Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2011
Drug Safety

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry and FDA Staff[1]

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is meant to describe best practices pertaining to conducting and reporting on ***pharmacoepidemiologic safety studies***[2] that use ***electronic healthcare data sets***, which include ***administrative claims data*** and ***electronic medical record (EMR)*** data. The guidance includes recommendations for documenting the design, analysis, and results of pharmacoepidemiologic safety studies to optimize FDA's review of protocols and final reports that are submitted to the Agency for these types of studies. For purposes of this guidance, the term *pharmacoepidemiologic safety study* refers to an ***observational study*** designed to assess the risk attributed to a drug exposure and to test pre-specified hypotheses. For ease of reference, this guidance uses the term *drug* to refer to all drug products, including biological products that also meet the definition of drug in the Federal Food, Drug, and Cosmetic Act (the FD&C Act), regulated by CDER and CBER. Medical devices are not within the scope of this guidance.

This guidance is intended to provide the following:

- Consistent guidance for industry to use when submitting pharmacoepidemiologic safety study protocols and final reports to FDA so that study protocols and final reports submitted to FDA contain sufficient information to permit thorough review;
- A framework for FDA reviewers to use when reviewing and interpreting these submissions; and
- Consistent guidance for FDA to use when conducting these studies.

The focus of this guidance is on best practices that specifically apply to pharmacoepidemiologic safety studies using electronic healthcare data sets. Although the guidance is not intended to

[1] This guidance has been prepared by the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] All terms presented in ***bold italics*** at first use in this guidance are defined in the Glossary.

address broad, basic epidemiologic principles, many of the concepts discussed in the guidance may apply more broadly to pharmacoepidemiologic safety studies using other types of data, as well as descriptive studies of drug exposure or safety outcomes using electronic healthcare data. FDA encourages industry to inform FDA of all pharmacoepidemiologic safety studies; to submit plans and protocols for such studies before study initiation; and to submit comprehensive final reports with detailed methods and results to FDA in a timely manner.[3]

This guidance does not address ***real-time active safety surveillance*** studies, as this field is still rapidly evolving and it is not possible at this time to recommend sound best practices.[4] This guidance is not intended to be prescriptive with regard to choice of study design or type of analysis and does not endorse any particular type of data resource or methodology. Finally, it does not provide a framework for determining the appropriate weight of evidence of studies from this data stream in the overall assessment of drug safety, as this appraisal represents a separate aspect of the regulatory decision-making process and is best accomplished in the context of the specific safety issue under investigation.

FDA's guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The process of FDA regulatory decision-making on drug safety issues has several interrelated aspects.

- Initially, there is reported evidence of an association between a particular drug and an adverse event. This evidence mostly emerges from one or more of the following data streams: randomized controlled trials (RCTs), spontaneous adverse event case reports, or pharmacoepidemiologic safety studies.
- Assessment of evidence from the pharmacoepidemiologic safety study data stream involves an evaluation of the design and conduct of studies and final reports pertaining to the purported association of drug and outcome; additional studies might be initiated to further examine the association.

[3] The Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) amended the the FD&C Act to require submission of information pertaining to required studies (see section 505(o)(3)(E)(ii) of the FD&C Act (21 U.S.C. 355(o)(3)(E)(ii))), as well as on the status of any required pharmacoepidemiologic studies and the status of other related studies undertaken to investigate a safety issue, including pharmacoepidemiologic safety studies.

Section 506B of the FD&C Act requires sponsors to report on studies that the sponsors have agreed to conduct; these requirements are included in the current FDA regulations for annual reports: 21 CFR 314.81(b)(2)(vii) for NDAs, 21 CFR 314.98 for ANDAs, and 21 CFR 601.70 for BLAs.

[4] More specifically, the use of electronic healthcare data sets for hypothesis-generation (signal detection) or hypothesis-strengthening (signal strengthening), which is an intermediate step between hypothesis-generation and hypothesis-testing, is beyond the scope of this guidance.

- The evidence generated from the different data streams is then integrated and weighed by a multidisciplinary team to arrive at an overall conclusion regarding the relationship of the risk of the drug and a re-assessment of benefit and risk.
- Finally, FDA determines whether regulatory action is warranted and what communication is needed to convey important safety information to medical providers, patients, and other stakeholders.

FDA regulatory decision-making on drug safety issues is an iterative process because regulatory decisions are informed by emerging evidence, including any additional studies that are initiated as mentioned above.

Drug-related adverse events of interest can be rare, making them difficult to study. For many potential associations between a drug and an adverse event, findings across studies can be inconsistent for a variety of reasons. However, because drug-related adverse events have the potential to broadly affect the public health, there is often an urgency to take regulatory action to address drug safety issues based on the available evidence, even if the data are less than optimal. One early aspect of regulatory decision-making is evaluating the evidence from pharmacoepidemiologic safety studies that formally test drug safety hypotheses. As described in this guidance, the best practices for the conduct and reporting of pharmacoepidemiologic safety studies using electronic healthcare data are intended to facilitate a more independent interpretation of findings from these studies.

A. Use of Electronic Healthcare Data Sets in Pharmacoepidemiologic Safety Studies

The advent of new technologies and the ability to efficiently assemble electronic healthcare data sets for use in drug safety studies have provided many new opportunities for conducting pharmacoepidemiologic studies of drug safety issues. These technologies allow for the possibility of studying safety issues quickly (relative to alternative approaches) in real world healthcare environments involving large populations of patients. In addition, the development of innovative statistical methods has allowed investigators to study complex drug safety questions previously considered too difficult to examine outside of a clinical trial setting. However, these developments have also precipitated a great deal of discussion over the appropriate use of electronic healthcare data and statistical methods in conducting pharmacoepidemiologic safety studies.

This guidance does not address the case-by-case decision to pursue a pharmacoepidemiologic safety study using electronic healthcare data over any other type of study, as this decision is unique to each specific safety issue of interest.[5] Generally, however, these studies may be particularly useful when other forms of ***observational studies*** or clinical trials would be

[5] In some instances, when FDA is concerned about a serious risk, applicants are required to complete postmarketing studies (postmarketing requirements, or PMRs). For a full discussion of PMRs, refer to the draft guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, which, when finalized, will represent the Agency's current thinking on this topic. FDAAA provides the specific circumstances when FDA can require the conduct of postapproval studies (see section 505(o)(3)(D)(i) of the Act).

infeasible (i.e., when the safety outcome is very rare) or when the study of outcomes or exposures in an interventional or prospective study would be unethical. There are also circumstances when a pharmacoepidemiologic safety study may not be appropriate or adequate to answer the safety question of interest, for example, if the safety outcome of interest is a subjective patient-reported outcome that is not typically collected in electronic healthcare data.

