications of the exposure onset and end.[1,2] The latter may be difficult to assess accurately in claims databases.

The major advantage of within-person comparisons, over between-person comparisons, is that confounding by fixed factors (e.g. genetic factors, family history, etc), whether measure or unmeasured, are inherently controlled. Thus, only risk factors that vary within individuals over time need to be addressed.

### *1.5 Between-person comparisons (i.e. cohort type designs)*

Classic epidemiologic designs employ between-person comparisons. These include cohort designs as well as case-control and case-cohort designs, both of which are equivalent to cohort designs but use efficient sampling techniques, rather than the full underlying cohort, to ascertain exposure and covariate distributions.[12,13] Although efficient sampling strategies are useful for studies in which resources (e.g. blood samples) are limited and/or costly (e.g. HOIs are rare), they offer no important practical advantages over full-cohort analyses for studies within electronic healthcare data.[14] In fact, analyses that sample from the underlying cohort may be less robust than approaches that use the full cohort.[4] Therefore, between-person comparisons should focus on full cohort analyses.

The key assumption for valid between-person comparisons is that between-person confounding can be adequately addressed. The extent to which between-person confounding can be addressed depends largely on whether an exchangeable comparison group can be identified. This entails decisions regarding use of truly unexposed comparison groups or those exposed to active comparators (if the assumptions for use of active comparators, described above, hold). Additional analytic choices may be required to further mitigate between-person confounding, such as matching, regression techniques, and methods to deal with time-varying confounding, etc).

Additional considerations about how best to implement between-person comparisons may also be specific to the given monitoring scenario. For example, stakeholders will need to determine whether it is appropriate to include prevalent users of the medical product of interest or whether only new (or "incident") users should be studied.[15] Restricting to incident users allows

investigators to capture HOIs that occur shortly after initiation and allows for the establishment of a clear temporal sequence among baseline patient characteristics, exposures, and outcomes.[16] The inclusion of prevalent users, on the other hand, can lead to depletion of susceptibles and subsequent false negative signals.

## Mapping of monitoring scenarios to design choices

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, which leads to misclassification of exposure; and (3) whether the exposure of interest is transient or sustained, which can reduce short-term exposure variation. When the key assumptions of self-controlled designs (i.e. transient exposure, lack of within-person, time-varying confounding, and abrupt HOI) were fulfilled, this approach was preferred to cohort-based approaches since self-controlled designs inherently avoid confounding by fixed, between-person factors. Although methods to address time-varying confounding in self-controlled designs are an area of active investigation, such methods have not yet been fully developed and evaluated. As such, we took a conservative view of within-person confounding that needs to be addressed. When time-varying confounding was assumed to be problematic, cohort-based approaches were generally, but not absolutely, preferred.

Assessing the extent to which timing issues (e.g. delayed onset, long duration of the exposure-risk window, and insidious nature of the HOI) may result in exposure misclassification (or misclassification of HOI timing) was important for design decisions since self-controlled designs are more susceptible to misclassification than are between-person comparisons.[1,2] Random misclassification of exposures or outcomes, which typically result in bias toward the null, can potentially obscure important safety signals. Thus, in the context of the Sentinel System, such misclassification cannot be considered conservative and should be avoided where possible. The cohort approach was generally preferred in situations in which issues that affect misclassification were present, but this was considered secondary to issues of confounding.

Recommendations also consider situations that may reduce variation in exposure; namely, when signal refinement questions pertain to sustained exposures. This is important not only because lack of exposure variability can reduce the power of self-controlled designs, but also because studying sustained exposures necessitates longer observation periods, which increases the likelihood that time-varying confounding can enter the analysis. Thus, cohort approaches were generally favored for sustained exposures.

