# Guidance for Industry and FDA Staff

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

**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)**

**May 2013**
**Drug Safety**

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*Contains Nonbinding Recommendations*

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# Guidance for Industry and FDA Staff[1]

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This guidance represents 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 describes best practices pertaining to conducting and reporting on ***pharmacoepidemiologic safety studies***[2] that use ***electronic healthcare data***, which include ***administrative claims data*** and ***electronic medical record (EMR)*** data.[3] 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 purposes of this guidance, the term *pharmacoepidemiologic safety study* refers to an ***observational study*** designed to assess the risk associated with a drug exposure and to test prespecified hypotheses. For ease of reference, this guidance uses the term *drug* to refer to drug and biological products regulated by CDER or CBER. Medical devices are not within the scope of this guidance.

This guidance is intended to provide the following:

- Consistent guidance for industry and FDA to use when designing, conducting, and analyzing pharmacoepidemiologic safety studies;

[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.

[3] This guidance uses the term EMR instead of electronic health record (EHR) because at this time, currently available electronic data sources used for pharmacoepidemiologic safety studies contain mainly EMR versus EHR data. Thus, although the adoption of EHRs is increasing, it is not yet possible to recommend best practices on their use in pharmacoepidemiologic safety studies.

- A framework for industry to use when submitting pharmacoepidemiologic safety study protocols and final reports to FDA; and
- A framework for FDA reviewers to use when reviewing and interpreting pharmacoepidemiologic safety study protocols and final reports.

The focus of this guidance is on best practices that specifically apply to pharmacoepidemiologic safety studies using electronic healthcare data. Although the guidance is not intended to address 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. FDA encourages industry to inform FDA of all pharmacoepidemiologic safety studies that it conducts; 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.[4]

The Prescription Drug User Fee Amendments of 2007 (PDUFA IV) authorized a significant expansion of the postmarket focus under the PDUFA program.[5] Under PDUFA IV, FDA agreed to specific commitments to enhance and modernize the drug safety system.[6] 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. The guidance focuses on the conduct and reporting of pharmacoepidemiologic safety studies that use electronic healthcare data because: (1) existing guidelines and checklists are not specifically

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[4] The Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require submission of information pertaining to certain postapproval (hereinafter referred to as postmarketing) studies, including the status of any required pharmacoepidemiologic studies undertaken to investigate a safety issue. See section 505(o)(3)(A), 505(o)(3)(B), and 505(o)(3)(E)(ii) of the FD&C Act (21 U.S.C. 355(o)(3)(A), (B), and (E)(ii)). In April 2011, FDA published a guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, that addresses submission requirements, including timetables and schedules, for postmarketing requirements (PMRs) and postmarketing commitments (PMCs). 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 the CBER guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Section 506B of the FD&C Act (21 U.S.C. 356b) requires sponsors to report on postmarketing 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 new drug applications, 21 CFR 314.81(b)(2)(vii) and 21 CFR 314.98(c) for abbreviated new drug applications. Section 601.70(b) of FDA regulations (21 CFR 601.70(b)) requires annual progress reports for required or agreed-upon postmarketing studies for biologics license applications, but it should be noted that § 601.70(a) limits the definition of "postmarketing studies" to those concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology.

[5] See FDAAA, Title I — Prescription Drug User Fee Amendments of 2007.

[6] 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.

directed to the use of electronic healthcare data in pharmacoepidemiologic safety studies; (2) an increasing number of these studies using electronic healthcare data have been conducted and submitted to FDA in recent years; and (3) studies that involve the use of electronic healthcare data have complex and unique characteristics that warrant more specific guidance.

FDA 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 and the draft guidance was published in February 2011. FDA carefully reviewed and considered all oral and written comments from the workshop and the draft guidance docket to create the current guidance.

This guidance does not address real-time active safety surveillance assessments (e.g., Mini-Sentinel and Sentinel (Robb, et al. 2012)), as this field continues to evolve and it is not yet possible to recommend sound best practices. 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. It does not provide a framework for determining the appropriate weight of evidence to be given to 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 currently best accomplished in the context of the specific safety issue under investigation.

This guidance also does not address the decision to pursue a pharmacoepidemiologic safety study using electronic healthcare data in any particular case over any other type of study, as this decision is unique to each specific safety issue of interest.[7] Generally, however, these studies may be particularly useful when clinical trials would be infeasible (e.g., 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 available in electronic healthcare data.

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

[7] In some instances, when FDA is concerned about a serious risk, applicants are required to complete postmarketing studies, which are one of an array of potential PMRs. For a full discussion of PMRs, refer to the guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*. FDAAA provides the specific circumstances when FDA can require the conduct of postmarketing studies (see section 505(o)(3)(D)(i) of the FD&C Act).

FDA postmarket regulatory decision-making on a drug safety issue generally involves several interrelated steps.

- FDA receives evidence of an association between a particular drug and an adverse event. This evidence generally comes from one or more of the following data streams: randomized controlled trials (RCTs), spontaneous adverse event case reports, pharmacoepidemiologic safety studies, and meta-analyses.

- FDA assesses the quality of both the design and conduct of the studies and reviews the final reports pertaining to the purported association of drug and outcome; additional studies might be initiated to further examine the association.

- The accumulated evidence is then integrated and weighed by a multidisciplinary team to reach an overall conclusion, to the extent possible based on the available data, regarding the relationship between the drug and the outcome. This is followed by an overall examination and a reassessment of the drug's benefits and risks.