B. Prior Guidelines and Guidance Documents

Previously published FDA guidance documents and other guidelines have informed the development of best practices for conducting pharmacoepidemiologic safety studies using electronic healthcare data. FDA's 2005 guidance entitled *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (FDA 2005 guidance), which is much broader in scope than the current guidance (focusing both on pharmacovigilance and all types of pharmacoepidemiologic studies), includes an abbreviated section on observational studies.[6] Another document on general best practices for pharmacoepidemiologic studies, the International Society for Pharmacoepidemiology's (ISPE's) *Guidelines for Good Pharmacoepidemiology Practices* (GPP) (ISPE guidelines), highlights the following critical factors for all pharmacoepidemiologic studies to address:

- Providing a written protocol, with dated amendments and justifications
- Performing a critical review of the literature to facilitate the identification of knowledge gaps in the current evidence base for safety issue(s) of interest and how the current or proposed study contributes to this evidence base
- Ensuring human subject protection
- Providing confidence intervals in addition to p-values; although p-values address the issue of statistical significance, confidence intervals quantify the precision of the risk estimates
- Including both absolute and relative risk estimates to assist in the interpretation of the public health impact of the findings
- Archiving of relevant study documents and data sets

The Consolidated Standards of Reporting Trials (CONSORT) statement (Moher, et al.), created to improve clinical trials research reporting and subsequently supported by medical journals, serves as an example of how basic reporting standards can improve the quality of reports on *clinical* trials. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm, et al.) provides guidelines for reporting *observational* studies.[7] STROBE was created to address the fact that there is often missing information in published observational epidemiologic studies (von Elm, et al. 344).

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[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or CBER guidance page at *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*.

[7] The term *reporting* in these documents means the transparent disclosure of information to the public describing critical methodological and scientific aspects of the study to enable the public to "assess the strengths and weaknesses of the study design, conduct, and analysis." The term does not refer to regulatory reporting requirements (von Elm, et al. 344).

The FDA 2005 guidance, the ISPE guidelines, and the STROBE provide general guidance applicable to **all** pharmacoepidemiologic safety studies. The unique characteristics of studies that involve the use of electronic healthcare data warrant more specific guidance. This best practices guidance provides criteria that apply specifically to the design, analysis, conduct, and documentation of pharmacoepidemiologic safety studies using electronic healthcare data with protocols and reported results submitted to FDA.

C. PDUFA IV Commitment: Identification of Pharmacoepidemiology Best Practices and Development of Best Practices Guidance

The Prescription Drug User Fee Amendments of 2007 (PDUFA IV) authorized a significant expansion of the postmarket focus under the PDUFA program.[8] Under PDUFA IV, FDA agreed to specific commitments to enhance and modernize the drug safety system.[9] One FDA commitment was to identify pharmacoepidemiologic safety study best practices and to develop a guidance describing these practices; the current guidance is intended to fulfill this commitment. Toward this end, FDA initially held a public workshop in May 2008 to obtain input from experts in the field and the public regarding the use of electronic healthcare data in pharmacoepidemiologic safety studies of drug safety issues. FDA carefully considered all oral and written public comments from the workshop and its docket when creating the current guidance.

III. BEST PRACTICES — GENERAL CONSIDERATIONS

FDA encourages investigators to develop thoughtful, scientific approaches to answer drug safety questions of interest. Overall, investigators should clearly articulate the science-based rationale for all choices made in the proposed study protocols and final reports. Investigators should submit protocols to FDA before study initiation and final reports upon completion for all pharmacoepidemiologic safety studies using electronic healthcare data.[10] A scientifically valid study protocol should be developed by the investigators by predefining certain elements related to the design, analysis, conduct, and reporting of the study. All those involved in developing the protocol and their roles should be specified. **All of the elements described within this guidance should be addressed in the protocol.** Any changes to the initial protocol after initial collection of data should be justified and documented. It is also important to discuss the potential impact of these protocol changes when interpreting results at the end of the study. Published studies submitted to FDA should be accompanied by supplemental documents that provide these elements.

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[8] FDAAA, Title I, Prescription Drug User Fee Amendments of 2007.

[9] See the letter from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record, at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

[10] 21 CFR 314.81(b)(2)(viii).

A. Title and Detailed Study Summary

Each protocol and final report should include a study title that indicates the type of pharmacoepidemiologic safety study design (e.g., cohort, case-control) employed in the study. The report should contain a detailed study summary that concisely describes the critical elements listed below. Although these elements are not uniquely applicable to pharmacoepidemiologic safety studies using electronic healthcare data, they are useful to summarize the key points of these types of studies.

- Scientific goals, study objectives, and pre-specified hypotheses
- Study design, including ***comparator groups***
- Study population and time period of study
- Data sources used
- Drug exposures of interest
- Drug safety outcomes of interest
- Methods to control for sources of bias
- Brief, balanced description of the results, interpretation of study findings, and key study limitations
- Public health impact

B. Background

A brief background of the drug(s) and safety concern(s) under investigation provides a context for the investigation. This information should include a **brief** description of prior evidence or suspicions prompting the study initiation, the strengths and weaknesses of previous studies on this issue, and some general information about the therapeutic class and use of the study drug(s). Based on this background and the identified gaps in evidence, investigators should establish concise study objectives and specific, feasible hypotheses. The subsequent development of the study design is then based on these objectives and hypotheses.

C. Study Approach Considerations

Once the pre-specified hypotheses are identified, the study approach, including the selection of data sources, study design, and analysis plan, can be developed. It is important for investigators to elaborate on the reasons for their choices of study design, selection of databases, and analysis plan as they pertain to these hypotheses. FDA encourages investigators to briefly describe any alternative study approaches and databases they considered before arriving at the proposed approach and to clarify why those alternatives were neither feasible nor optimal in the context of answering the specific study questions. The discussion should reflect an in-depth understanding of the use of the drug(s) of interest, the safety outcome(s) of interest, the usual treatment of the safety outcome(s) of interest, and the capture of both the exposure and safety outcome in relevant patient populations using electronic healthcare data sources. Results of any preliminary or feasibility studies should be included.