When either self-controlled or cohort approaches are recommended (or when one is preferred but the other is listed as a possibility), several additional considerations may be warranted to inform decisions. For example, design choice should consider whether absolute measures of risk (e.g. risk difference) can be estimated directly or indirectly and whether the design approach can handle issues such as time-varying confounding. Sentinel stakeholders will likely desire difference measures as the basis for fair benefit-risk assessment. However, signal refinement methods can produce ratio measures as long as the results communicated to FDA and to the public are in absolute terms. The availability of a reasonable active comparator is another important consideration. Active comparators, which serve as negative controls, can reduce confounding by indication (and other types of confounding such as the "healthy user effect") to the extent that reasons for use of the product are similar to reasons for use of the product being monitored.

Other, less tangible aspects of signal refinement methods should also be considered, such as the practicability, logistical feasibility, speed of implementation, and computational intensity. Given the desire to use Sentinel to monitor newly marketed medications, it is important to remember that self-control designs that adjust for exposure time trends will likely be necessary in many cases (particularly when uptake of a certain drug is rapid).

## Preliminary design choice recommendations

Several Mini Sentinel Work Groups are currently conducting work that may change recommendations. As such, this report should be viewed as a living document and these recommendations current only as of the time of this writing. Specific recommendations are detailed in the table. Below are general recommendations that summarize the patterns observed between recommended design choices and characteristics of the potential monitoring scenarios.

- When the basic assumptions of self-controlled designs are fulfilled (i.e. transient exposure, lack of within-person, time-varying confounding, and abrupt HOI), self-controlled designs are to be preferred because of their inherent ability to avoid confounding by time-invariant

confounding without having to measure those confounding factors; however, cohort approaches may be considered if between-person confounding is thought to be minor and adjustable through analytic techniques.

- When exposure is generally sustained but the other assumptions for self-controlled designs are fulfilled, a cohort approach should be preferred, but self-controlled designs may be considered. Considerations should focus on the severity of between-person confounding and the extent to which it can be addressed within the context of a cohort design (e.g. is an appropriate active comparator available, will analytic confounding adjustment techniques suffice, etc), and also on the typical duration of exposure to the monitoring product.

- When exposure is transient, both within- and between-person confounding is negligible, and one timing issue that predisposes to exposure misclassification (e.g. delayed HOI onset, long exposure-risk window, insidious HOI) exists, cohort designs are preferred, but self-controlled designs can be considered. Both approaches will require assumptions regarding the specific time issue, but the effect of misclassification in the cohort design is likely to be less problematic. When exposure is generally sustained but the scenario is otherwise as described, the cohort approach is strongly preferred.

- In scenarios in which both within- and between-person confounding are negligible, and more than one timing issue predisposing to exposure misclassification exists, cohort designs are strongly preferred.

- In all scenarios in which within-person confounding needs to be addressed but between-person confounding is negligible, the cohort approach is strongly preferred.

- In scenarios in which exposure is transient, within-person confounding is negligible, between-person confounding needs to be addressed, and at least one timing issue predisposing to exposure misclassification exists, either approach can be considered and the decision between the two should weigh the extent to which the between-person confounding

can be addressed in a cohort analysis with the likelihood that assumptions required to minimize misclassification hold. In other words, the decision should focus on whether adjusting between-person confounding or addressing misclassification is more tractable.

- If exposure is generally sustained, within-person confounding is negligible, between-person confounding needs to be addressed, but no time issues exist, then either approach can be considered. The decision should focus on the tractability of between-person confounding versus the effects of having a non-transient exposure. If one timing issue predisposing to exposure misclassification exists, a cohort approach is preferred, but a self-controlled approach can be considered, and if more than one timing issue predisposing to exposure misclassification exists, then cohort approach is strongly preferred.

- In scenarios in which exposure is transient, no timing issues predisposing to exposure misclassification exist, but both within- and between-person confounding exists, the cohort approach is preferred but a self-controlled design can also be considered. Otherwise, cohort approaches are strongly preferred in all situations where confounding exists on both dimensions.