- FDA then determines whether any regulatory action is required (e.g., labeling changes, requiring or modifying a Risk Evaluation and Mitigation Strategy, generation of additional data from one or more data streams, such as a postmarketing pharmacoepidemiologic safety study or trial, etc.)

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.

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 aspect of regulatory decision-making is evaluating the evidence from pharmacoepidemiologic safety studies. Electronic healthcare data are often useful in conducting these studies that are designed to 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 consistent and objective interpretation of findings from these studies.

## A. Electronic Healthcare Data in Pharmacoepidemiologic Safety Studies

Recent technological advances now allow investigators to efficiently assemble electronic healthcare data and, relative to alternative approaches, rapidly conduct pharmacoepidemiologic studies of drug safety issues in real-world healthcare settings and with large numbers of patients. In addition, innovative statistical methods allow investigators to study complex drug safety questions previously considered too difficult to examine outside of a clinical trial setting.

Indeed, these advances have opened up many new opportunities for conducting pharmacoepidemiologic studies.

### B. Prior Guidelines and Guidance Documents

Guidance documents previously published by the FDA, in addition to guidelines published by several other organizations, have informed the development of best practices for conducting pharmacoepidemiologic safety studies using electronic healthcare data. FDA's 2005 guidance *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (FDA 2005 guidance), which is much broader in scope than the current guidance, largely focuses on the practice of pharmacovigilance and the various types of pharmacoepidemiologic studies and includes an abbreviated section on observational studies..

The International Society for Pharmacoepidemiology's (ISPE's) *Guidelines for Good Pharmacoepidemiology Practices* (GPP) (ISPE guidelines 2008) recommends that all pharmacoepidemiologic studies address the following:

- 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; FDA considers the investigator to be responsible for ensuring that the data are Health Insurance Portability and Accountability Act (HIPAA) compliant and that all research performed complies with standards of privacy of individually identifiable health information and protects the rights of human subjects in research;
- Providing confidence intervals about estimates of risk 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; and
- Archiving of relevant study documents and data.

The Consolidated Standards of Reporting Trials (CONSORT) statement (Moher, et al. 2001), exemplifies 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. 2008) provides guidelines for reporting observational studies.[8] The

[8] 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).

STROBE recommendations were developed in response to the pervasiveness of missing information in published observational epidemiologic studies (von Elm, et al. 2008). The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) has developed a Checklist of Methodological Standards for ENCePP Study Protocols and a Guide on Methodological Standards in Pharmacoepidemiology to provide standards for pharmacoepidemiologic studies and to enhance awareness about scientific and methodological developments in pharmacoepidemiology.[9]

The FDA 2005 guidance, the ISPE guidelines, the STROBE reporting framework, and the ENCePP methods checklist and guide provide general guidance applicable to all pharmacoepidemiologic safety studies. Studies that involve the use of electronic healthcare data have complex and unique characteristics that warrant more specific guidance. This best practices guidance specifically addresses the design, analysis, conduct, and documentation of pharmacoepidemiologic safety studies using electronic healthcare data with protocols and reported results submitted to FDA.

## III. BEST PRACTICES — GENERAL CONSIDERATIONS

For all pharmacoepidemiologic safety studies using electronic healthcare data submitted to the Agency,[10] investigators should submit protocols to FDA before study initiation and final reports upon completion.

The scientifically valid protocol should include the names and roles of all individuals involved in its development. Investigators should predefine aspects of the study related to the design, analysis, conduct, and reporting of the study and articulate them in the study protocol and final reports, along with a science-based rationale for the scientific study choices pertaining to these aspects of the study; more information regarding these aspects is provided in sections IV, V, and VI of this guidance. Any changes to the initial protocol after data collection has commenced should be justified and documented in the final protocol and study report, along with a discussion of the impact of those changes on the final interpretation of study results. Published studies submitted to FDA for safety-related regulatory decision-making should be accompanied by supplemental documentation that addresses the aspects of study design, analysis, conduct, and reporting discussed in this guidance. **All of the issues described within this guidance should be addressed in the protocol, in the study report, or in accompanying documentation. At this time, FDA is not proposing a specific format for any of these documents when reporting on pharmacoepidemiologic safety studies that use electronic healthcare data.**

### A. Title and Detailed Study Summary

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[9] http://www.encepp.eu/standards_and_guidances/index.html. Last updated February 2, 2012.

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

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.

- Scientific goals, study objectives, and prespecified hypotheses;
- Study design, including ***comparator groups***;
- Study population and time period of study, including: (1) ***study time frame*** and (2) scheduled milestones (final protocol submission, study completion, and the final report);
- Data sources used;
- Drug exposures of interest;
- Drug safety outcomes of interest;
- Methods to control for sources of bias and confounding;
- Statistical analysis plan;
- Brief, balanced description of the results, interpretation of study findings, and key study limitations; and
- Public health impact.

## B. Background

A background section should be provided that includes a **brief** description of prior evidence or suspicions prompting the study initiation, a brief discussion of the strengths and weaknesses of previous studies on the safety issue, and some general information about the therapeutic class and use of the study drug(s). Investigators should then describe the concise study objectives and feasible hypotheses upon which the study design has been based.

## C. Study Approach Considerations

Once the prespecified hypotheses are identified, the study approach, including the selection of data sources, study design, and analysis plan, can be developed. The investigators should describe the reasons for their choices of study design, selection of databases, and analysis plan as they pertain to the hypotheses. The investigators should also briefly describe any alternative study approaches and databases they considered before deciding upon the proposed approach, and explain why the alternatives were neither feasible nor optimal in 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.