In the discussion of the study approach, it is important to explain if the use of more than one data source is appropriate. Multiple data sources can be used to increase study sample size by designing a multi-site study (using the same design and analysis plan across multiple data sources from different sites); if so, it is critical to address issues or concerns related to assembly of analytic data sets and data pooling in the development of the analysis plan. Multiple data sources can also be used separately, using the same and/or different design and analysis plans, to verify and replicate study findings. Use of multiple study designs and data sources may assist in addressing the hypotheses by increasing generalizability and robustness of findings and allowing for the study of different sub-populations of interest (Vandenbrouke 342).

Specific aspects of best practices for the selection of the data sources, study design, and analysis plan to be described and included in any regulatory submission are discussed in detail in sections IV, V, and VI of this guidance.

D. Study Team Expertise and Credentials

The protocol should include a description of the expertise and credentials of the study team, including their level of experience in using the specific data sources to be employed in the study. Because all existing electronic healthcare data sources used for pharmacoepidemiologic safety studies have unique features based on their original purpose and methods for collecting data and including patients, the inclusion of personnel on the study team with "hands-on" experience and knowledge of the data source will ensure appropriate use of the data. An experienced, balanced study team with the appropriate expertise is crucial to the successful execution of a safety study.

E. Interpretation of Findings

When interpreting findings, investigators should summarize the key results of the study, including the main measures of effect (including the absolute risk estimate if possible). In particular, findings of no association between the drug and safety outcome of interest should be presented in the context of the initial statistical power calculations; investigators should attempt to determine the level of risk that can be ruled out, given the study findings.

Because statistical significance can be easy to achieve in large electronic data sets and, alone, does not exclusively determine the importance of the findings, it is critical for clinical significance to be considered when interpreting findings. In addition, the confidence interval should be provided to quantify the precision of the risk estimates and thus inform the interpretation of findings.

Investigators should also discuss the limitations of the database and design and their impact on generalizability. Investigators should discuss key biases, the suspected magnitude and direction of those biases, and their impact on the interpretation of the study findings. Finally, investigators should place the study findings in the context of studies using other databases, populations, and study designs.

IV. BEST PRACTICES — DATA SOURCES

FDA does not specifically endorse one type of data source over another; however, FDA encourages selection of data source(s) that are most appropriate to address the specific hypotheses. When submitting protocols or final reports to FDA, investigators should include in an appendix the names of all data sources used for the study and other relevant descriptive information discussed in more detail below.

A. Appropriateness of Data Source(s) in Addressing Safety Questions of Interest

Investigators should demonstrate a complete understanding of the electronic healthcare data source and its appropriateness to address specific hypotheses. Existing electronic healthcare data systems were generated for purposes other than drug safety investigations, and it is important to understand this limitation to use the data systems appropriately for investigations of a drug's safety. For example:

- Administrative claims data are generated to support payment for care; policies governing the approval and denial of such payments should be considered before using these data for investigations.
- EMR data are generated in the process of providing routine clinical care; therefore, it is important to consider guidelines for patient care and common clinical practices within that healthcare system that will influence the collection of data and any investigation based on the data.

Investigators should also describe historical accessibility to the data source(s) proposed to be used in the study. This description should include:

- how long the data source has been available to the investigator community,
- how often this data source has been used for pharmacoepidemiologic safety studies, and
- references for any relevant publications, including ***validation*** studies of safety outcomes of interest in the proposed study that are captured in the database (to be described further in section E).

This information will allow FDA reviewers to better understand how experienced the investigator community is in using the data source(s) that will be employed.

Investigators should also demonstrate that each data source contains sufficient clinical granularity to capture the exposures and outcomes of interest in the appropriate setting of care. For example, outpatient data sources that do not include linkage to hospitalization data would not be appropriate for studying safety outcomes likely to result in hospitalization. It is also important to address the coding of available data and explain why the coding is sufficient for ascertainment of outcomes of interest and other important variables. For example, safety outcomes that cannot be identified using International Classification of Diseases (ICD) codes cannot be appropriately studied using data sources relying solely on ICD codes in claims data.

Access to specific patient populations of interest (e.g., psychiatric, pediatric) may be important. The relevant populations to be used in a study should be described, including what constitutes ***continuity of coverage*** (see section IV.B) of patients included within the data source, so that it is clear that relevant exposures and outcomes will be captured during the study period. It is also

important to ensure that the data source(s) contain a sufficient number of patients or patient follow-up time to ascertain outcomes of interest based on the hypothesized ***exposure risk window***. Providing information about the ***churn rate*** is particularly helpful in determining if the data source(s) selected are appropriate for ascertaining delayed safety outcomes.

B. Enrollment and Comprehensive Capture of Care

Investigators using administrative claims data sources should address continuity of coverage (enrollment and disenrollment). This concept particularly applies to claims data sources in the United States because patients often enroll and disenroll in different health plans in relation to changes in employment or other life circumstances (Strom 221). The validity of a study using these data, however, depends in part on ensuring that the migration of patients in and out of the electronic healthcare data sources can be documented. Such documentation allows only periods of enrollment during which data are available on the patients of interest to be included in the study, and periods of disenrollment when data are not available on patients can be appropriately excluded. Definitions of enrollment or continuous coverage need to be developed and documented, particularly in studies using more than one data source.

Continuity of coverage of patients within a data source is especially important when employing EMR data sources, as the entire continuum of the patient's care might not be available in one EMR system. For example, a patient's visits to multiple physicians for treatment in different doctors' offices or hospitals might not be captured by a single practice-based EMR data source. In addition, patients in the United States do not typically "enroll" in physician practices, but rather see physicians as needed or as their insurance coverage allows. Therefore, when using an EMR data source, it is crucial to employ and describe methods to ensure complete observation and capture of patient care over time to facilitate the likelihood that all exposures and safety outcomes of interest will be captured. In the United States, primary care-based EMR networks may not capture hospitalizations or visits to specialists. If these are events of interest, investigators should specify how these events will be captured.

If a hospital data source alone is proposed, it is important to report whether outpatient care data are relevant to the study because they are often not currently captured in this type of data source. For example, data on outpatient drug exposures of interest may not be available using inpatient data sources alone. The converse also applies — if an outpatient data source alone is proposed, it is important to note that detailed data on drug exposures in the hospital setting are most often not available.

Over-the-counter (OTC) medications and dietary supplements are not typically captured systematically in electronic healthcare data because they are not prescribed by physicians and their costs are not always reimbursable under insurance plans. If these exposures are particularly relevant to the study question, then investigators should describe how they will address this informational gap.

