Introduction

Pharmacoepidemiologic studies provide valuable information about the health effects of healthcare products. The ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP) are intended to assist investigators with issues pertaining to the planning, conduct, and interpretation of pharmacoepidemiologic research. This paper represents the fourth version and supersedes previous versions. While the overall structure and nature of the GPP has been preserved in the current revision, new sections have been added and the text has been updated to reflect current practice.

Pharmacoepidemiology is being used increasingly to evaluate health care systems, interventions, and health-related behaviors. Pharmacoepidemiology is the scientific backbone of therapeutic risk management—the process of assessing a product's benefits and risks, and developing, implementing, and evaluating strategies to enhance the overall balance of such benefits and risks. Pharmacoepidemiology is also the scientific backbone of comparative effectiveness research (CER). These guidelines are intended to address these activities and other pharmacoepidemiologic studies.

The GPP address the following areas:

- ***Protocol Development***
- ***Responsibilities, Personnel, Facilities, Resource Commitment, and Contractors***
- ***Study Conduct***
- ***Communication***
- ***Adverse Event Reporting***
- ***Archiving***

A. Goals

The GPP propose essential practices and procedures that should be considered to help ensure the quality and integrity of pharmacoepidemiologic research, and to provide adequate documentation of research methods and results. The GPP do not prescribe specific research methods, nor will adherence to guidelines guarantee valid research.

The GPP have the following specific goals:

1. To assist researchers in adhering to good pharmacoepidemiologic research principles, including the use of pharmacoepidemiologic studies for risk management activities and CER.
2. To promote sound pharmacoepidemiologic research by encouraging rigorous data collection, analysis, and reporting.
3. To provide a framework for conducting and evaluating pharmacoepidemiologic studies.
4. To facilitate the appropriate utilization of technical resources by promoting careful study design and planning of study conduct.
5. To facilitate transparency and ethical integrity in research conduct.

B. Scope and Application

The GPP are intended to apply broadly to all types of pharmacoepidemiologic research, including feasibility assessments, validation studies, descriptive studies, as well as etiologic investigations, and all of their related activities from design through publication.

Therapeutic risk management activities provide a formal framework in which medicine, pharmacoepidemiology and public health are integrated in the development and life-cycle management of healthcare products. Pharmacoepidemiology is the core science of risk assessment and the

evaluation of the effectiveness of risk minimization interventions. Therefore, the GPP also support risk management activities.

In a similar fashion, pharmacoepidemiology is the core discipline of comparative effectiveness research (CER). Such activities are based on problems from clinical medicine, by using rigorous methods to compare the outcomes of two or more therapeutic alternatives. Thereby, comparative effectiveness activities are defined by their research questions rather than by their methods

III. Responsibilities, Personnel, Facilities, Resource Commitment, and Contractors

A. Responsibilities

The organization(s) and individual(s) conducting and sponsoring the research shall be fully responsible for the research. The relationship, roles, and responsibilities of the organizations and/or individuals conducting and sponsoring the study should be described.

The individuals responsible for pharmacoepidemiologic research, along with the type of expertise and autonomy in conducting the research, should be stated clearly. For projects sponsored by one organization (such as a pharmaceutical company or government agency) but implemented by another (e.g., an academic institution or a contract research organization-CRO), responsibility for scientific integrity is shared by the collaborating institutions (e.g, sponsor, the principal investigator conducting the study, the senior qualified epidemiology staff within the CRO and the organization that employs the principal investigator). In such situations of shared responsibility, contractual arrangements should include a timeline for study completion and potential actions to be taken if the timeline cannot be met. In particular, the contract should delineate the roles and responsibilities to be assumed by the study sponsor and the contractor(s) in communicating various aspects of the study as well as data access, ownership and archiving.

B. Personnel

Personnel engaged in epidemiologic research and related activities should have the education, training, or experience necessary to perform the assigned functions competently. The organization should maintain a current summary of training and experience of these personnel. A list of individuals engaged in or supervising activities should be maintained and updated periodically with current job titles.

C. Facilities

Adequate physical facilities shall be provided to all those engaged in epidemiologic research and related activities. Suitable storage facilities shall be available to maintain technical records in a secure and confidential environment in compliance with local regulations.

D. Contractors

For the purposes of ensuring and documenting the contractor's conformance with the GPP, it is recommended that the study sponsor have the right during the course of the study, and for a reasonable period following completion of the study, to inspect the contractor's facilities, including equipment, technical record, programming, and records relating to the work conducted under the sponsor's contract. The nature of the audit, including procedures that ensure patient confidentiality, should be agreed upon at the outset of any contract.

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IV. Study Conduct

The principal investigator shall be responsible for the overall content of the research project, including the day-to-day conduct of the study, interpretation of the study data, and preparation and publication of the final report. These responsibilities extend to all aspects of the study, including periodic reporting of study progress as well as quality assurance.

The unusual decision to terminate a study prematurely should be taken with great caution, and should be based on good scientific and ethical reasons and documented in writing. There may be rare instances in which administrative reasons require study termination. Investigators and sponsors should specify and agree in advance about the circumstances under which the study could be terminated early. Included should be a mechanism for resolution of any disagreement.