Use of multiple study designs and data sources can assist in addressing the hypotheses by increasing the generalizability and robustness of findings and allowing for the study of different sub-populations of interest (Vandenbrouke 2008). The protocol should address whether the use of more than one data source is appropriate. The study sample size can be increased by designing a study that uses the same design and analysis plan across multiple electronic

healthcare data sources. Such protocols should address the critical factors related to assembly of analytic data 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.

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 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 increase the probability of 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 study findings, investigators should summarize the key results from (1) unadjusted analyses, if conducted, and (2) the prespecified ***primary*** and ***secondary analyses***. The summary should address the objectives and hypotheses of the study as specified in the protocol. Providing both absolute and relative effect measures whenever possible will provide the most information on the public health impact of the study results.

In interpreting the findings, the precision of the estimated effect measure from the study should be discussed. Confidence intervals are crucial in interpreting the precision of the risk estimates from the study. Confidence intervals can be used to provide a range of the effect measures consistent with the study findings. 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.

Conversely, statistical significance alone does not exclusively determine the clinical importance of the findings, because when dealing with large amounts of electronic healthcare data, statistical significance of very small effect measures can be common. Consideration should be given to both the clinical significance and potential biases.

Investigators should discuss potential biases and confounding, the suspected magnitude and direction of these effects, and their potential impact on the interpretation of the study findings. Results from sensitivity analyses might prove helpful in discussing these issues (refer to section VI.D). Investigators should also discuss the limitations of the database and the study design, and the impact of those limitations on generalizability. Finally, investigators should place the study

findings in the context of other evidence, including studies previously conducted on the same issue using other databases, populations, and study designs.

## IV. BEST PRACTICES — DATA SOURCES

FDA does not endorse one type of electronic healthcare data source over another. Investigators should select data sources that are most appropriate to address the specific study 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. Because existing electronic healthcare data systems were generated for purposes other than drug safety investigations, it is important that investigators understand their potential limitations and make provisions to use the data systems appropriately. For example:

- Administrative claims data are generated to support payment for care; the payor's policies governing the approval and denial of such payments should be considered before using these data for study investigations.

- EMR data are generated in the course of routine clinical care provision; therefore, it is important for investigators to consider the particular healthcare system's characteristics and guidelines for patient care and their common clinical practices, as these factors will have an impact on the data collected.

Investigators should also describe the historical accessibility of 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 research community;
- How often this data source has been used for pharmacoepidemiologic safety studies;
- The capability of the selected data source to validate the outcome and other study elements (e.g., exposures, key covariates, inclusion/exclusion criteria) based on the safety question; 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 IV.E).

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

In addition, investigators should 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 access to hospitalization data would not

be appropriate for studying safety outcomes likely to result in hospitalization. It is also important to address the data standardization and coding 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 that rely solely on ICD codes in claims data.

The protocol should describe the relevant populations to be used in a study, including whether access to specific patient populations (e.g., psychiatric, pediatric) may be important. Investigators should include a description of the ***continuity of coverage*** (see section IV.B) for patients included in the data source, and specify how all relevant exposures and outcomes will be captured during the study period. It is important for investigators 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***. Investigators should provide information about the ***churn rate***, as it may indicate whether the selected data source(s) are appropriate for ascertaining long latency safety outcomes.

### B. Enrollment and Comprehensive Capture of Care

Investigators using administrative claims data sources should address continuity of coverage (enrollment and disenrollment), particularly for 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 2005). The validity of the findings of a study using these data 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* should be developed and documented, particularly in studies using more than one data source.

It is important for investigators to address comprehensiveness and continuity of coverage when employing EMR data sources, as the entire continuum of the patient's care might not be available in a single EMR system. For example, patients receiving treatment from multiple physicians, offices, or hospitals might have their course of care captured in several different EMR data sources. 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, investigators using an EMR data source should describe the steps taken to ensure complete capture of patient care over time to facilitate the likelihood that all exposures and safety outcomes of interest will be captured. Furthermore, primary care-based EMR networks in the United States 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 protocol specifies hospital data as the sole data source, the investigator should discuss whether outpatient care data are relevant to the study because it is often not captured in this type of data source. Similarly, if an outpatient data source alone is proposed, detailed data on drug exposures in the hospital setting is usually not available. For either of these scenarios, the investigator should fully describe the relevant data source characteristics and their potential

impact on the interpretation of study results. In general, over-the-counter (OTC) medications and dietary supplements are not 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 information gap.

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

There are differences in the practice of medicine across the world, some of which are particular to the healthcare system. Certain differences affect whether a non-U.S. data source can be used to address specific drug safety hypotheses in a way that is relevant to the U.S. population. Various factors in non-U.S. healthcare systems, such as medication tiering (e.g., first-line, second-line) and patient coverage selection, influence the degree to which patients on a given therapy in other countries might differ in disease severity from patients on the same therapy in the United States.

Even within the United States, patients in different electronic healthcare databases may differ in disease severity. In addition, as we begin to learn more about the role of pharmacogenetics in drug-related harms, it will become increasingly important to consider the impact of potential pharmacogenetic profile variations on the feasibility and generalizability of safety studies relying on non-U.S. data sources.