C. Country of Origin and Health System: Relevance to the United States

In situations where use of a data source from a country other than the United States is proposed, it is important to provide:

- A discussion regarding why the data are most appropriate to address the specific hypotheses;
- Background information about the healthcare system (including method of diagnosis and preferred patterns of treatment of the disease(s) of interest) and to what degree relevant information is collected in the proposed data sources;
- A description of prescribing and utilization practices;
- Market availability for the treatment(s) of interest; and
- An explanation of how all these factors might affect the generalizability of the study results to the U.S. population.

Reporting on these points is critical as there might be significant differences in the practice of medicine (including prescribing and use of medications) that directly affect the ability of a non-U.S. data source to address the specific hypotheses. Because of differences in practice guidelines, medication tiering (e.g., first-line, second-line), and patient selection in non-U.S. healthcare systems, patients taking a drug in the United States might differ in disease severity from patients taking the same drug in other countries. Furthermore, in the future, as we learn more about the association of pharmacogenetics and the risk of drug-related harms, it will be important to discuss the impact of potential variations in the distribution of patients' pharmacogenetic profiles outside the United States on the feasibility and generalizability of a pharmacoepidemiologic safety study.

D. Selection of Study Population

FDA encourages the use of explicit inclusion and exclusion criteria for the selection of the study population and provision of an appropriate explanation for the criteria selected. For proposed studies, we recommend providing specific estimates of relevant population size in the proposed data source, including the size of the exposed population. For studies involving elderly patients (age 65 and older) in the United States, it is important to describe the level of completeness of medical care and drug coverage, including direct access or linkage to Medicare data.[11] Obtaining data on patients with some types of serious and life-threatening conditions (e.g., HIV/AIDS or cancer) can present a unique challenge as it might be difficult to fully capture drug coverage and medical care because state- or federal-based clinics, experimental clinical trial based therapies, and increased use of pharmaceutical company assistance programs are not captured in most electronic healthcare data sources. If these issues are relevant to the study question of interest, it is especially important to report how they will be addressed in the protocol. As previously stated, FDA encourages the use of multiple data sources and populations when possible to verify, validate, and replicate findings.

[11] For more information on Medicare data, please access the CMS Web site link: http://www.cms.hhs.gov/medicareGenInfo.

FDA recommends the use of a flow diagram or other accounting scheme to display the disposition of study subjects at various stages of inclusion or exclusion. A diagram or schematic provides an easily visible record of study process (Esposito, et al. 648; Friedman, et al. 1910; Schneeweiss, et al. 773; Weiner, et al. 663).

E. Quality Assurance (QA) and Quality Control (QC)

Investigators should ensure that they are aware of the ***quality assurance (QA)*** and ***quality control (QC)*** procedures used by the data holders and how the procedures could affect data integrity and the study. FDA recommends that investigators address the following topics:

- The general procedures used by the data holders to ensure completeness, consistency and accuracy of data collection and management
- The frequency and type of any data error corrections or changes in data adjudication policies implemented by the data holders during the period of relevant data collection
- A description of any peer reviewed publications examining data quality and/or validity, including the relationships of the investigators with the data source(s)
- Any updates and changes in coding practices (e.g., ICD codes) across the study period that are relevant to the outcomes of interest
- Any changes in key data elements (which can change over time) during the timeframe of the study and the potential effect of the changes on the study
- A report on the extent of missing data over time (i.e., the percentage of a particular variable of interest for which data are not available) and procedures for handling this issue (e.g., exclusion, imputation)

F. Study Timeframe and Lag Time Issues

Investigators should define the ***study timeframe*** (which spans from the beginning of the "look back period," when the investigator looks back in the database before drug exposure to ascertain baseline patient covariate data) to the end of the exposure risk window. Investigators should demonstrate that the timeframe they selected is appropriate to address the specific hypotheses; this should include a discussion of temporal changes in the standard of care, the availability of other treatments, and other factors. Use patterns of a drug may change over time and result in potential differences in the patients exposed to the drug over time that may be relevant for the safety outcome(s) of interest. Investigators should:

- address the interval from drug approval until the study timeframe begins,
- describe in detail the lag time between the actual occurrence of outcomes and the availability of data for investigations using the data source, and
- describe the effect of the lag time on the study timeframe, data completeness, and the proposed feasibility of the proposed study.

V. BEST PRACTICES — STUDY DESIGN

A. Study Design Considerations

1. Choice of Study Design

FDA does not endorse a specific type of study design because the choice of study design depends on both the drug and the safety issue of interest and should be tailored to address the specific hypotheses of interest. Investigators should start from the study questions of interest and then determine which data source(s) and design are most appropriate to address these questions. Clear reasons for selecting a particular study design should be included with the study protocol and final report.

2. Examples of Study Designs (Not All-Inclusive)

The most commonly used types of observational pharmacoepidemiologic safety studies include cohort studies, case-control studies, and nested case-control studies. Other designs, including case-cohort or case-crossover design, can be used depending on the study question of interest and what is known about the postulated relationship between drug exposure and the specific safety outcomes of interest. Overall, different study designs can be appropriate depending on the study question(s). FDA discourages the use of *one size fits all* study designs. For purposes of this guidance, a *one size fits all* study design is a design employed by an investigator in a number of pharmacoepidemiologic safety studies, irrespective of appropriateness in addressing study questions of interest and specific hypotheses.

3. Comparator Selection

Selection of an appropriate comparator group(s) is a critical part of a pharmacoepidemiologic safety study. FDA encourages the use of multiple comparator groups in any study design when it is feasible and relevant, as this strategy can serve to enhance the validity of safety studies (Waning, et al. 57). If multiple comparator groups are employed, the primary comparator for statistical purposes should be identified and the protocol should include an explanation of the rationale for the selection of each group with respect to the study questions of interest.

It is ideal to use a comparator group taking a drug used to treat the same disease, with the same level of severity, from the same time period as the cohort exposed to the drug of interest or cases for the study were selected. However, in some circumstances it may not be possible to find an appropriate comparator group from the same time period. In this case, investigators might elect to use ***historical comparators***, which are comparators selected from a different time period than the cases. If historical comparators are used, it is important to explain the rationale behind their use and to address the associated limitations.