## Worked examples

The following five hypothetical examples have been mapped to an appropriate design choice based on consensus regarding each scenario's characteristics. By mapping each of the characteristics to those in the table, we arrive at the recommended design choice. Note that not all of these examples represent cases in which an association (causal or otherwise) is thought to exist.

1. **Sustained use of lisinopril and angioedema** (see "Exposure characteristics" section for discussion
    - **Exposure persistence**: sustained (however, this could be classified as transient if the question or outcome of interest pertained to initiation of lisinopril)

- **Onset of exposure-risk window**: immediate
- **Duration of exposure-risk window**: long
- **Strength of within-person confounding**: negligible
- **Strength of between-person confounding**: negligible
- **HOI onset**: abrupt
- **Design choice**: cohort preferred

2. **Measles, mumps, and rubella vaccination and febrile seizures**
   - **Exposure persistence**: transient (however, if the outcome of interest were hypothesized to be related to some component of the vaccine that remained in the body for a long time, then the exposure could be classified as sustained)
   - **Onset of exposure-risk window**: immediate
   - **Duration of exposure-risk window:** short
   - **Strength of within-person confounding**: negligible
   - **Strength of between-person confounding**: needs to be addressed
   - **HOI onset**: abrupt
   - **Design choice**: self-controlled preferred but cohort to be considered (if between-person confounding can be addressed)

3. **Rosuvastatin and rhabdomyolysis**
   - **Exposure persistence**: sustained (however, this could be classified as transient if the question or outcome of interest pertained to initiation of rosuvastatin)
   - **Onset of exposure-risk window**: immediate
   - **Duration of exposure-risk window**: long
   - **Strength of within-person confounding**: negligible
   - **Strength of between-person confounding**: negligible
   - **HOI onset**: abrupt
   - **Design choice**: cohort approach strongly preferred

4. **Amphotericin B and acute liver failure**

- **Exposure persistence**: transient (however, some patients may be exposed repeatedly such that persistence could be regarded as sustained making this a difficult decision; nevertheless, given the other characteristics of this particular scenario whether exposure persistence is classified as transient or sustained does not change the design choice recommendation)
- **Onset of exposure-risk window**: immediate
- **Duration of exposure-risk window**: long
- **Strength of within-person confounding**: needs to be addressed
- **Strength of between-person confounding**: needs to be addressed
- **HOI onset**: abrupt
- **Design choice**: cohort approach strongly preferred

5. **Mechanical heart valve and thromboembolism**
    - **Exposure persistence**: sustained (however, certain questions could be formulated so as to pertain to the placement and initial exposure to the device, in which case persistence could be considered transient)
    - **Onset of exposure-risk window**: immediate
    - **Duration of exposure-risk window**: long
    - **Strength of within-person confounding**: needs to be addressed
    - **Strength of between-person confounding**: needs to be addressed
    - **HOI onset**: abrupt
    - **Design choice**: cohort approach strongly preferred

## Recommended next steps

This report must be regarded as a living document that will continue to evolve, particularly as the work of the other three Mini-Sentinel Work Groups proceeds. It is important to note that the current iteration of this document provides little guidance on analytic and signaling methods choices.

Findings of the Mini-Sentinel Signal Evaluation Work Group will be instrumental in furthering our understanding about appropriate *analytic choices* and recommendations on *signaling methods* will depend critically on the methods under development and evaluation by the Mini-Sentinel Sequential Work Group. Additionally, many of the issues concerning *design choices* are being investigated in great detail by the Mini-Sentinel Work Group on Case-Based Designs, which will inevitably lead to improvements in recommendations contained herein.

The practical experiences gained and challenges encountered in the ongoing AMI pilot active surveillance example will also further enrich this working document leading to refinements of the recommendations it contains.

Finally, in a supplementary document, the Mini-Sentinel Methods Core provide recommendations for future Mini-Sentinel methods work that is partially informed by this Taxonomy Project but also by other Mini-Sentinel Methods Work Groups and by ongoing research outside of Mini-Sentinel. Future work to address these gaps will further promote sound decision making in active medical product signal refinement, particularly with regard to *analytic choices* and *signaling methods*. Recommendations for future work are summarized under the "Signal Generation" and "Signal Refinement" rubrics.

## Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

| Monitoring scenario characteristics with implication for design choice[a] | | | | | | | Monitoring scenario characteristics with implication for analytic choice[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Characteristics of the (potential) exposure-HOI link | | | | | | | | |
| | | | Strength of confounding | | | | | | |
| **Exposure persistence** *(transient, sustained)* | **Onset of exposure risk window** *(Immediate, delayed)* | **Duration of exposure risk window** *(short, long)* | **Within-person** *(negligible, needs to be addressed)* | **Between-person** *(negligible, needs to be addressed)* | **HOI onset** *(abrupt, insidious)* | **Design choice**[b] *(self-controlled, cohort)* | **Background frequency of exposure** *(infrequent, rare)* | **Background frequency of HOI** *(infrequent, rare)* | **Analytic choice** |
| Transient (e.g. vaccine, *initiation* of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature) | Immediate | Short | Negligible | Negligible | Abrupt | 1 self-controlled (or cohort) | Infrequent | Infrequent | 1 |
| | | | | | | | | Rare | 2 |
| | | | | | | | Rare | Infrequent | 3 |
| | | | | | | | | Rare | 4 |
| | | | | | Insidious | 2 cohort (or self-controlled) | Infrequent | Infrequent | 5 |
| | | | | | | | | Rare | 6 |
| | | | | | | | Rare | Infrequent | 7 |
| | | | | | | | | Rare | 8 |
| | | | | Needs to be addressed | Abrupt | 3 self-controlled (or cohort) | Infrequent | Infrequent | 9 |
| | | | | | | | | Rare | 10 |
| | | | | | | | Rare | Infrequent | 11 |
| | | | | | | | | Rare | 12 |
| | | | | | Insidious | 4 self-controlled or cohort | Infrequent | Infrequent | 13 |
| | | | | | | | | Rare | 14 |
| | | | | | | | Rare | Infrequent | 15 |
| | | | | | | | | Rare | 16 |
| | | | Needs to be | Negligible | Abrupt | 5 | Infrequent | Infrequent | 17 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | addressed | | | cohort | | Rare | 18 |
| | | | | | | | Rare | Infrequent | 19 |
| | | | | | | | | Rare | 20 |
| | | | | | Insidious | [6] cohort | Infrequent | Infrequent | 21 |
| | | | | | | | | Rare | 22 |
| | | | | | | | Rare | Infrequent | 23 |
| | | | | | | | | Rare | 24 |
| | | | | Needs to be addressed | Abrupt | [7] cohort (or self-controlled) | Infrequent | Infrequent | 25 |
| | | | | | | | | Rare | 26 |
| | | | | | | | Rare | Infrequent | 27 |
| | | | | | | | | Rare | 28 |
| | | | | | Insidious | [8] cohort | Infrequent | Infrequent | 29 |
| | | | | | | | | Rare | 30 |
| | | | | | | | Rare | Infrequent | 31 |
| | | | | | | | | Rare | 32 |
| | | Long | Negligible | Negligible | Abrupt | [9] cohort (or self-controlled) | Infrequent | Infrequent | 33 |
| | | | | | | | | Rare | 34 |
| | | | | | | | Rare | Infrequent | 35 |
| | | | | | | | | Rare | 36 |
| | | | | | Insidious | [10] cohort | Infrequent | Infrequent | 37 |
| | | | | | | | | Rare | 38 |
| | | | | | | | Rare | Infrequent | 39 |
| | | | | | | | | Rare | 40 |
| | | | | Needs to be addressed | Abrupt | [11] self-controlled or cohort | Infrequent | Infrequent | 41 |
| | | | | | | | | Rare | 42 |
| | | | | | | | Rare | Infrequent | 43 |
| | | | | | | | | Rare | 44 |
| | | | | | Insidious | [12] self-controlled or cohort | Infrequent | Infrequent | 45 |
| | | | | | | | | Rare | 46 |
| | | | | | | | Rare | Infrequent | 47 |