For studies that propose the use of a data source from a country other than the United States, the investigator should provide:

- The rationale for selecting the particular data source(s) to address the specific hypotheses;
- Background information about the healthcare system, including method(s) of diagnosis and preferred patterns of treatment for the disease(s) of interest, and the degree to which such information is collected in the proposed data sources;
- A description of prescribing and utilization practices, including approved indications, formulations, and doses for non-U.S. settings;
- Information on the market availability of 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.

### D. Selection of Study Population

Investigators should use explicit inclusion and exclusion criteria for the selection of the study population and provide an appropriate explanation in the protocol 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 completeness of medical care and drug coverage, including direct access or linkage to Medicare data.[11]

Obtaining comprehensive drug coverage and medical care data on patients with some types of serious and life-threatening conditions (e.g., HIV/AIDS or cancer) can present a unique challenge. These patients may receive treatment in state- or federal-based clinics, in experimental clinical trials, or under pharmaceutical company assistance programs, which may not be fully captured in most electronic healthcare data sources. If these issues are relevant to the study question of interest, the investigators should report how they will be addressed in the protocol.

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 (see Esposito 2009; Friedman 2008; Schneeweiss 2008; Weiner 2008).

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

Investigators should fully understand the ***quality assurance (QA)*** and ***quality control (QC)*** procedures used by the data holders and how these procedures could have an effect on the integrity of the data and the overall validity of 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 relevant period of 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 during the study time frame and their potential effect on the study; and
- A report on the extent of missing data over time (i.e., the percentage of data not available for a particular variable of interest) and a discussion on the procedures (e.g., exclusion, imputation) employed to handle this issue. Investigators should also address the implications of the extent of missing data on study findings and the missing data methods used.

[11] For more information on Medicare data, please access the Centers for Medicare and Medicaid Services (CMS) Web site at http://www.cms.hhs.gov/medicareGenInfo.

### F. Study Time Frame and Lag Time Issues

Investigators should define the study time frame (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 follow up period) in the protocol and discuss the suitability of the time frame in addressing the specific hypotheses associated with the study. The discussion should address temporal changes in the standard of care, the availability of other treatments, and any other relevant factors. For example, a given drug's patterns of use may change over time, and any potential corresponding differences in the patients exposed to the drug over time could be relevant to the safety outcome(s) of interest. Investigators should discuss the impact of changes in use patterns over time on the exposed group and develop the study approach accordingly.

***Lag times*** in data availability can be of particular concern for studies that use electronic healthcare data. Investigators should specifically designate the time period for ascertainment of the relevant outcomes and covariates in the protocol and ensure that complete data are available for the selected time frame. The use of clear diagrams and pictorial displays to describe study time frames is encouraged (Schneeweiss and Avorn 2005).

## V. BEST PRACTICES — STUDY DESIGN

### A. Study Design Considerations

#### *1. Choice of Study Design*

FDA does not endorse a specific type of study design for pharmacoepidemiologic safety studies that use electronic healthcare data because the choice should be made uniquely in the context of the drug, the safety issue, and the specific hypotheses of interest. Investigators should first establish the study questions of interest and then determine which data source(s) and design are most appropriate to address these questions. Investigators should discuss their rationale for selecting a particular study design in the study protocol and final report.

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

Several study designs are commonly used in observational pharmacoepidemiologic safety studies, including, among others, cohort, case-control, nested case-control, case-cohort, and case-crossover studies. The selection of the most appropriate study design depends 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 will be appropriate depending on the study question(s). FDA discourages investigators from applying a *one size fits all* approach to study design, irrespective of the design's suitability in addressing the particular study questions and hypotheses.

#### *3. Comparator Selection*

Selection of an appropriate comparator group or control group is a critical part of a pharmacoepidemiologic safety study. FDA encourages the use of multiple comparator groups in those study designs where it is feasible and relevant, as this strategy can enhance the validity of safety studies (Waning 2001). If multiple comparator or control groups are employed, the protocol should identify the primary comparator and include a discussion of the rationale for each group and its importance to the study questions of interest.

In cohort studies, it is ideal to use a comparator group taking a drug used to treat the same disease, with the same level of disease severity, and from the same time period as the exposed cohort. For example, when selecting a comparator group, investigators should consider the impact that formulary status (e.g., medication tiering or prior authorization issues) could have on the level of disease severity of the exposed group and the comparator group. If it is not possible to find an appropriate comparator group from the same time period as the exposed group, investigators might elect to use ***historical comparators*** (i.e., a comparator group selected from a different time period than the exposed cases). If investigators choose to use historical comparators, they should explain the rationale for their choice and discuss how the use of historical comparators might have an impact on the interpretation of study results (e.g., consideration of the impact on changes in medical practice over time).

Pharmacoepidemiologic safety studies conducted on preventative therapeutics, such as vaccines, present issues that call for special considerations in study design. One such issue is the *healthy vaccinee effect*. Because vaccines are generally given to persons who are healthy, confounding could occur if vaccinated persons are compared to unvaccinated persons, as the latter may, for example, be more ill or lack access to primary medical care. The sheer avoidance of or delay in, vaccination may be associated with an increased risk of the outcomes of interest (Fine 1992). Although there are various ways to address this issue, it may be appropriate to use self-control or case-crossover designs, where the same person serves as his or her own control (Maclure 1991). Regardless of which study approach is used, the protocol and final report should describe the relevant limitations of the comparator group's selection.

#### *4. Study Time Frame*

Refer to section IV.F, Study Time Frame and Lag Time Issues.