A. Protection of Human Subjects

Approval by an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or other appropriate body, should be obtained for all research involving human subjects. Studies using commercially or publically available de-identified secondary data sources, or which meet certain other criteria, are not considered research involving human subjects in some countries and may be exempt from IRB review. Informed consent beyond that already obtained for participants in a research database may be needed when the research imposes a risk for patients or data containing personal identifiers is required by the investigator (e.g., medical record). The legal definition of a personal identifier varies across countries; therefore, national and local laws should be consulted when proposing to obtain this type of data.

In some circumstances, and in some countries, disclosure of relevant personal medical information (e.g., medical record) without consent is permissible under public health laws, for example when government organizations conduct infectious disease surveillance or monitoring and reporting adverse drug reactions through secondary data sources (see section II, O on Active Surveillance).

Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. Whenever feasible, study files should be coded and stripped of personal identifiers, and code keys stored separate from study files. All personnel with access to data containing personal identifiers should sign a pledge to maintain the confidentiality of study subjects. For additional information, please consult the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health .

Blood and serum sample collections stored after completion of clinical studies are a valuable resource. However, protecting confidentiality in such data requires special consideration and investigators are encouraged to consult guidelines developed by the NHLBI.

B. Data Collection, Management, and Verification

All data collected for the study should be recorded accurately, promptly, and legibly. The individual(s) responsible for the integrity of the data, computerized or hard copy, shall be identified, and shall have the education, training, and experience needed to perform the assigned tasks.

All procedures used to obtain, verify and promote the quality and integrity of the data should be recorded in sufficient detail so that others can replicate them. A historical file of these procedures

shall be maintained, including all revisions and the dates of such revisions. Any changes in data entries shall be documented. For any endpoint or covariate status ascertainment (in a cohort study or trial) or exposure ascertainment (in a case-control study) that requires adjudication, all measures taken to assure blinding of the adjudicators to the exposure (cohort) or outcome (case-control) status of the subject should be outlined in the protocol. Documentation of these measures needs to be maintained with the data files throughout the course of the study and archiving period.

Security of the data should be maintained at all times. Access should be limited to authorized individuals. Control systems, such as document encryption, should be used to ensure the authenticity, integrity and confidentiality of electronic records when transmitted over open networks (e.g., the internet). Adequate back up of the data should be maintained throughout the course of the study.

C. Analysis

1. 1. A clearly defined statistical analysis plan, including statistical procedures and shell tables should be documented. The statistical analysis plan should be finalized before the end of data collection

2. 2. All data management and statistical analysis programs and packages used in the analyses should be documented and archived. Reasonable effort should be made to document and validate interim steps in the analysis.

3. 3. The analysis should be directed toward the unbiased estimation of the epidemiologic parameters of interest (e.g., risk or rate differences, risk or rate ratios). The precision of effect estimates should be quantified using confidence intervals. Comparability of populations for pooled estimates should be assured, and missing of important variables should be addressed. *Interpretation of statistical measures, including confidence intervals, should be tempered with appropriate judgment and acknowledgements of potential sources of error and limitations of the analysis, and should never be taken as the sole or rigid basis for concluding that there is or is not a relation between an exposure and outcome. Sensitivity analyses should be conducted to examine the effect of varying potentially critical assumptions of the analysis.*

D. Study Reports

Describe the need and purpose of an interim report or analysis when applicable. If required, the issuance of such reports must be pre-specified in the study protocol.

Completed studies shall be summarized in a final report that accurately presents the study objectives, methods, results, strengths and limitations of the study, and interpretation of the findings.

The final report shall include at minimum:

1. A descriptive title;

2. An abstract;

3. Purpose (objectives) of the research, as stated in the protocol;

4. The names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators;

5. Name and address of each sponsor;

6. Dates on which the study was initiated and completed;

7. Introduction with background, purpose, and specific aims of the study;

8. A description of the research methods, including:
   a. source population and selection of study subjects;
   b. data collection methods and, if questionnaires or surveys are involved, complete copies (including skip patterns);
   c. transformations, calculations, or operations on the data;
   d. statistical methods used in data analyses.

9. A description of circumstances that may have affected the quality or integrity of the data; *Describe the limitations of study approach and the methods used to address them (e.g., response rates, missing or incomplete data). All sensitivity analyses conducted to assess the impact of critical assumptions should be listed.*

10. Analysis of the data; *Include sufficient tables, graphs, and illustrations to present the pertinent data and to reflect the analyses performed. Epidemiologic parameters (e.g., risks, rates, risk or rate differences, risk or rate ratios) are the most typical epidemiologic measures to report. Both unadjusted and adjusted results should be presented. Effect measures should not be described as "significant" or "not significant." Precision of estimates should be quantified using confidence intervals. Confidence intervals communicate both the strength of the relationship and the precision of the measure and are therefore more informative than point estimates accompanied by p-values.*

11. A discussion of strengths, limitations and possible bias of the study, including direction and magnitude of bias, if known.