| | | | | | | | | Rare | 48 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Needs to be addressed | Negligible | Abrupt | 13 cohort | Infrequent | Infrequent | 49 |
| | | | | | | | | Rare | 50 |
| | | | | | | | Rare | Infrequent | 51 |
| | | | | | | | | Rare | 52 |
| | | | | | Insidious | 14 cohort | Infrequent | Infrequent | 53 |
| | | | | | | | | Rare | 54 |
| | | | | | | | Rare | Infrequent | 55 |
| | | | | | | | | Rare | 56 |
| | | | | Needs to be addressed | Abrupt | 15 cohort | Infrequent | Infrequent | 57 |
| | | | | | | | | Rare | 58 |
| | | | | | | | Rare | Infrequent | 59 |
| | | | | | | | | Rare | 60 |
| | | | | | Insidious | 16 cohort | Infrequent | Infrequent | 61 |
| | | | | | | | | Rare | 62 |
| | | | | | | | Rare | Infrequent | 63 |
| | | | | | | | | Rare | 64 |
| | Delayed | Short | Negligible | Negligible | Abrupt | 17 cohort (or self-controlled) | Infrequent | Infrequent | 65 |
| | | | | | | | | Rare | 66 |
| | | | | | | | Rare | Infrequent | 67 |
| | | | | | | | | Rare | 68 |
| | | | | | Insidious | 18 cohort | Infrequent | Infrequent | 69 |
| | | | | | | | | Rare | 70 |
| | | | | | | | Rare | Infrequent | 71 |
| | | | | | | | | Rare | 72 |
| | | | | Needs to be addressed | Abrupt | 19 self-controlled or cohort | Infrequent | Infrequent | 73 |
| | | | | | | | | Rare | 74 |
| | | | | | | | Rare | Infrequent | 75 |
| | | | | | | | | Rare | 76 |
| | | | | | Insidious | 20 self-controlled or cohort | Infrequent | Infrequent | 77 |
| | | | | | | | | Rare | 78 |
| | | | | | | | Rare | Infrequent | 79 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Rare | 80 |
| | | | Needs to be addressed | Negligible | Abrupt | 21 cohort | Infrequent | Infrequent | 81 |
| | | | | | | | | Rare | 82 |
| | | | | | | | Rare | Infrequent | 83 |
| | | | | | | | | Rare | 84 |
| | | | | | Insidious | 22 cohort | Infrequent | Infrequent | 85 |
| | | | | | | | | Rare | 86 |
| | | | | | | | Rare | Infrequent | 87 |
| | | | | | | | | Rare | 88 |
| | | | | Needs to be addressed | Abrupt | 23 cohort | Infrequent | Infrequent | 89 |
| | | | | | | | | Rare | 90 |
| | | | | | | | Rare | Infrequent | 91 |
| | | | | | | | | Rare | 92 |
| | | | | | Insidious | 24 cohort | Infrequent | Infrequent | 93 |
| | | | | | | | | Rare | 94 |
| | | | | | | | Rare | Infrequent | 95 |
| | | | | | | | | Rare | 96 |
| | | Long | Negligible | Negligible | Abrupt | 25 cohort | Infrequent | Infrequent | 97 |
| | | | | | | | | Rare | 98 |
| | | | | | | | Rare | Infrequent | 99 |
| | | | | | | | | Rare | 100 |
| | | | | | Insidious | 26 cohort | Infrequent | Infrequent | 101 |
| | | | | | | | | Rare | 102 |
| | | | | | | | Rare | Infrequent | 103 |
| | | | | | | | | Rare | 104 |
| | | | | Needs to be addressed | Abrupt | 27 self-controlled or cohort | Infrequent | Infrequent | 105 |
| | | | | | | | | Rare | 106 |
| | | | | | | | Rare | Infrequent | 107 |
| | | | | | | | | Rare | 108 |
| | | | | | Insidious | 28 self-controlled or | Infrequent | Infrequent | 109 |
| | | | | | | | | Rare | 110 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | cohort | Rare | Infrequent | 111 |
| | | | | | | | | Rare | 112 |
| | | | Needs to be addressed | Negligible | Abrupt | 29 cohort | Infrequent | Infrequent | 113 |
| | | | | | | | | Rare | 114 |
| | | | | | | | Rare | Infrequent | 115 |
| | | | | | | | | Rare | 116 |
| | | | | | Insidious | 30 cohort | Infrequent | Infrequent | 117 |