#### *5. Identification and Handling of Confounders and Effect Modifiers*

Biases that are either unidentified or inadequately addressed can compromise the validity of pharmacoepidemiologic safety studies. Therefore, it is important for investigators to describe the processes used to identify potential biases and to provide a scientific and clinical rationale for the methods selected to handle them. ***Channeling*** and ***confounding by indication*** are two related biases that can be particularly problematic in pharmacoepidemiologic safety studies (Strom 2005). Although these biases can be managed by using certain methods, such as propensity or disease risk scores, restriction, or by using multiple or self-comparison groups, they could be so pervasive as to entirely preclude the use of an observational study to examine the safety issue (Petri and Urguhart 1991, McMahon 2003).

Channeling refers to the situation where drugs are prescribed to patients differently based on the presence or absence of factors prognostic of patient outcomes. In other words, the potential for a given outcome differs between the groups (those who receive the drug or medical product of interest and the comparison group) because of patient characteristics that were present prior to drug treatment. When these characteristics are also related to prescribing patterns of the drug of interest, a biased estimate of risk may result. As such, channeling may introduce a bias that can make a drug seem either more beneficial or more harmful than it actually is. (Petri 1991; Journal of American Medical Association Online Dictionary). Confounding by indication is a type of channeling bias that occurs when the indication, which is associated with the drug exposure, is an independent risk factor for the outcome; this is of particular concern in pharmacoepidemiologic safety studies using electronic health data because these data do not generally identify the indication for drug use.

There are various epidemiologic and statistical methods for identifying and handling confounding in pharmacoepidemiologic safety studies using electronic healthcare data, and FDA does not endorse or suggest any particular method. FDA encourages the continued development, use, and evaluation of innovative methods to adjust for confounding.

Propensity score modeling is one approach that is often used to address confounding in pharmacoepidemiologic studies. A propensity score for an individual is the predicted probability for treatment 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 those exposed to the drug of interest and the comparator group, with respect to the measured covariates (Rosenbaum and Rubin 1983; D'Agostino et al. 1998). When propensity score modeling is used, investigators should present ***diagnostics*** of the propensity score model to allow for an assessment of its performance and fit. A full discussion of propensity scores is beyond the scope of this guidance; however, many articles in the literature, some of which are cited in this guidance's bibliography, provide a more in-depth discussion of this model and its appropriate application to pharmacoepidemiologic safety studies.

Another approach to address confounding in pharmacoepidemiologic safety studies is to exclude patients who have risk factors for the safety outcome that are unrelated to drug use. This strategy can be appropriate, but can also have the unintended consequence of reducing the size of the study population, precluding examination for effect modification, and limiting the generalizability of the results. An alternative approach to excluding such patients is for the investigator to stratify the patients by the relevant risk factors. The decision-making process for excluding or stratifying should be made in the context of the specific study hypotheses and fully explained and documented in the protocol. FDA discourages the exclusion of patients because it prevents investigators from enhancing the generalizability of the study results, compromises statistical power, and precludes the examination for effect modification by these other risk factors. However, if a particular group of patients is to be excluded from a study, the investigator should justify this approach, provide a detailed explanation of the exclusions, and discuss the resulting limitations in study interpretation.

All confounders, particularly ***time-varying confounders***, and effect modifiers should be operationally defined and justified.

Unmeasured confounders can affect the study validity. Investigators should consider how they might explore the impact of these unmeasured confounders. Any assumptions regarding these variables and any sensitivity analyses used to test these assumptions should be fully described. Sometimes supplemental information can be used to explore the potential impact of unmeasured confounders on the study findings. For example, in a pharmacoepidemiologic safety study of nonsteroidal anti-inflammatory medications, investigators supplemented electronic pharmacy data with survey data on OTC medications, which served as a proxy for OTC nonsteroidal anti-inflammatory drug use (Graham, et al. 2005). In another example, the functional status of study subjects was obtained through medical chart review, which enabled researchers to more accurately estimate the impact of the subject's frailty (a confounder that typically would not be available in electronic health data) on the risk of harms associated with a vaccine (Jackson, et al. 2006; Jackson, et al. 2008).

The potential for effect modification by main demographic variables (e.g., age, sex, 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.

#### *6. Sample Size and Statistical Power*

Sample size and statistical power should be estimated before initiating the study. In addition, investigators should explain how the sample size was determined and provide 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 and database 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) and long latency outcomes. 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 investigator should define the exposure risk window for the outcome of interest and describe in detail the measurement of the window in the selected data source(s). FDA recommends that the investigators obtain information about the postulated exposure risk window from other sources, such as spontaneous report data, to increase the likelihood that only relevant periods of exposure are examined. 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, which could result in biased risk estimates. All assumptions made in defining the exposure risk window should be clearly articulated and justified, including 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).

Investigators should justify the units selected for the exposure risk window (e.g., person-time, patients, and prescriptions). Relevant drug interactions that could affect the measurement of the exposure risk window for the drug of interest should also be operationally defined. For example, if investigators are operationally defining concomitancy, they should state whether drugs are considered as being used concomitantly by the same patient if:

- they are dispensed on the same day;
- they have overlapping days supply;
- they have ever received prescriptions for the two drugs during the study period; or
- another relevant definition is appropriate.

If a different definition of concomitancy is used, it should be described in detail.

Dispensed prescriptions are commonly used to define the exposure risk window for studies conducted using administrative claims data. If investigators elect to define the exposure in other ways (e.g., using other clinical characteristics or medical diagnoses, or prescription orders from EMR data), they should discuss the demonstrated validity of these definitions.

