

Guidelines for good pharmacoepidemiology practices (GPP)[†]

INTRODUCTION

Pharmacoepidemiologic studies provide valuable information about the health effects of healthcare products. The ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) are intended to assist investigators with issues pertaining to the planning, conduct, and evaluation of pharmacoepidemiologic research. The first revision, in 2004 revised and superseded the Guidelines for Good Epidemiologic Practice (GEP) developed in 1996. In that revision, the scope of the guidelines was broadened geographically and conceptually, to reflect ISPE's international membership, to include risk management and pharmacoeconomic activities, and to address more clearly the role of epidemiologic studies from industry and regulatory perspectives. Specifically, the 2004 revision provided guidance on regulatory reporting requirements as they relate both to individual cases and to aggregate data (see Section 'Adverse Event Reporting From Pharmacoepidemiology Studies'). The focus of the second revision has been on the use and communication of statistical measures and to add clarification to specific items throughout the document.

ISPE recognizes that pharmacoepidemiologic research—the study of the use and effects of healthcare products (e.g., including pharmaceuticals, devices, and vaccines)—has expanded to include clinical, economic, and other health outcomes, requiring study methods that were not covered in previous guidelines. 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. These guidelines are intended to address these activities and other pharmacoepidemiologic studies.

The Guidelines for GPP have been adapted from a document prepared by the Chemical Manufacturer's Association Epidemiology Task Group.¹ When appropriate, we have (with permission) retained the text of that document. In addition, readers should also consult the ICH Guideline on Good Clinical Practice (GCP) (<http://www.emea.eu.int/pdfs/human/ich/013595en.pdf>), and the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Ethical Review of Epidemiological Studies (http://www.cioms.ch/frame_1991_texts_of_guidelines.htm).

The GPP address the following areas:

- Protocol development.
- Responsibilities, personnel, facilities, resource commitment, and contractors.
- Study conduct.
- Communication.
- Adverse event reporting.
- Archiving.

Goals

The GPP propose minimum 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.

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[†]No conflict of interest was declared.

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.
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.

Scope and application

The GPP are intended to apply broadly to all types of pharmacoepidemiologic research, including feasibility studies, 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. As such, the GPP also support risk management activities.

PROTOCOL DEVELOPMENT

Each study should have a written protocol. A protocol should be drafted as one of the first steps in any research project, and the protocol should be amended and updated as needed throughout the course of the study. The protocol should include the following elements:

- A. A descriptive title and version identifier (e.g., date).
- B. The names, titles, degrees, addresses, and affiliations of all responsible parties, including the principal investigator, co-investigators, and a list of all collaborating primary institutions and other relevant study sites.
- C. The name and address of each sponsor.
- D. An abstract of the protocol.
- E. The proposed study tasks, milestones, and timeline.

- F. A statement of research objectives, specific aims, and rationale.

Research objectives describe the knowledge or information to be gained from the study. Specific aims list key exposures and outcomes of interest, and any hypotheses to be evaluated. The protocol should distinguish between a limited number of a priori research hypotheses and hypotheses that are generated based on knowledge of the source data. The rationale explains how achievement of the specific aims will further the research objectives.

- G. A critical review of the literature to evaluate pertinent information and gaps in knowledge.

The literature review should describe specific gaps in knowledge that the study is intended to fill. The literature review might encompass relevant animal and human experiments, clinical studies, vital statistics, and previous epidemiologic studies. The literature review should also cite the findings of similar studies, and the expected contribution of the current study.

- H. A description of the research methods, including:

1. The overall research design, strategy, and reasons for choosing the proposed study design.

Research designs include, for example, case-control, cohort, cross-sectional, nested case-control, safety trials, or hybrid designs.

2. The population or sample to be studied.

The population is defined in terms of persons, place, time period, and selection criteria. The rationale for the inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, description of the population and details of sampling methods should be provided.

3. The strategies and data sources for determining exposures, health outcomes, and all other variables relevant to the study objectives, such as potential confounding variables and effect measure modifiers.