12. A statement of the conclusions drawn from the analyses of the data;

13. A discussion of the implication of study results; *Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research. Inferences about causal effects should be based on a variety of factors that should be explored in the discussion section. These factors include strength of relationship, temporal relationship, biological mechanism, plausibility of alternative theories, biases, confounding, precision, and others.*

14. Acknowledgements

15. References.

V. Communication

Each organization and its advisory board, if there is one, shall predetermine procedures under which communications of the intent, conduct, results, and interpretation of an epidemiologic study will occur, including what function individuals associated with the research must fulfill. These individuals should include the principal investigator, study director, and/or the sponsor. This procedure may be documented in the form of a company standard operating procedure, in the study protocol, or through contractual agreement.

ISPE encourages communicating quantitative estimates of epidemiologic measures in the results section, generally by using point estimates and confidence intervals, either directly or graphically. It is useful in reporting results of safety studies to include both the relative and absolute risk estimates. Inferences about causal effects should be based on a variety of factors that should be explored in the discussion section. These factors include strength of relationship, temporal relationship, biological mechanism, plausibility of alternative theories, biases, confounding, precision, and others. Investigators should not make inferences about causation based solely on the outcome of a test of significance (e.g., a p-value or a statement about the confidence interval including or not including the null value).

There is an ethical obligation to disseminate findings of potential scientific or public health importance. For findings which could have a significant impact on public health there may be legal, as well as ethical requirements to report the results immediately to the appropriate regulatory authorities. Scientific peers shall be informed of study results in a timely fashion by publication in the scientific literature and presentations at scientific conferences, workshops, or symposia. Presentations at meetings should not be considered as a substitute for publication in the peer-reviewed literature. Authorship of study manuscripts should follow the guidelines established by the International Committee of Medical Journal Editors . All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Potential conflicts of interest, financial and non-financial, should be disclosed. Agreement to adhere to these guidelines should be described in the protocol.

Finally, research sponsors (government agencies, private sector, etc.) shall be informed of study results in a manner that complies with local regulatory requirements. Sources of research funding, including direct funding and provision of drugs, should always be acknowledged, whether results are presented orally or in writing.

VI. Reporting of Adverse Drug Events from Pharmacoepidemiology Studies:-

Pharmacoepidemiologic studies are usually designed to assess the relation between certain exposures and health events based on comparisons of the event frequency in groups with and without the exposure of interest via statistical analyses (i.e., analytic studies). The primary goal of these analytic studies is to determine whether a drug exposure increases the risk of an adverse event or provides protection against it. Therefore, causality assessment and reporting of individual exposed cases offers little, if any, scientific value to this goal.

For primary data collection studies, reporting of adverse events is required by law in most countries. Since information on suspected adverse events may be identified during the course of a study, but not as a formal part of the protocol-defined study objectives, procedures for follow-up and reporting of safety information in the study should be defined by the sponsor and research team at the time of protocol development. For specific requirements, relevant regulatory guidance documents should be consulted (see Table 1). As requirements change repeatedly, the latest versions of regulatory guidance should be consulted prior to study commencement.

Aggregate analysis of electronic healthcare databases may also identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but do not require reporting of adverse events or adverse reactions. Secondary data source studies that include medical record or narrative text review by a human reviewer, e.g., studies in which endpoint validation is performed using medical record review, are an exception. These studies are generally required to report adverse drug reactions documented in the medical record/narrative text only.

If reporting requirements apply, the protocol should specify what data are being collected and how they will be reported. Regardless of whether individual reporting requirements apply, sponsors should convey findings of their analytic studies in aggregate form as study reports.

VII. Archiving

Secure archives must be maintained for the orderly storage and expedient retrieval of all study related material. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any materials that by their general nature are not retained in the study archive. Access to the archives shall be controlled and limited to authorized personnel only. Special procedures may be necessary to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected (see, II. Protocol Development, Section I).

Where there are no specified national or regional requirements for retention of study materials, the archive should be maintained for at least five years after final report or first publication of study results, whichever comes later. At minimum, the study archive should contain, or refer to, the following:

A. A final report of the study;

B. All source data and, where feasible, any biologic specimens. A printed sample of the master computer data file(s), if feasible, with reference to the location of the machine-readable master. All "source data" should comprise the raw data that provided the basis for the final analysis of the study. The archival material should be sufficiently detailed to permit re-editing and re-analysis;

C. Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see section IV(C): Study Conduct);

D. Copies of electronic versions of analytic data sets and programs, computer printouts, if feasible, including relevant execution code, which form the basis of any tables, graphs, discussions, or interpretations in the final report. Any manually developed calculations shall be documented on a work sheet and similarly retained;

E. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits. Communication of study results to the sponsor, regulators, and scientific community should be documented; *Include, for example, questionnaires, name, make and model numbers of relevant measurement instruments, calibration information and procedures.*

F. Documentation relating to the collection and processing of study data, including laboratory/research notebooks, training and reference documents for abstracts, interviews, and coders.

VIII. other guideline and guidance:-

Table 1 summarizes other important guidelines for pharmacoepidemiology research. This list is not meant to be exhaustive but provides an overview of important guidelines available at the time of the GPP revision.