Issues that are especially relevant to comparator selection for pharmacoepidemiologic safety studies of preventative therapeutics, such as vaccines, should be considered. One such issue is the "healthy vaccinee effect." In contrast to most drugs, vaccines are generally given to persons who are healthy. As a result, confounding could occur if vaccinated persons are compared to

unvaccinated persons, who might be very different (e.g., they may be more ill or lack access to primary medical care). Many factors associated with avoidance or delay in vaccination may be associated with an increased risk of the outcomes of interest (Fine, et al. 122). It can also be appropriate to use self-control, or case-crossover designs, where the same person serves as his or her own control (Maclure 145). If this approach is employed, the protocol and final report should describe the relevant limitations of this study design.

4. Study Timeframe

It is important to explain the rationale behind the study timeframe selected with respect to the safety outcomes of interest. As previously defined, the study timeframe spans from the beginning of the "look back period," when the investigator looks back in the database before drug exposure to ascertain baseline patient covariate data, to the end of the follow-up period.

Although the selection of study timeframe is important in all pharmacoepidemiologic studies, this factor is especially important for such studies using *electronic healthcare data* because there are usually significant lag times in data availability. Investigators should specifically include the time period for ascertainment of the relevant outcomes and covariates in the protocol, with assurance that complete data are available for the timeframe selected. The use of clear diagrams and pictorial displays to describe study timeframes is encouraged (Schneeweiss and Avorn 329).

5. Identification and Handling of Confounders and Effect Modifiers

The suspicion of unidentified or inadequately addressed confounding can threaten the validity of all pharmacoepidemiologic safety studies. Therefore, it is important for investigators to describe the processes used to identify potential confounders and to provide a scientific rationale for the methods selected to handle them. The specific methods and an assessment of their performance should be addressed in study protocols and reports. There are multiple epidemiologic and statistical methods, some traditional (e.g., multiple regression) and some innovative (e.g. propensity scores), for identifying and handling confounding. Although FDA does not endorse or require any particular method, a few methods that have been used frequently in pharmacoepidemiologic safety studies using electronic healthcare data are discussed in this guidance. FDA encourages the continued development, use, and evaluation of innovative methods for controlling confounding in pharmacoepidemiologic safety studies using electronic healthcare data.

One approach that has been used increasingly to address confounding is based on the propensity score. A propensity score for an individual is the predicted probability of being treated with a particular drug (usually the drug under study) conditioned on the individual's measured covariate values within the relevant database(s). The score can be used to achieve balance in the distribution of potential confounding factors between the exposed (to the drug of interest) and comparator with respect to the measured covariates (Rosenbaum and Rubin; D'Agostino). ***Diagnostics*** of the propensity score model should be presented to allow for assessment of its performance and fit. A full discussion of propensity scores is beyond the scope of this guidance but the articles cited in the bibliography of this guidance, as well as others, discuss this model and its appropriate application to pharmacoepidemiologic safety studies in greater depth.

Another approach used by some investigators to address confounding is to exclude patients who have risk factors for the outcome that are not related to the exposure of interest. This strategy can be appropriate, but might also have the unintended consequence of reducing sample size, precluding examination for effect modification, and limiting the generalizability of the results. An alternative approach to excluding such patients is to stratify by the unrelated risk factors, sample size permitting. The decision whether to exclude or stratify certain groups of patients based on other risk factors in a study should be made in the context of the specific hypotheses and fully explained and documented in the protocol. In general, it is preferable to stratify rather than exclude patients because it allows investigators to include all patient populations in the study, to maximize statistical power, and to study the impact of effect modification of these other risk factors. In general, the potential for effect modification by main demographic variables (e.g., age, gender, and race), or pertinent co-morbidities, should be examined in the study. If significant effect modification is found, the risk estimates should be presented appropriately. However, if a particular group of patients is to be excluded from a study, the investigator should provide a detailed explanation of the exclusions and a discussion of the resulting limitations in study interpretation.

C*onfounding by indication**, or "****channeling****,"* can be particularly problematic in pharmacoepidemiologic safety studies (Strom 797-8). Confounding by indication might lead to the appearance of an association between a drug and a safety outcome when the association is actually due to the underlying disease or indication for which the drug is prescribed. This is especially likely to occur when the drug of interest is preferentially prescribed to more severely ill patients. This type of confounding can be amenable to methods for controlling it or can be so pervasive as to preclude an observational study of the issue. Approaches to address this potential source of bias should be fully discussed by investigators in the study protocol.

Drug exposures and medical conditions that are considered to be covariates should be measured **prior** to exposure to the drug of interest, to avoid controlling for factors that may actually be on the causal pathway (Hernan, et al. 176). It is critical to specify the "look back period," which is the period of time the investigator looks back in the electronic healthcare data set to determine baseline covariates occurring prior to first drug exposure. Investigators should also indicate how ***time-varying confounders*** and potential unmeasured confounders (e.g., smoking, OTC drug use, or dietary supplement use) are operationally defined or explored. If a study takes place over many years, as the use of electronic healthcare data often makes possible, the investigators should consider ***time trend bias***, which refers to the evolution of medical practice and the diagnosis and treatment of disease over time, and report how this is addressed in the study.

6. Sample Size and Statistical Power

Sample size requirements and statistical power should be estimated before initiating the study. In addition, investigators should explain how the sample size was determined, including but not limited to relevant assumptions with pertinent justifications, formulas used to calculate the sample size, and a description accounting for the impact of anticipated exclusion criteria applied to the study population that was selected. It is especially important to provide the rationale behind the determination of sample size for rare outcomes (e.g., specific vaccine issues related to

an adverse outcome). The initial power calculations and the validity of underlying assumptions should be revisited at the end of the study in the context of the results, particularly in the case of negative findings.

B. Study Design: Exposure Definition and Ascertainment

1. Exposure Definition

The definition of relevant exposure to a medical drug for the outcome of interest (referred to as the exposure risk window) and its measurement should be described in detail, both conceptually and operationally using the data source(s) chosen. By obtaining information from other sources, such as spontaneous report data, about the postulated exposure risk window, the likelihood of focusing on only relevant periods of exposure can be increased. For example, if an adverse outcome is known to only occur immediately after initial use of a drug and the exposure definition includes all of the patient's time on a drug, a significant amount of nonrelevant exposure time could be included and could produce biased risk estimates. All assumptions made in defining the exposure risk window should be clearly articulated and justified, including but not limited to when information about the timing of exposure and outcome is not known during the study design process. Sensitivity analyses might prove helpful in testing these assumptions (refer to section VI.D).