Data sources might include, for example, questionnaires, hospital discharge files, abstracts of primary clinical records, electronic medical records, ad hoc clinical databases, administrative records such as

eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, or exposure/disease registries. Use validated instruments and measures whenever such exist, and describe the validation method. If data collection methods or instruments will be tested in a pilot study, plans for the pilot study should be described. Any expert committees and evaluation procedures to be used to validate diagnosis should be described.

4. Clear operational definitions of health outcomes, exposures, and other measured risk factors as well as selection criteria and comparison groups.

An operational definition is one that can be implemented independently using the data available in the proposed study. For example, 'pneumocystis carinii pneumonia, episode' is not an operational definition; a better description would be 'hospitalization with a primary discharge diagnosis of ICD-9-CM code 136.3.'

5. Projected study size, statistical precision, and the basis for their determination.

Describe the relation between the specific aims of the study and the projected study size in relation to each outcome. In most circumstances, it is desirable to express study goals in terms of precision sought for study estimates rather than statistical power. For safety studies, it may be useful to specify the sample size that can minimally detect a pre-specified risk with a pre-specified power. For example, 'the study has an 80% power to detect a relative risk of three or greater for drug x compared to treatment with other drugs commonly used in this condition.'

6. Methods used in assembling the study data.

This should include a description of, or reference to any pre-testing procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders, or data entry personnel. This should also include procedures for linkage and data mining of administrative databases.

7. Procedures for data management.

Describe data management and statistical software programs and hardware to be used in the study.

Describe data preparation and analytical procedures as well as the methods for data retrieval and collection.

8. Methods for data analysis.

Data analysis includes all the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, or modify raw data. Data analysis comprises comparisons and methods for analyzing and presenting results, categorizations, and procedures to control sources of bias and their influence on results, that is, possible impact of biases due to selection bias, misclassification, confounding, and missing data. The statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, for instance, should be presented. Any sensitivity analyses should be described.

9. A description of quality assurance and quality control procedures for all phases of the study.

Mechanisms to ensure data quality and integrity should be described, including, for example, abstraction of original documents, extent of source data verification, and validation of endpoints. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups.

10. Limitations of the study design, data sources, and analytic methods.

At a minimum, issues relating to confounding, misclassification, selection bias, generalizability, and random error should be considered. The likely success of efforts taken to reduce errors should be discussed.

- I. A description of plans for protecting human subjects.

This section should include information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects, and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study. Conditions under which a clinical trial would be terminated for ethical reasons (stopping

rules) should be described. Procedures for monitoring results should be described, and the use of a Data Safety Monitoring Board (DSMB) for clinical trials should be considered for this purpose. The need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent should be considered in accordance with local law. See Subsection 'Protection of human rights.'

J. A description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication.

There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed medication). Authorship should follow guidelines established by the International Committee of Medical Journal Editors (<http://www.icmje.org/>). See also, Section 'Communication.' The Consolidated Standards of Reporting Trials (CONSORT) statement (<http://www.consort-statement.org/statement/revision-statement.htm>) refers to randomized studies, but provides useful guidance applicable to nonrandomized studies as well.

K. Resources required to conduct the study.

Describe time, personnel, services (e.g., database access), and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.

L. Bibliographic references.

M. Dated amendments to the protocol.

Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, along with the rationale, should be documented in writing. Any changes made after data analysis has begun should be documented as such and the rationale provided.

RESPONSIBILITIES, PERSONNEL, FACILITIES, RESOURCE COMMITMENT, AND CONTRACTORS

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.

For safety studies sponsored and conducted by a pharmaceutical company, 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 contingency plans 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.

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.

Facilities

Adequate physical facilities shall be provided to all those engaged in epidemiologic research and related activities. Sufficient resources, for example, office space, relevant equipment, and office/professional supplies, shall be available to ensure timely and proper completion of all studies. Suitable storage facilities shall be available to maintain technical records in a secure and confidential environment in compliance with local regulations.