*2. Exposure Ascertainment — Study Design*

As previously mentioned, the study design should be tailored to the study question of interest and justified in the study protocol; FDA does not advocate the use of any specific study designs. However, one design increasingly being used is the new (incident) user design, which is based on the first exposure to or use of the drug of interest. This approach merits discussion here, as it provides advantages over the prevalent user design, which is susceptible to ***survivor bias***. The prevalent user design can also be susceptible to other biases that arise from controlling for covariates in the causal pathway. If employing a new user design (Ray 2003), the investigator should operationally define *new use* and provide a rationale for this definition in the context of the study question. This information will allow reviewers to critically evaluate the accuracy of the exposure definition.

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. A new user design might focus on patients newly switching from a first-line to second-line therapy or on patients adding a new medication to existing therapy. If investigators choose to employ a prevalent user design, they should provide sound justification and fully describe the time during which follow up to prevalent use begins; the rationale for this selection; and the implications for covariate measurement. Investigators should include a discussion on the limitations of this approach and the potential impact on study findings.

*3. Exposure Ascertainment — Data Source*

It is critical that the proposed data source sufficiently capture the drug exposures during the defined study period, and a relevant discussion should be included in the study protocol. The operational exposure definitions should be based on the coding system of the selected data source(s) 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 operational definition should include the appropriate pharmacy codes (National Drug Codes or NDC codes) and/or procedure ("J") codes[12] to capture the use of the drug(s) in various settings. This is particularly important in the case of non-oral drugs, which may be assigned different codes depending on how they are obtained. For example, patients using an injectable drug can purchase it from the pharmacy, in which case the NDC code would be recorded, or the provider can purchase it for the patient and bill for both the drug and its administration using the "J" code.

When investigators use an insurance-based data source, it is important for them to address lack of capture of prescriptions not associated with insurance claims if these drugs are relevant exposures for the study. Uncaptured prescriptions might include low cost generics and drugs obtained through programs at a standardized discount price; samples provided by pharmaceutical companies and dispensed by healthcare providers; and drugs sold through the Internet. In addition, OTC medications and dietary supplements are not generally captured in insurance-based data sources. Study investigators should address the presence and extent of incomplete exposure ascertainment and its effect on study validity.

#### *4. Exposure Ascertainment — Gaps in Therapy and Censoring*

Because patients often do not obtain refills exactly on time, gaps in therapy could exist in electronic healthcare data, and decisions should be made as to when these gaps are long enough to suggest true interruption of chronic therapy. FDA recommends that investigators clearly describe and justify in the protocol how they will address potential gaps in therapy, especially for chronic therapies. Intermittent therapies (e.g., drugs used to treat pain on an as needed basis) and therapies for which samples are often provided to patients (e.g., oral contraceptives) present special challenges in accurately assessing the actual exposure time. It is critical that investigators establish operational definitions of exposure when studying these types of therapies.

It is also important that investigators define the window of time after discontinuation during which the events of interest might still be attributed to the drug. It might be most appropriate for this period of time to be the same as the gap allowance used to define continuous enrollment. Alternatively, the period of time can be established based on the relationship between the known mechanisms of action of the drug and the outcome of interest. Overall, the censoring of follow-up time and events should be clearly defined by the investigator. For example, events can be counted using an approach in which only time on drug (or perhaps time on drug plus a window of time after drug exposure) is included in the analysis. Alternatively, the approach might be to include all follow-up time in the analysis, including time off the drug. For further discussion of the exposure risk window, refer to section V.B.1.

[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.

*5. Exposure Ascertainment — Dose*

Although electronic healthcare data capture drugs that are either prescribed for or dispensed to patients, they do not capture patients' actual drug exposure because this depends on patients' adherence to the prescribed therapy. In certain cases, such as drugs used chronically or drugs with fixed-dose regimens, it can be appropriate to infer dosage information from electronic healthcare data. Investigators should provide the specific assumptions made when estimating the dose of the exposure (drug) of interest, especially for pediatric patients. It is also important for investigators to report how different dosage forms will figure into the dosage calculation, if multiple forms are available. Sensitivity analyses may prove helpful in testing these assumptions (refer to sections VI.D and V.B.1).

*6. Exposure — Other Factors*

In pharmacoepidemiologic studies of drugs using inpatient data, it is important for investigators to consider the order in which inpatient drugs are administered, both in relation to each other and to the outcomes of interest; this information may not be readily available in electronic healthcare data. In addition, if the exposure of interest is available as both a fixed combination product and the individual component of a fixed combination product, it is important to account for this fact when ascertaining total exposure (e.g., drugs to treat hypertension are commonly prescribed as combination drugs). Another important consideration in defining and ascertaining exposure is switching between drugs within the same therapeutic drug class. Repeated switching can significantly complicate exposure definition, but for many drugs this will reflect real-world patient experience. In these cases, the investigator should describe the approach taken to account for switching and discuss the potential impact on the study's generalizability.

In most EMR data, information on exposure is generally limited to products prescribed by healthcare providers. In the absence of a linkage between prescribing and dispensing systems, it cannot be assumed that the patient actually filled the prescription and thus the investigator cannot assume the patient is exposed. It is important for investigators to describe their approaches 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 can 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. To avoid selection bias when evaluating the effect of drug exposures, FDA recommends that investigators refrain from defining cases (and their controls if part of the study design) based on the presence or absence of these exposures before or after the occurrence of the outcome of interest.