| | | | | | | | | Rare | 118 |
| | | | | | | | Rare | Infrequent | 119 |
| | | | | | | | | Rare | 120 |
| | | | | Needs to be addressed | Abrupt | 31 cohort | Infrequent | Infrequent | 121 |
| | | | | | | | | Rare | 122 |
| | | | | | | | Rare | Infrequent | 123 |
| | | | | | | | | Rare | 124 |
| | | | | | Insidious | 32 cohort | Infrequent | Infrequent | 125 |
| | | | | | | | | Rare | 126 |
| | | | | | | | Rare | Infrequent | 127 |
| | | | | | | | | Rare | 128 |
| Sustained (e.g. *chronic* drug use, continuous exposure to an implanted device) | Immediate | Short | Negligible | Negligible | Abrupt | 33 cohort (or self-controlled) | Infrequent | Infrequent | 129 |
| | | | | | | | | Rare | 130 |
| | | | | | | | Rare | Infrequent | 131 |
| | | | | | | | | Rare | 132 |
| | | | | | Insidious | 34 cohort | Infrequent | Infrequent | 133 |
| | | | | | | | | Rare | 134 |
| | | | | | | | Rare | Infrequent | 135 |
| | | | | | | | | Rare | 136 |
| | | | | Needs to be addressed | Abrupt | 35 self-controlled or cohort | Infrequent | Infrequent | 137 |
| | | | | | | | | Rare | 138 |
| | | | | | | | Rare | Infrequent | 139 |
| | | | | | | | | Rare | 140 |
| | | | | | Insidious | 36 | Infrequent | Infrequent | 141 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | cohort (or self-controlled) | | Rare | 142 |
| | | | | | | | Rare | Infrequent | 143 |
| | | | | | | | | Rare | 144 |
| | | | Needs to be addressed | Negligible | Abrupt | 37 cohort | Infrequent | Infrequent | 145 |
| | | | | | | | | Rare | 146 |
| | | | | | | | Rare | Infrequent | 147 |
| | | | | | | | | Rare | 189 |
| | | | | | Insidious | 38 cohort | Infrequent | Infrequent | 149 |
| | | | | | | | | Rare | 150 |
| | | | | | | | Rare | Infrequent | 151 |
| | | | | | | | | Rare | 152 |
| | | | | Needs to be addressed | Abrupt | 39 cohort | Infrequent | Infrequent | 153 |
| | | | | | | | | Rare | 154 |
| | | | | | | | Rare | Infrequent | 155 |
| | | | | | | | | Rare | 156 |
| | | | | | Insidious | 40 cohort | Infrequent | Infrequent | 157 |
| | | | | | | | | Rare | 158 |
| | | | | | | | Rare | Infrequent | 159 |
| | | | | | | | | Rare | 160 |
| | | Long | Negligible | Negligible | Abrupt | 41 cohort | Infrequent | Infrequent | 161 |
| | | | | | | | | Rare | 162 |
| | | | | | | | Rare | Infrequent | 163 |
| | | | | | | | | Rare | 164 |
| | | | | | Insidious | 42 cohort | Infrequent | Infrequent | 165 |
| | | | | | | | | Rare | 166 |
| | | | | | | | Rare | Infrequent | 167 |
| | | | | | | | | Rare | 168 |
| | | | | Needs to be addressed | Abrupt | 43 cohort (or self-controlled) | Infrequent | Infrequent | 169 |
| | | | | | | | | Rare | 170 |
| | | | | | | | Rare | Infrequent | 171 |
| | | | | | | | | Rare | 172 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Insidious | 44 cohort | Infrequent | Infrequent | 173 |
| | | | | | | | | Rare | 174 |
| | | | | | | | Rare | Infrequent | 175 |
| | | | | | | | | Rare | 176 |
| | | | Needs to be addressed | Negligible | Abrupt | 45 cohort | Infrequent | Infrequent | 177 |
| | | | | | | | | Rare | 178 |
| | | | | | | | Rare | Infrequent | 179 |
| | | | | | | | | Rare | 180 |
| | | | | | Insidious | 46 cohort | Infrequent | Infrequent | 181 |
| | | | | | | | | Rare | 182 |
| | | | | | | | Rare | Infrequent | 183 |
| | | | | | | | | Rare | 184 |
| | | | | Needs to be addressed | Abrupt | 47 cohort | Infrequent | Infrequent | 185 |