It is also critical to provide a rationale for the selection of the appropriate units for the exposure risk window (e.g., person-time, patients, prescriptions). Relevant drug interactions that could affect the measurement of the exposure risk window for the drug of interest should also be operationally defined if applicable. For example, if investigators are operationally defining concomitancy, they should state whether:

- drugs are considered as being used concomitantly by the same patient only if they are dispensed on the same day,
- drugs are considered as being used concomitantly by the same patient only if they have overlapping days supply,
- the patient has ever received prescriptions for the two drugs during the study, or
- another relevant definition is appropriate.

It is common practice to use dispensed prescriptions to define exposure risk windows in administrative claims data. If exposure is defined in other ways (e.g., using other clinical characteristics or medical diagnoses, prescription orders from EMR data), a discussion of the demonstrated validity of these definitions should be included.

2. Exposure Ascertainment — Study Design

As previously mentioned, the study design should be tailored to the study question of interest; FDA does not advocate for the use of any specific study designs. One type of cohort study design that has gained popularity is the new (incident) user design, based on first exposure to or use of the drug of interest. When employing a new user design, new users should be defined operationally and a rationale for this definition in the context of the study question should be provided. This information is critical for evaluating the accuracy of the exposure definition.

When defining new users, investigators should bear in mind that patients may have entered the electronic healthcare data system already using the drug of interest; therefore, look back periods should be defined to ensure that such patients are not incorrectly classified as new users.

3. Exposure Ascertainment — Data Source

For a defined study period, it is important to demonstrate sufficient capture of drug exposures by the proposed data source. Exposure definitions should incorporate the coding system of the data source(s) used and reflect an understanding of the prescription, delivery and reimbursement characteristics of the drug in that data source. For example, in the United States, the definition should include the appropriate use of pharmacy codes (National Drug Codes or NDC codes) and/or procedure ("J") codes[12] to capture drug use in various settings, especially in the case of non-oral drugs. For example, patients may be required to purchase the injectable drug in the pharmacy (NDC code) or the provider may purchase the injectable drug for the patient and bill for the drug and its administration ("J" code).

When using an insurance-based data source, it is also important to address lack of capture of prescriptions not associated with co-payments if these drugs are relevant exposures for the study. Uncaptured prescriptions might include low cost generics and drugs obtained through programs in which certain drugs are provided at a standardized discounted rate, samples provided by pharmaceutical companies and dispensed by health care providers, and drugs sold through the Internet. This lack of capture and its effect on study validity should be addressed.

4. Exposure Ascertainment — Gaps in Therapy

FDA recommends that investigators clearly explain how they will address potential gaps in therapy in the context of exposure ascertainment over time, especially for chronic therapies. Since patients often do not obtain refills exactly on time, apparent gaps in therapy often exist in electronic healthcare data, and decisions need to be made as to when these gaps are long enough to suggest true interruption of treatment. Intermittent therapies (e.g., drugs used to treat pain on an as-needed basis) and therapies for which samples are provided to patients (e.g., oral contraceptives) represent special challenges with regard to assessing actual time of exposure. It is critical that investigators address how they will operationally define exposure when studying these types of therapies.

5. Exposure Ascertainment — Dose

Electronic healthcare data capture only what is either prescribed or dispensed to a patient, but not what the patient actually ingests. In certain circumstances, particularly in the case of drugs used chronically or those with fixed-dose regimens, it can be appropriate to infer dosage information from electronic healthcare data. FDA encourages investigators to provide the specific assumptions made when estimating the dose of the exposure (drug) of interest; this information is especially important when studying pediatric patients. It is also important to report how different dosage forms will be incorporated into the dosage calculation, if multiple forms are

[12] A drug's *J code* — more properly, the Health Care Financing Administration (HCFA) common procedures coding system code — is used for submitting Medicare claims for reimbursement of outpatient care.

available. This is an area in which sensitivity analyses may prove helpful in testing assumptions (refer to sections VI.D and V.B.1).

6. Exposure — Other Factors

When using inpatient data, it is also important to consider the order of administration of drugs in relation to each other and to the outcomes of interest. This information may not be readily available in electronic healthcare data. If the exposure of interest is available as combination therapy, it is important to account for this fact when ascertaining total exposure (e.g., drugs to treat hypertension are commonly prescribed as combination drugs). If switching within the therapeutic class of the exposure of interest is common, it is important to address how exposure will be ascertained and defined. Repeated switching could significantly complicate exposure definition, but for many drugs will reflect real-world patient experience. In these circumstances, the approach taken to account for this phenomenon and the potential impact on generalizability should be described.

When using most EMR data, information on exposure is generally limited to products prescribed by health care providers. Without linkage to dispensing systems, it cannot be assumed that the patient actually filled the prescription. It is important for investigators to ensure the validity of EMR prescribing information before using it to define patient drug exposures.

C. Study Design: Outcome Definition and Ascertainment

One of the most crucial steps in selecting a data source is determining whether it is appropriate for capturing the outcomes of interest. Because electronic healthcare data typically capture outcomes that are treated (or at least brought to the attention of a healthcare professional), outcomes representing mild symptoms — or the other extreme of sudden death without medical care — will not be well captured. Outcomes on the continuum between these two extremes may be captured to varying degrees by different types of data sources and should be assessed carefully before study initiation.

1. Medically and Scientifically Relevant Case Definition of Safety Outcomes of Interest

When developing the case definition for the outcomes of interest, it is important to obtain both epidemiologic and clinical input. Case definitions for outcomes should be developed independently of drug exposure status, and exposure to the drug should not be an inherent component of the outcome definition. FDA recommends that investigators refrain from defining cases based on future exposure and/or excluding cases based on undocumented clinical judgment.