### *2. Validation of Outcomes*

Because administrative claims data are not collected for investigative purposes, but rather for patient care or reimbursement purposes, investigators should ensure that the selected medical outcomes of interest are validated (Lanes 2006). Specifically, outcome validation involves establishing a clinically appropriate outcome definition and determining the positive predictive value of that definition. Although validation can be performed using different techniques, the determination of the positive predictive value of a code-based (e.g., ICD) operational outcome definition often involves selecting all or a sample of cases with the codes of interest from the data source and conducting a review of their primary medical data (generally medical charts) to determine whether or not each patient actually experienced the coded event. Although validation is critical for all safety studies, it is especially important for certain vaccine outcomes for which coding practices cannot be known or assumed.

If the outcome has previously been validated, the investigator should cite the specific literature references. The validated algorithm should be described in detail, including the population and database in which the validation was performed, its performance characteristics, and the time frame during which the validation was performed. For studies lacking prior outcome validation, the investigator should provide appropriate justification of the outcome definition used.[13]

For pharmacoepidemiologic safety studies, the sensitivity of the outcome definition is an important consideration because it is often not possible to completely ascertain the outcome of interest when using electronic healthcare data. For example, although an operational outcome definition could have high positive predictive value, it could have low sensitivity if the outcome of interest does not often come to medical attention and therefore is missed. Thus, investigators should discuss (1) the positive predictive value of the outcome definition and potential implications on the study's internal validity and (2) the sensitivity of the outcome definition, namely, the extent to which the outcome can be ascertained in the selected data sources and

[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 can facilitate comparisons of analyses between different studies.

study population. The discussion should include potential implications for the external validity, or generalizability of the study findings, to the real world patient population.

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" practices are commonly used to maximize reimbursement (Strom 2005). Therefore, when using claims data, it is preferable to use and validate inpatient codes in defining outcomes whenever possible because these codes are generally more reliable and tend to reflect more serious diseases. In addition, investigators should report their ability to capture outcome severity in the databases employed. This is especially pertinent for outcomes that patients can manifest differently and with varying degrees of severity. For example, an allergic reaction can range from a skin rash to a life-threatening experience such as anaphylactic shock.

The strategy described above for validation in administrative claims data might not be relevant when EMR data are used, because the EMR might represent the only primary medical data available for validating the patient encounter. There is still a scientific need, however, to develop and employ strategies for ensuring that the coded electronic data accurately reflect patient experience. To gain more information, investigators might, for example, review pertinent paper files and documents, review clinical detail from free text in the EMR, or follow up with the healthcare providers. As implementation of EMRs becomes more widespread, FDA encourages investigators to develop innovative strategies to confirm electronic exposure and outcome data. This will serve to strengthen the validity of studies relying upon these data.

*3. Outcome Definition — Procedures or Diagnoses*

When defining outcomes, if the investigator is using procedure data instead of or in addition to diagnosis data as outcomes, he or she should explain the rationale behind this choice. Validation of the codes used, or a justification for not performing validation, should also be included.

*4. Mortality as an Outcome*

Death is a particularly difficult outcome to ascertain reliably and completely using electronic healthcare data. Although deaths that occur while a patient is 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; however, determining the cause of death may call for 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 1970). The use of death certificate data is subject to all the known limitations of such data (Lenfant 1067; Cambridge and Cina 2010).

Because deaths that occur while the patient is not under medical care might not be captured in electronic healthcare data systems, patients who die might only be observed in electronic healthcare data as either not filing any further claims or not receiving any additional care past a particular date. For studies in which the outcomes may often be fatal, it is important that investigators not exclude patients who appear to be *lost to follow up* at any time following their exposure to the study drug. These patients should be included in searches of NDI or other systems to see whether 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

If investigators have conducted any ***feasibility analyses***, the study protocol should discuss the results, including their impact on the prespecified analysis plan and study.

The prespecified analysis plan should address the specific study objectives and specify the details of the primary analysis and any secondary analyses. The plan should be included in the protocol; however, depending on the level of detail, it may be preferable to include the plan in an appendix to the protocol. At a minimum, the plan should include details on the statistical models and tests, sample size estimation, the significance level and power of the study, handling of missing values, subgroup analyses and the assessment of effect modification, and the method of confounding adjustment. Operational definitions of exposures, covariates, and outcomes should also be delineated.

Careful consideration of the adjustment for confounders is critical for studies that employ electronic healthcare databases. Because these databases are often large, the studies can have high power to obtain statistically significant results. However, results might be biased because of unmeasured confounding and small effects can be statistically significant. The potential impact of unmeasured confounders and other relevant sources of bias should be discussed and, when possible, evaluated analytically. Unadjusted results and results that have been adjusted for confounding both should be presented and discussed in the final analysis to facilitate both a qualitative and quantitative evaluation of the adjustments.

### B. Study Analyses

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

Unadjusted analyses/analyses with nonvalidated outcomes: If investigators plan to perform unadjusted analyses (analyses that do not adjust for confounders and examine effect modification) or analyses with nonvalidated outcomes, in addition to adjusted analyses and analyses with validated outcomes, they should prespecify the plan for these analyses and explain the rationale for conducting these analyses (e.g., to describe study covariates). For further discussion of the identification and handling of confounders, examination of effect modification, and outcome validation, refer to sections V.A.5 and V.C.2.

Primary analyses address the prespecified study hypotheses.