| | | | | | | | | Rare | 186 |
| | | | | | | | Rare | Infrequent | 187 |
| | | | | | | | | Rare | 188 |
| | | | | | Insidious | 48 cohort | Infrequent | Infrequent | 189 |
| | | | | | | | | Rare | 190 |
| | | | | | | | Rare | Infrequent | 191 |
| | | | | | | | | Rare | 192 |
| | Delayed | Short | Negligible | Negligible | Abrupt | 49 cohort (or self-controlled) | Infrequent | Infrequent | 193 |
| | | | | | | | | Rare | 194 |
| | | | | | | | Rare | Infrequent | 195 |
| | | | | | | | | Rare | 196 |
| | | | | | Insidious | 50 cohort | Infrequent | Infrequent | 197 |
| | | | | | | | | Rare | 198 |
| | | | | | | | Rare | Infrequent | 199 |
| | | | | | | | | Rare | 200 |
| | | | | Needs to be addressed | Abrupt | 51 cohort (or self-controlled) | Infrequent | Infrequent | 201 |
| | | | | | | | | Rare | 202 |
| | | | | | | | Rare | Infrequent | 203 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Rare | 204 |
| | | | | | Insidious | 52 cohort | Infrequent | Infrequent | 205 |
| | | | | | | | | Rare | 206 |
| | | | | | | | Rare | Infrequent | 207 |
| | | | | | | | | Rare | 208 |
| | | | Needs to be addressed | Negligible | Abrupt | 53 cohort | Infrequent | Infrequent | 209 |
| | | | | | | | | Rare | 210 |
| | | | | | | | Rare | Infrequent | 211 |
| | | | | | | | | Rare | 212 |
| | | | | | Insidious | 54 cohort | Infrequent | Infrequent | 213 |
| | | | | | | | | Rare | 214 |
| | | | | | | | Rare | Infrequent | 215 |
| | | | | | | | | Rare | 216 |
| | | | | Needs to be addressed | Abrupt | 55 cohort | Infrequent | Infrequent | 217 |
| | | | | | | | | Rare | 218 |
| | | | | | | | Rare | Infrequent | 219 |
| | | | | | | | | Rare | 220 |
| | | | | | Insidious | 56 cohort | Infrequent | Infrequent | 221 |
| | | | | | | | | Rare | 222 |
| | | | | | | | Rare | Infrequent | 223 |
| | | | | | | | | Rare | 224 |
| | | Long | Negligible | Negligible | Abrupt | 57 cohort | Infrequent | Infrequent | 225 |
| | | | | | | | | Rare | 226 |
| | | | | | | | Rare | Infrequent | 227 |
| | | | | | | | | Rare | 228 |
| | | | | | Insidious | 58 cohort | Infrequent | Infrequent | 229 |
| | | | | | | | | Rare | 230 |
| | | | | | | | Rare | Infrequent | 231 |
| | | | | | | | | Rare | 232 |
| | | | | Needs to be addressed | Abrupt | 59 cohort | Infrequent | Infrequent | 233 |
| | | | | | | | | Rare | 234 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Rare | Infrequent | 235 |
| | | | | | | | | Rare | 236 |
| | | | | | Insidious | [60] cohort | Infrequent | Infrequent | 237 |
| | | | | | | | | Rare | 238 |
| | | | | | | | Rare | Infrequent | 239 |
| | | | | | | | | Rare | 240 |
| | | | Needs to be addressed | Negligible | Abrupt | [61] cohort | Infrequent | Infrequent | 241 |
| | | | | | | | | Rare | 242 |
| | | | | | | | Rare | Infrequent | 243 |
| | | | | | | | | Rare | 244 |
| | | | | | Insidious | [62] cohort | Infrequent | Infrequent | 245 |
| | | | | | | | | Rare | 246 |
| | | | | | | | Rare | Infrequent | 247 |
| | | | | | | | | Rare | 248 |
| | | | | Needs to be addressed | Abrupt | [63] cohort | Infrequent | Infrequent | 249 |
| | | | | | | | | Rare | 250 |
| | | | | | | | Rare | Infrequent | 251 |
| | | | | | | | | Rare | 252 |
| | | | | | Insidious | [64] cohort | Infrequent | Infrequent | 253 |
| | | | | | | | | Rare | 254 |
| | | | | | | | Rare | Infrequent | 255 |
| | | | | | | | | Rare | 256 |