2. Validation of Outcomes

Because *electronic* administrative claims data are not collected for investigative purposes, but rather for patient care or reimbursement purposes, it is vitally important to ensure that medical outcomes of interest are validated (Lanes). Validation of administrative claims data is the

process through which primary medical data (generally medical charts) are abstracted and reviewed to determine whether the patient actually experienced the event coded (or suggested by the algorithm if applicable) in the electronic data. Although this validation is critical for all safety studies, it is especially important for certain vaccine outcomes, as they are often rare events for which coding practices cannot be known or assumed. If the outcome has previously been validated, it is critical to reference literature documenting when and in which databases the validation was done. If referring to previous validation work, the investigator should describe it in detail, include a description of the population and database in which validation was performed, and provide the timeframe during which the validation work was performed. For studies without outcome validation, the investigator should provide appropriate justification of the outcome definition used.[13]

FDA recommends that outcome definitions be specified and explained *a priori* and incorporate the coding system of the data source(s) used. In some situations, it can be appropriate to validate only a sample of cases. Information gathered in the outcome validation process should be incorporated into the analysis plan and protocol and, if appropriate, be submitted as a final protocol amendment. Investigators should consider the rarity of the outcome when considering the desired sensitivity and specificity of the coding algorithm. It is important to consider the often arbitrary ranking of coded primary and secondary hospital discharge diagnoses, and the associated limitations of these categories when selecting which diagnoses to choose as outcomes (e.g., the order of discharge diagnoses may not correspond to their medical importance). ICD codes in claims data are generally considered more reliable for inpatient outcomes than for outpatient outcomes, where "upcoding" and "downcoding" are practices commonly used to maximize reimbursement (Strom 220). Therefore, when using claims data, it is preferable to use and validate inpatient codes when defining outcomes whenever possible because these codes are often more reliable and generally reflect more serious diseases. In addition, it is important to report on the investigators' ability to capture outcome severity in the databases employed.

When describing the outcome validation process, it is also recommended to report on and justify the validation of key covariates (defined by medical claims diagnoses) that will be used in the primary analysis. If such justification is not available, this should be noted.

It is important to note that the concept of validation is not as well defined when using EMR data. The strategy described above for validation in administrative claims data might not be relevant because the EMR might represent all available primary medical data for the patient encounter to be validated. There is still a scientific need, however, to develop and employ strategies for ensuring that the electronic data accurately reflect patient experience. For example, investigators might review any paper files or documents or follow up with health care providers to gain more information. As implementation of EMRs becomes more widespread, investigators will be challenged to develop innovative strategies to confirm electronic exposure and outcome data,

[13] One example of justification is referencing standardized case definitions. For example, for vaccine studies investigators could reference collections of standardized case definitions such as the International Brighton Collaboration (http://www.brightoncollaboration.org), which provides a growing repertoire of such definitions for vaccine safety investigations. The use or adaptation of definitions from these types of standardized case definition collections may facilitate comparisons of analyses between different studies.

and FDA encourages such efforts as they are critical to ensure the validity of studies relying upon these data.

3. Outcome Definition — Procedures or Diagnoses

If the investigator is using procedures instead of or in addition to diagnoses as outcomes, it is important to explain the rationale behind this choice. Validation of the codes used, or justification for not validating, should also be included.

4. Mortality as an Outcome

Death is a particularly difficult outcome to ascertain reliably using electronic healthcare data. Although deaths that occur while under medical care are often documented in these data systems, reliable ascertainment of deaths can only be accomplished through linkage with vital statistics or other systems such as the Social Security Administration (SSA) or National Death Index (NDI) (NDI Web site).[14] These linkages can provide confirmation of death and date of death, but cause of death may require further information obtained from death certificates (NDI data provide cause of death information from the state death certificate but SSA data do not) (MacMahon and Pugh 76). The use of death certificate data is subject to all the known limitations of such data.

Given that deaths while not under medical care may not be captured in electronic healthcare data systems, patients who die may simply be observed in electronic healthcare data sets as not filing any further claims or not receiving any additional care past a particular date. For studies in which outcomes may often be fatal, it is important therefore not to exclude patients who appear to be "lost to follow up" at any time following their drug exposure. These patients should be included in searches of NDI or other systems to see if their absence (disenrollment) from the system has been caused by death, specifically by death related to the study outcome of interest.

VI. BEST PRACTICES — ANALYSES

A. Prespecified Analysis Plan

In the study protocol, investigators should include a prespecified analysis plan that addresses the specific study objectives. The plan should specify primary and any secondary analyses. If investigators plan to perform ***preliminary analyses***, they should prespecify the plan. ***Preliminary analyses*** are analyses that involve nonvalidated outcomes without appropriate justification or when adjustments for confounders and examination for effect modification are lacking. Prespecifying a plan is critical because risk estimates for safety outcomes of interest may be substantially different before and after validation and adjustment. These differences may significantly affect the ultimate findings of the study. Investigators should also note if there is a lack of statistical power to detect rare outcomes of interest.

Investigators should present both unadjusted and adjusted results in the final analysis. This presentation is critical for studies that employ electronic healthcare data sets because significant statistical power can often be obtained in these types of studies; as a result, without adequate

[14] National Death Index Web site: http://www.cdc.gov/nchs/ndi.htm..

adjustment for potential confounders, statistically significant results that are inaccurate can easily be found. However, adjustment for measured confounders does not guarantee accurate results, and the potential impact of unmeasured confounders must be addressed. Unadjusted results facilitate both qualitative and quantitative comparison with the adjusted results to examine the effect of adjustment.

B. Additional Analyses

Significant findings in subgroup analyses may be considered hypothesis-generating unless prespecified and adequately powered. If subgroup analyses are employed, investigators should describe methods used to examine subgroups and interactions (von Elm, et al. 346). It is recommended that ***post hoc analyses*** be clearly described as such to aid interpretation.

C. Use of Specific Statistical Techniques (e.g., To Minimize Confounding)

Investigators should ensure that appropriate statistical techniques are used to address confounding and assess effect modification and that these techniques are well described and justified, including a clear delineation of relevant assumptions and limitations. The reported results should be stratified by the key effect modifier. It is important to discuss in detail the performance of the techniques in specific databases used and the impact on the interpretation of the study findings. Diagnostics, both graphical and analytical, are often relevant and facilitate the evaluation of assumptions and performance of the techniques. Planned statistical techniques and diagnostic methods should be outlined in the analysis plan.

D. Sensitivity Analyses

FDA recommends the use of sensitivity analyses to determine the impact of various study decisions relating to design, exposure definition and outcome definition. Such analyses can be very helpful in determining the potential impact of varying assumptions on study results, and can facilitate better interpretation of study results in light of significant limitations. It is important for investigators to clearly identify and describe sensitivity analyses that are performed and to provide their own interpretation of the impact of these analyses on the interpretation of the study findings.

E. Linking or Pooling Data from Different Sources

If applicable, the analysis plan should include information on how data are to be pooled from different sources. If relevant, investigators should also describe how data are linked or standardized to allow for pooling.