Secondary analyses (e.g., prespecified analyses to address secondary objectives, subgroup analyses, ***post hoc analyses***), which are defined as analyses conducted in addition to the primary study analyses, should also be described. Significant findings in subgroup analyses can be considered hypothesis-generating unless prespecified and adequately powered. If subgroup analyses are employed, investigators should describe methods used to examine the subgroups and interactions (von Elm, et al. 2008). Post hoc analyses are analyses that were "not anticipated or described" in the analysis plan or study protocol (Begaud 2000). 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. These techniques should be well described and justified, including a clear delineation of relevant assumptions and limitations. Diagnostics, both graphical and analytical, are often relevant and facilitate the evaluation of assumptions and performance of the techniques. The statistical analysis plan should specify the planned statistical techniques and diagnostic methods before the data are reviewed. The study report should present the results of the statistical analysis and accompanying diagnostics. When there are key effect modifiers, the report should also present results for the subgroups defined by the effect modifiers.

### 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, and of deficiencies in the data source(s) selected. Such analyses can be very helpful in determining the potential impact of varying assumptions (e.g., changing cutpoints for categorical variables, limiting or expanding case or outcome definitions, changing definitions of current exposure) on study results, and can facilitate better interpretation of study results in light of significant uncertainty. 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 multiple data sources are to be used in the study, the reason for the multiple data sources and the details on how they will be used should be provided. As mentioned in the study approach section above (III.C), multiple data sources can be linked to provide more complete information on a set of patients (e.g., a healthcare database can be linked with national mortality records). For this use, the details of linking and the expected accuracy of the linking should be provided.

Another use of multiple data sources is to provide a larger or more diverse sample of patients. For this use, details on whether and how the data sources are to be pooled should be provided. The data sources can be pooled on a patient level, or because of privacy or other limitations, the data sources can be pooled at a summary statistical level. In some cases, it may be possible to use summary statistics or other de-identified information to pool information across the data sources to produce an analysis that is equivalent to pooling the patient-level data. In other cases, it may be important to employ study-level meta-analytical techniques to obtain a pooled estimate. In either case, careful consideration should be given to the heterogeneity of the data sources and individual data source summaries (e.g., baseline characteristics, follow-up time) and results should be provided.

### F. Assessment and Handling of Missing and Uninterpretable Data

Investigators should develop a plan to assess and handle missing and uninterpretable data. 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 myocardial infarction) 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 QC and QA plan for the construction of the analytical data and the analysis of data should be clearly described. QC consists of the steps taken during the analysis to ensure that it meets prespecified standards 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 in the Office of Surveillance and Epidemiology (OSE)*, (FDA MAPP 6700.2), provides an example of how QC and 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).

In certain circumstances, FDA might 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

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

such re-analyses while ensuring personal data protection. FDA will address the need for accessing original analytic data on a case-by-case basis.

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

The 2008 ISPE guidelines highlight the importance of describing "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 2008). FDA encourages investigators to describe these processes used for managing and preparing their data. It is important that analysts performing and reviewing data management and analysis have appropriate training or prior experience in the use of the particular analytic software that is being used. FDA considers documentation a very important component of the analytic process and recommends that all analytic programs be thoroughly annotated with comments that clearly describe the intent or purpose of each step.

## 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]." (Strom 2005).

**Channeling:** A situation where drugs are prescribed to patients differently based on the presence or absence of factors prognostic of patient outcomes.

**Confounding by indication:** Confounding by indication is a type of channeling bias that occurs when the indication, which is associated with the drug exposure, is an independent risk factor for the outcome

**Churn rate:** Individuals may enroll or disenroll from a health plan over time, especially as, in the United States, most healthcare coverage is employer-based and thus coverage changes over time with changes in employer. The churn rate, also known as attrition rate, is the proportion of enrollees that disenroll from a health plan in a given time period.

**Comparator (comparison) group:** Any group to which patients with either the exposure or outcome of interest are compared (Porta 2008).

**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:** Analytic data 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 2008). 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 (National Alliance for Health Information Technology (NAHIT) Report 2008).

**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 should 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. (Begaud 2000).

**Feasibility analyses:** Analyses conducted before the development of the protocol and analysis plan to determine if a study is feasible (i.e., the enumeration of patients exposed to the therapies of interest, the evaluation of the magnitude of the safety outcome in the population of interest).

**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. (Porta 2008).

**Lag time:** Lag time is the time of a patient's actual date of service to the date when the adjudicated claim first appears in the data source. Different types of claims (pharmacy, physician, and hospital) have different average lag times. This phenomenon causes varying degrees of under-ascertainment near the data cut-off date.

**Observational studies:** In observational studies, "the investigator does not control the therapy, but observes and evaluates the results of ongoing medical care." (Strom 2005). For purposes of this guidance, observational study designs do not involve random allocation and include case-control, nested case-control, case-cohort, and case-crossover designs.

**Pharmacoepidemiologic safety study:** An observational study designed to assess the risk associated with 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 2000).

**Primary analyses:** Analyses that address the prespecified primary study hypotheses.

**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 standards and that the drug or service is reproducible (FDA MAPP 6700.2).

**Secondary analyses:** Analyses conducted in addition to the primary analyses (e.g., prespecified analyses to address secondary objectives, subgroup analyses, post hoc analyses).

**Study time frame:** The time frame 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.

**Survivor bias**: A specific type of selection bias arising from differences in competing risks or loss to follow-up between exposure groups (Rothman 2008).

**Time-varying confounder:** A confounder variable whose values change over the study time frame (Platt 2009).

**Validation:** Validation involves the establishment of a clinically appropriate definition for the variable (e.g., patient attribute, medical condition, outcome) of interest and the determination of the positive predictive value of that definition.

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