[a]Some characteristics are subjective (e.g. immediate versus delayed onset) and can vary in definition in each scenario.
[b]If only one design is listed, then this design option is strongly preferred. If both options are listed but with one in parenthesis, the option not in the parenthesis is preferred, but either option could be considered. If both options are listed with no parenthesis, then either option is valid and will depend on the relative trade-offs between confounding and misclassification in the particular scenario.

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## Glossary

*Abrupt onset:* refers to a sudden occurrence of a health outcome of interest with a sharp contrast between absence and incidence such that the time of the event is easy to define and determine (e.g. mortality).

*Analytic choices:* pertain to statistical methods, applied within the context of design choices, to promote valid estimation of associations.

*Design choices*: are defined as constraints on observation time intended to yield the most valid comparisons. For example, constraints may be used to restrict signal refinement to a particular patient population defined by a certain age range or by presence of a specific underlying medical condition. Constraints could also be used to define a period observation time to serve as a basis for comparison, such as the identification of a comparator group (through matching or restriction, for example) or ascertainment of an alternate observation period in a patient's history.

*Insidious onset:* refers to an outcome that occurs gradually and for which the definition of onset time may be ambiguous (e.g. incidence of multiple sclerosis).

*Signal evaluation*:* consists of the implementation of a formal epidemiological analysis to more definitively establish or refute causality between exposure to the medical product and the health outcome of interest.

*Signal generation*:* includes a collection of methods for identifying potential associations between medical products and health outcomes of interest.

*Signal refinement*:* is an epidemiological process for evaluating the magnitude and clinical significance of a suspected association.

*Monitoring scenarios:* refer to pairs of pre-specified medical products and health outcomes of interest categorized by a unique constellation of exposure characteristics, outcome characteristics, and characteristics of the links between them.

*Signaling methods:* imply analytic approaches used to determine when sufficient evidence – beyond chance – exists, indicating a product-health outcome of interest association requiring further attention (e.g. a test statistic or a decision rule).

*Transient exposure:* is defined as an exposure lasting only for a short time. It is important to note that this does not preclude subsequent periods of exposure (for example, each as-needed dose of an anti-inflammatory drug would be considered a transient exposure if the health outcome of interest pertained to the initiation of the medication).

*The terms “signal evaluation,” “signal generation,” and “signal refinement” are suggested and defined by FDA.