Resource commitment

Sufficient commitment shall be made at the beginning of each study to ensure its timely and proper completion.

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, 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.

STUDY CONDUCT

The principal investigator shall be responsible for the overall content of the individual 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. Such decisions should be independent of any study results. 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.

Protection of human subjects

Approval by IRB, IEC, or other appropriate body, should be obtained for all research involving human subjects. Informed consent will be needed when the research imposes a risk for patients. Informed consent also is normally required if the study requires data containing personal identifiers. Studies conducted entirely using administrative databases or records that do not contain any personal identifiers, or which meet certain other criteria, may require only abbreviated review or may not require formal review, at the discretion of the IRB/IEC.

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 will sign a pledge to maintain the confidentiality of study subjects, and will maintain an ability to verify the origin and integrity of data sets from which personal identifiers will have been removed. For additional information, please consult the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health (<http://www.pharmacoepi.org/resources/privacy.cfm>). 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.²

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 and hard copy, shall be identified, and shall have the education, training, and experience 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.

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.

Analysis

1. A clearly defined statistical analysis plan with statistical procedures should be presented.
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. 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 separately using confidence intervals.

Interpretation of statistical measures, including confidence intervals, should be tempered with appropriate judgment and acknowledgments 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 the study population inclusion/exclusion criteria, the assumptions regarding exposure, potential effects of misclassification, unmeasured confounders, and the definitions of potential confounders and outcomes on the association between the a priori exposure of interest and the outcome(s).

Study reports

Describe need and purpose of interim report 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 and completely presents the study objectives, methods, results, 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).

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. Estimation is preferable to tests of statistical significance. 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 statement of the conclusions drawn from the analyses of the data.
12. 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.
13. References.

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 estimates of epidemiologic measures quantitatively 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). See also: Guidelines established by the International Committee of Medical Journal Editors, <http://www.icmje.org/>, Section 'Study Conduct,' and CONSORT Statement, <http://www.consort-statement.org/Statement/examples20.htm>.

There is an ethical obligation to disseminate findings of potential scientific or public health importance. 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 reports should follow the guidelines established by the International Committee of Medical Journal Editors (<http://www.icmje.org/>). 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 should always be acknowledged, whether results are presented orally or in writing.

ADVERSE EVENT REPORTING FROM PHARMACOEPIDEMIOLOGY STUDIES

The findings of epidemiologic studies of health risks associated with healthcare products must be reported by pharmaceutical sponsors to regulatory agencies according to local and international requirements. Depending on the nature of the result and the regulations in effect, the result may need to be reported in an expedited manner (e.g., as 'new relevant safety information'). In any case, results of all epidemiologic studies of healthcare product safety should be included by companies in their periodic aggregated regulatory reports, such as Periodic Safety Update Reports (PSUR) and similar regulatory documents.

Relevant regulatory guidance documents should be consulted.

It is useful to distinguish reporting of aggregate results from epidemiologic studies (i.e., study reports) from the reporting of individual adverse drug events (ADEs). Pharmacoepidemiologic studies are usually designed to assess the relation between certain exposures and health outcomes based on aggregate analyses. In such studies, particularly in case-control studies and others that may be based on retrospectively collected data, it is generally not possible or appropriate for companies to assess the causality of individual cases, although aggregate analysis of a series of study cases might identify a newly recognized adverse effect. In studies where there is no assessment of causality for individual cases, sponsors should report aggregate findings as study reports, not as individual spontaneous reports.

In prospective clinical trials where clinicians are systematically asked to report adverse events and to indicate whether each event could have been related to treatment, serious events indicated by the investigator to be at least possibly related are reportable.

Individual case reporting may be appropriate in prospective cohort studies aimed at elucidating information about a specific ADE (e.g., a drug safety registry). It is appropriate, therefore, to consider the potential value of, and necessity for, collecting such data when designing the study, taking into account existing safety experience with the drug being studied and the objectives of the study.