F. Assessment and Handling of Missing and Uninterpretable Data

Investigators should develop a plan to assess and handle missing and uninterpretable data (e.g., a claim is paid for by an insurance company, but the claim is not clinically accurate). It is important to provide the percentage of missing data for key variables of interest. Missing information is sometimes falsely interpreted. For example, lack of positive information on the

occurrence of an event (such as dialysis) or a risk factor (such as smoking) might not mean that the event or risk factor was nonexistent. Care should be given to default values of data and the implications of lack of information on data values.

G. Quality Assurance (QA) and Quality Control (QC)

The quality control (QC) and quality assurance (QA) plan for the construction of the analytical data set(s) and analysis of data should be clearly described. QC consists of the steps taken during the analysis to ensure that it meets prespecified requirements and that it is reproducible. QA consists of activities undertaken to evaluate quality control. CDER's Manual of Policy and Procedures (MAPP) 6700.2 *Standards for Data Management and Analytic Processes* provides an example of how quality control (QC) and quality assurance (QA) planning and implementation can be accomplished.[15]

Investigators should describe the approaches taken to ensure data integrity (confidentiality and security of information from authorized access or revision) and data validity (correctness of data that is collected and stored).

FDA could request access to the original analytic data set to conduct re-analyses of the data to verify study results; thus, the lead study investigator should ensure that analytic data sets used in the study are archived in a way that provides access for the purpose of such re-analyses while ensuring personal data protection.

H. Describe Procedures To Ensure Accuracy of Data Management and Analysis Process

ISPE highlights that it is important to "describe data management and statistical software programs and hardware to be used in the study" and "data preparation and analytical procedures as well as the methods for data retrieval and collection" (ISPE guidelines 202). FDA encourages investigators to describe these processes to ensure transparency about how data sets are managed and prepared. It is important for analysts performing and reviewing data management and analysis to have appropriate training or prior experience in the use of the particular analytic software. Documentation is another very important component of the analytic process. FDA recommends that all analytic programs be thoroughly annotated with comments that clearly describe the intent or purpose of each step.

[15] MAPPS are available on the Internet at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm#ODS.

GLOSSARY

The following terms are defined for the purposes of this guidance.

Administrative claims data: "Claims data arise from a person's use of the healthcare system [and reimbursement of healthcare providers for that care]. When a patient goes to a pharmacy and gets a drug dispensed, the pharmacy bills the insurance carrier for the cost of that drug, and has to identify which drug was dispensed, the milligrams per tablet, number of tablets, etc. Analogously, if a patient goes to a hospital or to a physician for medical care, the providers of the care bill the insurance carrier for the cost of the medical care, and have to justify the bill with a diagnosis" (Strom 220).

Churn rate: The churn rate is the rate at which a population moves in and out of a health plan; most healthcare coverage in the United States is employer based and thus coverage changes over time with changes in employer.

Comparator (comparison) group: Any group to which patients with either the exposure or outcome of interest are compared (Porta 47).

Confounding by indication (channeling): "Physicians prescribe drugs in light of diagnostic and prognostic information available at the time of prescribing. The factors influencing this decision vary by physician and over time and frequently involve patients' clinical, functional, or behavioral characteristics that are not directly recorded in administrative databases. If some of these factors that are imbalanced among drug users and non-users are also independent predictors of the study outcome, then failing to control for such factors can lead to confounding bias. The confounding then results from selecting patients into drug exposure groups (confounding by indication)" (Schneeweiss and Avorn).

Continuous coverage/Continuity of coverage: The period of time over which a patient is enrolled in a healthcare system and during which any medical service or drug prescription would be captured in the healthcare system's electronic record system.

Diagnostics: Methods used to assess the performance of a statistical model and/or evaluate the fit of the method or model to the data.

Electronic healthcare data set: An analytic data set that is "an organized set of [healthcare] data or collection of files available by computer through electronic format which can be used for the conduct of pharmacoepidemiologic [safety] studies" (Hartzema, et al. 519). It is derived from a raw electronic healthcare database.

Electronic medical record (EMR): An electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one healthcare organization (NAHIT Report).

Exposure risk window: Interval of exposure (to the drug of interest) time considered to be relevant in the design or analysis of a pharmacoepidemiologic study. In case-control studies, it is essential to define a priori the period during which the possible exposure to the drug of interest will be investigated in the previous history of the cases and comparators. An equivalent period must be defined for the comparators. Similarly, in a cohort study, the time window defines the period after the beginning of exposure during which the occurrence of an event (safety outcome) of interest will be attributed to the exposure. The a priori choice of an exposure risk window can be challenging if the outcome of interest is poorly documented. An inappropriate exposure risk window can strongly bias the estimate of risk (Begaud 156).

Historical comparators: Comparator group for whom data were collected at a time preceding that at which the data were gathered on the group of interest. Because of secular trends, use of a historical comparator group can lead to bias in the risk estimates (Porta 117).

Observational studies: In observational studies, "the investigator does not control the therapy, but observes and evaluates the results of ongoing medical care. These are the study designs that do not involve random" allocation. For purposes of this guidance, observational studies include case-control, cohort, and case-crossover studies (Strom 862).

Pharmacoepidemiologic safety study: An observational study designed to assess the risk attributed to a drug exposure and test prespecified hypotheses (2005 FDA guidance).

Post hoc analysis: "An analysis that was not anticipated or described" in the analysis plan or study protocol (Begaud 115).

Preliminary analysis: Analyses are preliminary if they involve nonvalidated outcomes without appropriate justification or when adjustments for confounders and examination for effect modification are lacking.

Quality assurance (QA): Quality assurance consists of activities undertaken to evaluate quality control (FDA MAPP 6700.2).

Quality control (QC): Quality control consists of steps taken during the generation of a drug or service to ensure that it meets prespecified requirements and that the drug or service is reproducible (FDA MAPP 6700.2)

Real-time active safety surveillance: Drug-based, real-time active surveillance systems that investigate large numbers of patients exposed to new molecular entities (NMEs) after their launch for all or specified adverse events. This type of system can also examine the use of drugs and modes of clinical practice (RFI).

Study timeframe: The timeframe from the beginning of the "look back period," when the investigator looks back in the database before drug exposure to ascertain baseline patient covariate data, to the end of the follow-up period.

Time trend bias: The evolution of medical practice and the diagnosis and treatment of disease over time.

Time-varying confounder: A confounder variable whose values change over the study timeframe (Platt 687).

Validation: The process through which primary medical data (generally medical charts) are abstracted, reviewed, and adjudicated to determine whether the patient actually experienced the event coded in the electronic data.

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