The principal aim of expedited reporting of individual ADEs from studies to regulatory authorities is to contribute to recognition of unexpected effects (e.g., 'signal detection'). In general, an individual study case should be reported on an expedited basis by pharmaceutical sponsors when, after an evaluation of the circumstances of the individual patient, the adverse event is considered serious and unexpected (unlabeled) and there is a reasonable possibility that a healthcare product may have contributed to the occurrence of the adverse event. Expedited individual case reporting is generally required when all of the following conditions obtain: (1) the study prospectively gathers data on individual patients, (2) the study involves direct contact with patients, (3) study personnel are trained on gathering and reporting adverse events and determining whether events might be considered 'expected' for a specific product, (4) a serious event is identified by someone who has direct contact with the patient, (5) the event is considered unexpected, and (6) the reporter believes there is a causal association with the product or that causality

cannot be ruled out. The suspicion that a drug is responsible for an event will usually be that of the study investigator or other clinical personnel with direct contact with the patient, although the pharmaceutical company may report on the basis of its own suspicion even if the study personnel do not infer a causal relation.

Occasionally information on suspected adverse events may be identified during the course of a study, but not as a formal part of the protocol-defined data collection. Procedures for follow-up and reporting of such information should be defined by the sponsor and research team at the time of protocol development.

Increasingly, automated databases are being used by universities, pharmaceutical companies, and other commercial enterprises to evaluate the relationship between exposure to a healthcare product and adverse events. Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines. Aggregate analysis should not be confused with the automated search for signal detection using algorithms to detect disproportionate reporting rates in data sets of spontaneous reports (data mining), which should always be considered as hypothesis generating or refinement techniques. Results obtained from these techniques should always be accompanied by the caveats regarding reporting rates and biases inherent in the collection of spontaneous reports.

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 Section 'Protocol Development,' Subsection I).

The archive should be maintained for at least 5 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. Study protocol and all approved modifications.
 - B. A final report of the study.
 - C. 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.
 - D. Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see Subsection 'Analysis').
 - E. 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.
 - F. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed IRB 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.*
- G. Documentation relating to the collection and processing of study data, including laboratory/research notebooks, training and reference documents for abstracts, interviews, and coders.

ACKNOWLEDGEMENTS

The following persons contributed to this work: Elizabeth B. Andrews (MPH, PhD, FISPE), Félix M. Arellano (MD, FISPE), Jerry Avorn (MD, FISPE), Edward A. Bortnichak (MPH, PhD), Robert Chen (MD, MA, FISPE), Wanju S. Dai (MD, DrPH, FISPE), Francisco J. de Abajo (MD, PhD), Gretchen S. Dieck (MPH, PhD), Corinne de Vries (MSc, PhD), Stanley Edlavitch (PhD, MA), Joel Freiman (MD, MPH), Judith K. Jones (MD, PhD, FISPE), Linda Koo

(MD), David W. Kaufman (Sc.D.), Xavier Kurz (MD, MSc, PhD), Stephan Lanes (PhD), Allen A. Mitchell (MD, FISPE), Robert C. Nelson (PhD, FISPE), Ineke Neutel (PhD, FACE, FISPE), Byung-Joo Park (MD PhD, FISPE), Susana Perez-Gutthann (MD, MPH, PhD, FISPE), Susan Sacks (PhD, FISPE), Nancy Santanello (MD, MS), Paul Stang (PhD, FISPE), Andrew Stergachis (PhD, FISPE), Brian L. Strom (MD, MPH, FISPE), Til Stürmer (MD, MPH, FISPE), Anne Trontell (MPH, MD), Alexander M. Walker (MD, DrPH, FISPE), Patrick Waller (BMS, MD, MPH, FRCP), Douglas J. Watson (PhD), Suzanne

West (MPH, PhD, FISPE), Karen Wilcock (PhD, MPH), Robert P. Wise (MD, MPH, FISPE).

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